Electronic Supplementary Material

Efficacy and Safety of Sarecycline in Chinese Patients with Moderate-to-Severe Acne Vulgaris: Randomized Phase 3 Clinical Trial with Open-label Follow-up

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Appendix S1 Study investigators and institutions

The list with the names of the 34 participating centers and 35 principal investigators at each center:

Center Name	City	Principal Investigator
Peking University People's Hospital	Beijing	Jianzhong Zhang
First Affiliated Hospital of Kunming Medical University	Kunming	Li He
Beijing Tongren Hospital, CMU	Beijing	Xiumin Yang
China-Japan Friendship Hospital	Beijing	Yong Cui
First Hospital of Shanxi Medical University	Shanxi	Shuping Guo
Dermatology Hospital of Southern Medical University (Guangdong Provincial Dermatology Hospital)	Guangzhou	Zhenfeng Liu
Henan Provincial People's Hospital	Zhengzhou	Shoumin Zhang
Shengjing Hospital of China Medical University	Shenyang	Xiuping Han
The Second Affiliated Hospital of Xi'an Jiaotong University (Xibei Hospital)	Xi'an	Songmei Geng
Sir Run Run Shaw Hospital Zhejiang University School of Medicine	Hang Zhou	Hao Cheng
The Third Xiangya Hospital of Central South University	Changsha	Jianyun Lu
Zhejiang Provincial People's Hospital	Hangzhou	Xiaohua Tao
Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology	Wu Han	Hui Chen
First Affiliated Hospital of Xi'an Jiaotong University	Xi'an	Kuanhou Mou
Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine	Hang Zhou	Liming Wu
Qingdao Municipal Hospital (Group)	Qingdao	Tongxin Shi
Beijing Tsinghua Changgung Hospital	Beijing	Yi Zhao
The First Affiliated Hospital of China Medical University	Shenyang	Xinghua Gao
Peking University Third Hospital	Beijing	Chunlei Zhang
Beijing Children's Hospital, Capital Medical University	Beijing	Lin Ma
The Second Hospital of Anhui Medical University	Hefei	Chunjun Yang
Chonqing Traditional Chinese Medicine Hospital	Chonqing	Dan Ke
Yantai Yuhuangding Hospital	Yantai	Xiujuan Xia
Shenzhen Children's Hospital	Shenzhen	Ping Li

Center Name	City	Principal Investigator
Children's Hospital, Capital Institute of Pediatrics	Beijing	Ying Gao
The First Hospital of Jilin University	Jilin	Shanshan Li
Union Hospital, Tongji Medical College of Huazhong University of Science and Technology	Wuhan	Juan Tao
Nanyang First People‘s Hospital	Nan Yang	Xiaodong Bi
Guangdong Provincial People's Hospital	Guangdong	Xiuqin Dong and Jianji Wan[a]
Chengdu Second People's Hospital	Chengdu	Yanyan Feng
Baotou Central Hospital	Baotou	Guohui Zhang
The Second Hospital of Dalian Medical University	Dalian	Aoxue Wang
Wuxi Second People's Hospital	Wuxi	ShiqinTao
Wuhan No.1 Hospital	Wu Han	Xianyu Zeng

[a] There was a change of principal investigator during the study.

APPENDIX S2: List of members of the ethics committees (including name of the Committee Chair), patient information and informed consent form (ENGLISH TRANSLATION).

The Ethics Committee of Peking University People's Hospital, No. 11, Xizhimen South Street, Xicheng District, Beijing, acting as a **central** Ethics Committee for all the participating centers, reviewed the study on their session of 23/Mar/2021.

The members of this central Ethics Committee were: Kaiyan Liu (President), Zhaolong Cao (Vicepresident), Puyu Wang, Hongyi Wang, Yi Feng, Shuang Mu, Hao Jiang, Tiezheng Sun, Haihong Zhang, Xiaohong Chang, Libo Zhao, Huiying Rao, Yuan Jia, Leili Gao and Zhende Cui.

The **local** Ethics Committees of the centers (if any) also overviewed the ethical conduct of the study, and their members are listed in the table below.

Local Ethics Committees	
Center: name and city	**Members**
First Affiliated Hospital of Kunming Medical University, Kunming	Aiyun Zhang (President), Qinglin Hao (President), Xiufeng Xu (Vicepresident), Ling Zhang (Vicepresident), Zhong Zeng, Fei He, Qingying Xiao, Xuesong Li, Hui Ren, Jian Dong, Jun Zhang, Jin Shen, Ruihong Zhang, Ping Luo, Ling Na, Xiaoqin Zheng (Alternate), Yaning Xie and Zhida shen (Alternate).
Beijing Tongren Hospital, CMU, Beijing	
China-Japan Friendship Hospital, Beijing	Yong Cui (President), Wenying Yang (Vicepresident), Yanping Bai, Ruihua Sun, Bifa Fan, Zhenguo Zhai, Guangying Zhu, Hong Jiang, Jintong Li, Chaoyang Liang, Jian Kang, Xiuyun Yin and Jie Zhou.
First Hospital of Shanxi Medical University, Shanxi	Qinghua Han, Yuezhong Sun, Chunming Zhang, Zhongguo Liu, Shanlin Chang, Lijuan Huo, Xiaoyun Hu, Huaiqing Yin, Hongbo Guo, Qing Li, Wenguang Li, Shuping Guo, Liaoyun Zhang, Xiuzhu Tian, Zhigang Wei, Xin Yan, Jin Zhang, Sha Liu, Qiaohong Wang, Bin Zhou, Rui Deng,Ling Cui

Dermatology Hospital of Southern Medical University (Guangdong Provincial Dermatology Hospital), Guangzhou	
Henan Provincial People's Hospital, Zhengzhou	
Shengjing Hospital of China Medical University, Shenyang	
The Second Affiliated Hospital of Xi'an Jiaotong University (Xibei Hospital), Xi'an	
Sir Run Run Shaw Hospital Zhejiang University School of Medicine, Hang Zhou	
The Third Xiangya Hospital of Central South University, Changsha	
Zhejiang Provincial People's Hospital, Hangzhou	
Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wu Han	
First Affiliated Hospital of Xi'an Jiaotong University, Xi'an	
Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hang Zhou	
Qingdao Municipal Hospital (Group), Qingdao	
Beijing Tsinghua Changgung Hospital, Beijing	
The First Affiliated Hospital of China Medical University, Shenyang	

Peking University Third Hospital, Beijing	
Beijing Children's Hospital, Capital Medical University, Beijing	
The Second Hospital of Anhui Medical University, Hefei	
Chonqing Traditional Chinese Medicine Hospital, Chonqing	
Yantai Yuhuangding Hospital, Yantai	
Shenzhen Children's Hospital, Shenzhen	
Children's Hospital, Capital Institute of Pediatrics, Beijing	
The First Hospital of Jilin University, Jilin	
Union Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan	
Nanyang First People‘s Hospital, Nan Yang	
Guangdong Provincial People's Hospital, Guangdong	
Chengdu Second People's Hospital, Chengdu	
Baotou Central Hospital, Baotou	
The Second Hospital of Dalian Medical University, Dalian	
Wuxi Second People's Hospital, Wuxi	
Wuhan No.1 Hospital, Wu Han	

Fig. S1 Trial design

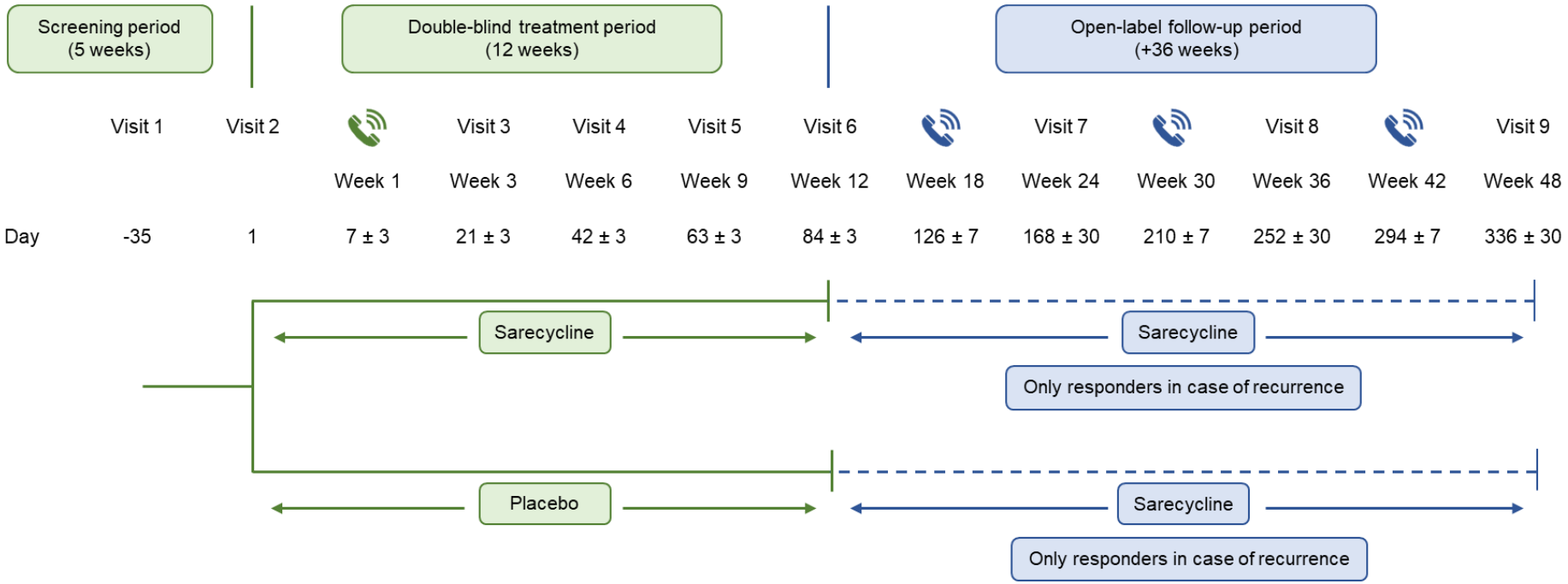
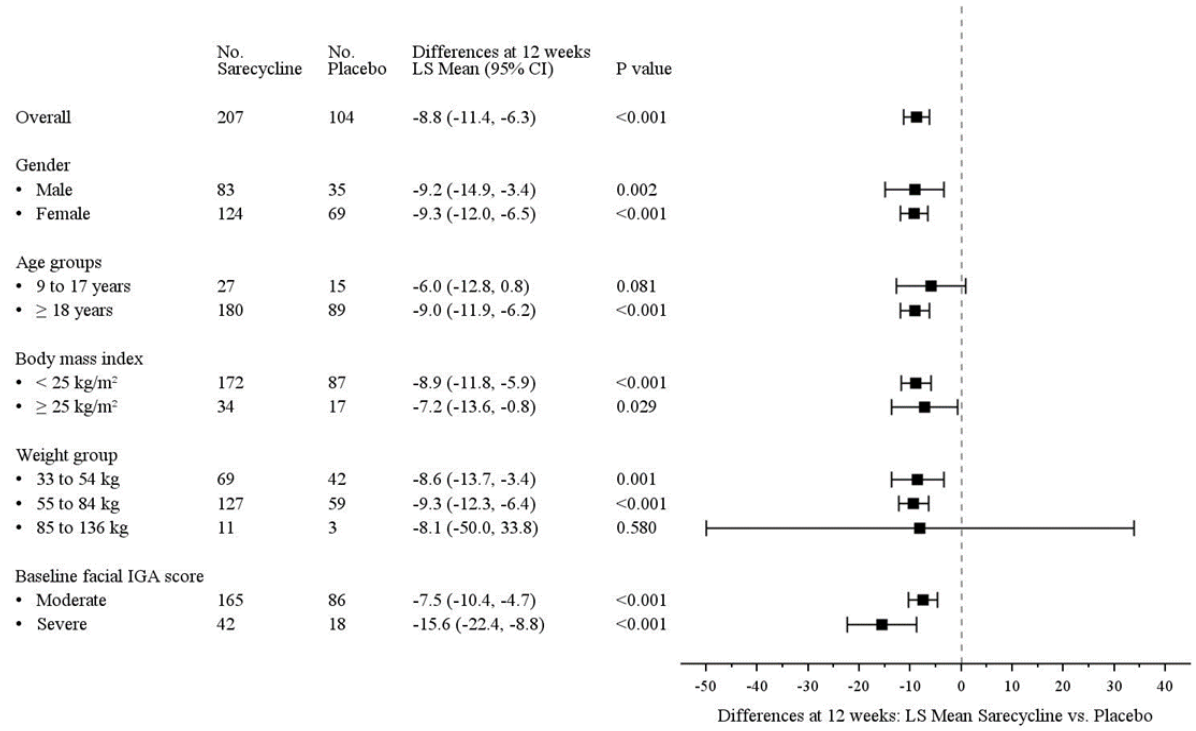
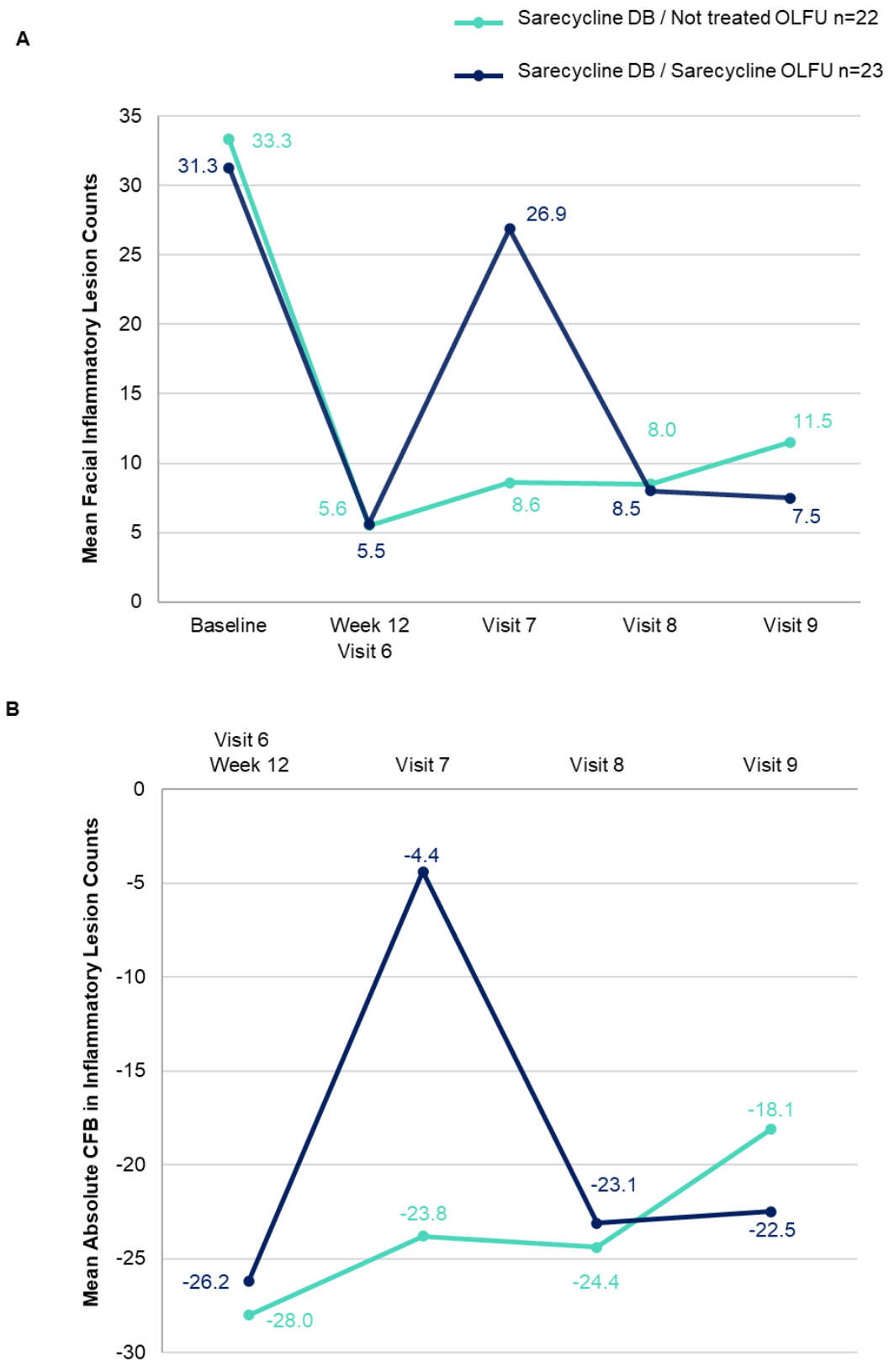


Fig. S2 Subgroup analysis – differences between sarecycline and placebo for absolute change from baseline in facial inflammatory lesion counts at week 12 — OC population (ITT analysis set)



Abbreviations: LS mean, least squared mean; OC, observed cases.

Fig. S3 Maintenance of efficacy of sarecycline up to week 48



Abbreviations: CFB, change from baseline; DB, double-blind period; OLFU, open-label follow-up period.

Table S1 Facial inflammatory lesion counts absolute change from baseline to weeks 6, 9, and 12 — PP population

	Visit	Sarecycline (N=262)	Placebo (N=129)	LS mean difference 95% CI *P* Value
LS mean (SE) absolute change from baseline using PP [a]	Week 6	-16.9 (0.8)	-11.4 (1.1)	-5.4 -7.9; -2.9 **p < 0.001**
	Week 9	-21.9 (0.7)	-14.1 (1.1)	-7.8 -10.3; -5.4 **p < 0.001**
	Week 12	-24.4 (0.8)	-15.7 (1.1)	-8.7 -11.2; -6.2 **p < 0.001**

Abbreviations: CI, confidence interval; LS mean, least squared mean; NA, not available; OC, observed cases; PP, per protocol SE, standard error

The analysis of covariance (ANCOVA) models include fixed categorical effects of treatment group, pooled site, and fixed continuous covariates of baseline values of total facial inflammatory lesion counts.

[a] Missing data are imputed using a multiple imputation method. The variables included in the imputation model are age, sex, and the raw measurement of the corresponding endpoint counts at baseline, week 3, 6, 9, and 12. Combined estimate for LS means and SEs are obtained by combining LS means and SE from ANCOVA of the different imputed data sets, using Rubin's formula. *P* Value of < 0.05 was considered statistically significant

Table S2 Facial non-inflammatory lesion counts absolute and percent change from baseline to weeks 3, 6, 9, and 12 — OC (ITT analysis set)

	Visit	Sarecycline (N=262)	Placebo (N=129)	LS mean difference 95%CI *P* Value
Adjusted absolute change from baseline LS mean (SE)	Week 3	-11.8 (0.9)	-8.3 (1.3)	-3.4 -6.5, -0.4 **p = 0.025**
	Week 6	-19.0 (1.0)	-13.6 (1.4)	-5.3 -8.7, -2.0 **p = 0.002**
	Week 9	-25.1 (1.2)	-13.7 (1.6)	-11.4 -15.1, -7.6 **p < 0.001**
	Week 12[a]	-30.7 (1.1)	-18.7 (1.6)	-12.1 -15.9, -8.3 **p < 0.001**
Adjusted percent change from baseline LS mean (SE)	Week 3	-25.4 (2.4)	-15.7 (3.3)	-9.7) -17.6, -1.9 **p = 0.015**
	Week 6	-39.6 (2.1)	-28.1 (3.0)	-11.6 -18.6, -4.5 **p = 0.001**
	Week 9	-52.7 (3.0)	-27.3 (4.1)	-25.4 -35.2, -15.7 **p < 0.001**
	Week 12[a]	-62.7 (2.7)	-36.2 (3.8)	-26.5 -35.5, -17.5 **p < 0.001**

Abbreviations: CI, confidence interval; LS mean: Least squared mean; SE, standard error; OC, observed cases.
The ANCOVA models include fixed categorical effects of treatment group, pooled site as well as fixed continuous covariates of baseline values of total facial non-inflammatory lesion count.
[a] Missing data are imputed using a multiple imputation method. The variables included in the imputation model are age, sex, and the raw measurement of the corresponding endpoint counts at baseline, week 3, 6, 9, and 12. Combined estimate for LS means and SEs are obtained by combining LS means and SE from ANCOVA of the different imputed data sets, using Rubin's formula.
P Value of < 0.05 was considered statistically significant.

Table S3 Percentage of patients with facial investigator's global assessment success at weeks 3, 6, 9, and 12 — OC (ITT analysis set)

	Visit	Sarecycline (N=262)	Placebo (N=129)	Percentage success rate difference 95% CI[a] *P* Value[b]
Percentage facial IGA success rate (95% CI)	Week 3	1.2 0.0; 2.6	0.0 0.0; 0.0	1.2 -0.2; 2.6 NE
	Week 6	3.4 1.1; 5.7	4.9 1.1; 8.8	-1.5 -6.0; 2.9 p = 0.413
	Week 9	21.2 15.8; 26.6	10.9 5.1; 16.7	10.3 2.3; 18.3 **p = 0.016**
	Week 12[c]	39.7 33.3; 46.2	16.2 9.5; 22.9	2.5 1.6; 3.8 **p < 0.001**

Abbreviations: CI, confidence interval; LOCF, last observation carried forward; IGA, Investigator's Global Assessment; NE, not estimable; OC, observed cases.

Facial Investigator's Global Assessment (IGA) success is defined as the proportion of patients with a score of clear (0) or almost clear (1) and at least 2 points decreased from baseline in IGA.

[a] Estimated IGA success rate difference and 2-sided Wald-type 95% confidence intervals.

[b] Cochran-Mantel-Haenszel test adjusted by pooled site using Wilson-Hilferty transformation.

[c] Missing data are imputed using a multiple imputation method. The variables included in the imputation model are age, sex, and the raw measurement of the corresponding endpoint counts at baseline, Week 3, Week 6, Week 9, and Week 12. Combined estimate for success rate, success rate difference and theirs 95% CIs are obtained by combining the corresponding rate and its SE of the different imputed data sets, using Rubin's formula.

P Value of < 0.05 was considered statistically significant.

Table S4 Percentage of patients with at least a 1-point decrease in the chest, back, and neck IGA assessment from baseline at weeks 3, 6, 9, and 12 — OC (ITT analysis set)

	Visit	Sarecycline (N=262)	Placebo (N=129)	Percentage success rate difference 95% CI [a] *P* Value [b]
Percentage chest IGA success rate (95% CI)	Week 3	46.2 36.1; 56.4	36.7 23.2; 50.2	9.5 -7.4; 26.4 p = 0.065
	Week 6	67.8 58.1; 77.4	57.8 43.3; 72.2	10.0 -7.4; 27.4 p = 0.162
	Week 9	79.5 70.5; 88.4	62.8 48.3; 77.2	16.7 -0.3; 33.7 **p = 0.030**
	Week 12	86.1 78.4; 93.7	70.0 55.8; 84.2	16.1 0.0; 32.2 **p = 0.036**
Percentage back IGA success rate (95% CI)	Week 3	46.2 37.6; 54.7	36.4 24.8; 48.0	9.8 -4.6; 24.2 p = 0.196
	Week 6	69.4 61.2; 77.5	53.2 40.8; 65.6	16.1 1.3; 31.0 **p = 0.033**
	Week 9	75.7 67.7; 83.7	63.2 50.6; 75.7	12.5 -2.3; 27.4 p = 0.116
	Week 12	81.8 74.6; 89.0	66.1 53.7; 78.5	15.7 1.4; 30.1 **p = 0.042**
Percentage neck IGA success rate (95% CI)	Week 3	44.7 34.6; 54.7	41.5 28.2; 54.8	3.2 -13.5; 19.8 p = 0.364
	Week 6	64.8 54.8; 74.8	52.0 38.2; 65.8	12.8 -4.3; 29.8 p = 0.049
	Week 9	73.4 63.7; 83.2	60.9 46.8; 75.0	12.5 -4.6; 29.7 **p = 0.017**
	Week 12	80.0 71.2; 88.8	77.5 64.6; 90.4	2.5 -13.1; 18.1 p = 0.645

Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; OC, observed cases.
Success is defined as an Investigator's Global Assessment (IGA) score with at least a 1-point decrease improvement from baseline score on the IGA assessment in the chest, back, or neck for patients who have a baseline IGA ≥1.
[a] Estimated IGA success rate difference and 2-sided Wald-type 95% confidence intervals.
[b] Cochran-Mantel-Haenszel test adjusted by pooled site.
P Value of < 0.05 was considered statistically significant.

Table S5 Number of acne recurrences, time to recurrence, and patterns of sarecycline use during the open-label follow-up period

	Sarecycline in DB period N=45	Placebo in DB period N=9	Overall N=54
Patients with ≥1 recurrence[a], n (%)	23 (51.1)	2 (22.2)	25 (46.3)
Number of recurrences, n (%)			
1 recurrence	22 (48.9)	2 (22.2)	24 (44.4)
2 recurrences	1 (2.2)	0 (0.0)	1 (1.9)
Time to recurrence, weeks from end of DB period, median	28.4	NE	NE

Abbreviations: DB, double-blind period; NE, not estimable.
[a] Recurrence = IGA score of ≥3.

Table S6 Maintenance of efficacy of sarecycline during the open-label follow-up period by visit - OC

	Visit	Sarecycline DB / Sarecycline OLFU N=23	Sarecycline DB / Not treated N=22	Placebo DB / Sarecycline OLFU N=2	Placebo DB / Not treated N=7	Overall N=54
Absolute change from baseline in facial inflammatory lesion count, mean (SD)	Week 12 (Visit 6)	-26.2 (7.4)	-28.0 (8.0)	-33.0 (15.6)	-18.5 (5.2)	-26.3 (8.2)
	Visit 7	-4.4 (10.7)	-23.8 (10.8)	-22.5 (17.7)	-18.6 (12.1)	-14.3 (14.2)
	Visit 8	-23.1 (8.9)	-24.4 (9.6)	-32.5 (13.4)	-23.0 (10.2)	-24.0 (9.3)
	Visit 9	-22.5 (6.5)	-18.1 (8.5)	-24.0 (NA)	-20.0 (7.1)	-20.2 (7.4)
Facial inflammatory lesion count, mean (SD)	Baseline[a]	31.3 (8.2)	33.3 (7.9)	41.0 (12.7)	26.0 (6.6)	31.8 (8.3)
	Week 12 (Visit 6)	5.5 (4.4)	5.6 (5.3)	8.0 (2.8)	8.3 (5.5)	6.0 (4.9)
	Visit 7	26.9 (9.8)	8.6 (7.4)	18.5 (4.9)	7.6 (7.2)	17.3 (12.4)
	Visit 8	8.5 (7.7)	8.0 (6.7)	8.5 (0.7)	4.5 (3.1)	7.9 (6.8)
	Visit 9	7.5 (10.7)	11.5 (6.9)	8.0 (NA)	5.5 (0.7)	9.2 (8.2)

Abbreviations: DB, double-blind period; NA, not available; OC, observed cases.
[a] Baseline value used is the baseline for the double-blind period.