Apremilast for the Treatment of Mild-to-Moderate Hidradenitis Suppurativa in a Prospective, Open-Label, Phase 2 Study

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Conflicts of Interest

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Abstract

Background: Treatment options are limited for patients with hidradenitis suppurativa (HS). Apremilast, an oral phosphodiesterase 4 inhibitor, may offer an attractive therapeutic option for patients with mild-to-moderate HS.

Methods: This open-label, phase 2 clinical trial enrolled adults (≥ 18 years of age) with mild-to-moderate HS. Patients received apremilast 30 mg twice daily for 24 weeks after a 5-day titration period. Therapy was discontinued at week 24; data were collected up to week 28. Hidradenitis Suppurativa Clinical Response 30 (HiSCR30), i.e., proportion of patients with a ≥ 30% reduction in abscesses and nodules at week 16, was the primary endpoint. HiSCR50, i.e., ≥ 50% reduction, was also explored. Mean changes from baseline to week 24 in the modified Sartorius, Physician's Global Assessment, visual analog scale (VAS) for pain, and Dermatology Life Quality Index (DLQI) scores were analyzed using the Wilcoxon Rank-Sum test. Adverse events (AEs) were summarized.

Results: Twenty patients (mean age, 32.5 years) were enrolled in the study. HiSCR30 was achieved in 65% of patients at weeks 16 and 24. A similar proportion of patients achieved HiSCR50. Significant mean improvements from baseline were observed for all assessments. At week 24, the overall Sartorius score improved from 35.6 to 13.9 (-21.7 change; $P < 0.001$), the PGA score from 2.7 to 1.6 (-1.1 change; $P < 0.01$), the VAS pain score from 27.6 to 10.9 (-16.8 change; $P < 0.05$), and the DLQI score from 11.6 to 5.4 (-6.2 change; $P < 0.01$). Diarrhea (20%), nausea (15%), and depression (10%) were the most commonly reported AEs. No serious AEs or deaths were reported.

Conclusions: Apremilast was safe and effective in improving HS disease activity, pain, and QoL in patients with mild-to-moderate HS. These data suggest that apremilast may have a role in the early treatment of less severe HS.

Keywords: apremilast, hidradenitis suppurativa, modified Sartorius, pain, quality of life

Introduction

Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory skin disease of the hair follicle[1] that affects nearly 1% of the general population.[1-3] This rare condition is most common in adults aged 20-29 years, after which the prevalence decreases with age.[1,4] HS is also more common in women than men,[1,4] and may have an increased prevalence in people with skin of color.[5]

HS is typically characterized by painful, deep-seated, often malodorous lesions (including nodules, abscesses, and fistulas), and hypertrophic scars in areas with skin-to-skin contact and apocrine-rich areas, including the groin, armpits, underneath breasts, anus, buttocks, and inner thighs.[6,7] Increased inflammation causes abscesses to rupture and release pus, and as abscesses heal, skin damage and permanent scarring often occur. These painful clinical manifestations can significantly impair the quality of life (QoL) of those affected,[8,9] underscoring a substantial need for effective treatments.

While surgery remains a common option to remove permanent sequelae caused by HS, and nonsurgical treatments seldom result in a lasting cure,[10] a treatment that could prevent disease progression would be highly valuable. While no specific treatment algorithm has been established, European guidelines suggest patients be treated based on individual subjective impact and objective disease severity; with increasing severity, treatments typically begin with topical to systemic therapy, or increase in invasiveness for surgical options.[10] Biologics are also suggested for more severe disease.[10] The only FDA-approved biologic for patients with moderate-to-severe HS is adalimumab, a human, IgG1 monoclonal antibody that targets tumor necrosis factor α (TNF-α).[11]

Apremilast is a highly specific, oral drug designed to inhibit the phosphodiesterase 4 enzyme, elevate intracellular cyclic adenosine monophosphate levels, and regulate pro- and anti-inflammatory mediators in inflammatory cells. The objective of this study was to evaluate the clinical safety and efficacy of apremilast for the treatment of mild-to-moderate HS. Patients with less severe disease were studied in an attempt to determine efficacy in early disease, since future strategies should prevent progression to more severe disease with irreversible sequelae.

Methods

Study Design

This phase 2, open-label, single-center study (NCT02695212) evaluated the clinical safety and efficacy of apremilast on improvements in HS disease activity and QoL in patients with moderate HS. Patients received 10, 20 or 30 mg apremilast during a titration period on Days 1 through 5, then on Day 6 received a stable dose of 30 mg apremilast twice per day and continued this dosage and schedule through week 24. Patients were taken off of therapy at week 24 and were monitored until week 28 during the observation period.

The study was reviewed and approved by an institutional review board prior to study enrollment, and the study was conducted in accordance with all applicable regulatory guidelines and Good Clinical Practice principles. All patients signed written informed consent before participating in the study.

Study Participants

Generally healthy adults (≥ 18 years of age) were enrolled if they had an HS diagnosis in the last 6 months, a Physician's Global Assessment (PGA) score of 2 or 3, HS lesions in at least 2 areas (one of which was at least Hurley Stage II), and stable disease of at least 2 months prior to study screening. Negative pregnancy tests were required of all women, and if sexually active, men and women had to use approved contraceptives while taking apremilast and up to 28 days after the last dose. Patients were required to use daily topical antiseptics (limited to chlorhexidine gluconate, triclosan, benzoyl peroxide, or diluted bleach) for their HS lesions.

Patients were excluded if they had a PGA score 4 or 5, any uncontrolled, clinically significant disease, abnormal laboratory findings, history of suicide attempt or psychiatric illness requiring hospitalization, active or prior history of substance abuse within 6 months of study screening, malignancy or history of malignancy (except for treated basal or squamous cell *in situ* carcinomas or treated cervical cancer with no recurrence within 5 years), Crohn's disease, prior treatment or known allergies to apremilast, serious/invasive infections, history of lymphoproliferative disease, or any other active skin disease or condition.

Patients could not have used any investigational drug within 4 weeks prior to study enrollment or any prior biologics, or be currently using any prohibited HS treatments (minocycline, tetracycline, clindamycin, rifampicin, and steroids). Stable use of analgesics was allowed, but new opiates were not permitted during the study. Use of oral antibiotic therapy was not permitted; however, antibiotic rescue (minocycline or doxycycline) was permitted at weeks 4 or 8 if PGA was ≥ 2 from their baseline score. Any concomitant therapy taken during the study period was reported, and may have included the daily antiseptic washes, wound care dressings (limited to alignates, hydrocolloids, and hydrogels), and approved analgesic therapy to alleviate pain, including ibuprofen, acetaminophen, or tramadol. Painful lesions requiring an immediate intervention received either a protocol-approved injection of intralesional triamcinolone acetonide suspension or incision and drainage.

Efficacy Endpoints

Study assessments occurred at baseline and at weeks 4, 8, 12, 16, 20, 24, and 28. The primary endpoint was the proportion of patients at week 16 achieving the Hidradenitis Suppurativa

Clinical Response (HiSCR), defined as a ≥ 30% reduction in the total number of abscess and inflammatory nodules, with no increase in the number of abscesses or draining fistulas (HiSCR30) when compared with baseline.[12] The proportion of patients with a ≥ 50% reduction in the HiSCR (HiSCR50) at week 16 was an exploratory endpoint. Secondary efficacy endpoints included the proportion of patients achieving a ≥ 30% and ≥ 50% reduction in HiSCR at week 24; changes from baseline to week 16 and week 24 in the modified Sartorius scale, PGA score, visual analog scale (VAS) for pain, and the Dermatology Life Quality Index (DLQI) score; and the proportions of patients achieving a 1-point reduction in the PGA score and a 10- and 20-point reduction in the VAS pain score at weeks 16 and 24.

The PGA score was based on a cumulative global assessment of nodule, abscess, and fistula counts corresponding to a 5-point score (0 = clear, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe). A modified Sartorius scale was also used to assess disease activity by evaluating the number of involved anatomical regions, the number and type of lesions, and the distance between lesions. Pain was assessed using a 100-mm VAS (0 = no pain, 100 = maximum pain). The DLQI is a 10-question, dermatology-specific, health-related QoL questionnaire calculated by summing the scores of 10 questions; total scores range from 0 (no impairment) to 30 (severely impaired).

Statistical Analysis

For HiSCR assessments, reductions in abscesses and nodules were analyzed at week 16 and week 24 using last observation carried forward (LOCF). A responder analysis based on treatment failures was conducted, with non-responders or failures being defined as patients who

discontinued apremilast treatment due to an AE or lack of efficacy. Mean scores and mean changes from baseline to all time points up to week 24, and from week 24 to week 28 for all continuous outcomes were calculated, and changes from baseline were analyzed using the non-parametric Wilcoxon Rank-Sum test. All continuous variables, including modified Sartorius, PGA, VAS pain, and DLQI, were assessed in an intention-to-treat (patients who received at least one dose of apremilast) population using LOCF. Another analysis using only the available data from the treated patients was performed.

Adverse events (AEs) and serious AEs were descriptively summarized based on incidence, severity, and relatedness to treatment. The incidence of AEs summarizes the number of patients who experienced a specific AE (patients who had more than one occurrence of the same AE were counted once).

Results

Patient Disposition and Demographics

Of the 20 patients enrolled and treated during the 24-week treatment phase of the study, 11 (55%) completed the study (Figure 1). Reasons for discontinuation were AEs (n = 4), lack of efficacy (n = 1), and other (n = 4; Figure 1).

The mean age of the population was 32.5 years, and most were female (Table 1). At baseline, clinical characteristics were typical of mild-to-moderate HS disease (Table 1). Patients had an average of 8.8 nodules and 0.9 fistula. The mean baseline overall modified Sartorius score for all patients was 35.6 and PGA was 2.7.

Efficacy

The HiSCR30 was observed in 13 (65%) patients at week 16 (primary endpoint); a similar proportion of patients was seen at week 24 (Figure 2A). Similarly, 11 (55%) patients and 12 (60%) patients achieved the HiSCR50 at weeks 16 and 24, respectively (Figure 2B). Overall, a high response rate (based on non-responders [patients who discontinued apremilast due to an AE or lack of efficacy]) was observed with apremilast at week 16 (80%) and at week 24 (75%).

The overall mean Sartorius score improved from 35.6 at baseline to 16.8 (-18.9 mean change) at week 16 and further improved to 13.9 at week 24 (-21.7 mean change; $P < 0.001$; Table 2; Figure 3A). After discontinuation of apremilast at week 24, the mean change in the overall Sartorius score significantly increased from week 24 to week 28 ($P < 0.05$; Table 2; Figure 3A). A similar pattern was observed for all individual Sartorius score components, except for the abscess score (Table 2).

Patients also had significant improvements from baseline in PGA, VAS pain, and DLQI scores. The mean PGA score decreased (improved) from 2.7 at baseline to 2.1 (-0.6 mean change) at week 16 and to 1.6 (-1.1 mean change) at week 24 ($P < 0.01$; Figure 3B), but significantly increased from week 24 to week 28 ($P < 0.01$). At week 16, the mean VAS pain score improved from 26.3 at baseline to 13.9 (-13.8 mean change) and at week 24 to 10.9 (-16.8 mean change; $P < 0.05$; Figure 3C). The VAS pain score numerically increased (P = NS) from week 24 to week 28. At week 16, the mean DLQI score improved from 11.6 at baseline to 5.9 (-5.7 mean

change) at week 16 and to 5.4 (-6.2 mean change) at week 24 ($P < 0.01$), and from week 24 to 28, it significantly increased ($P < 0.05$; Figure 3D).

Nearly half of all treated patients achieved a 1-point reduction in PGA at week 16 (45%) and week 24 (50%; data not shown). Likewise, one half or more of all patients achieved a 10-point reduction in VAS pain at week 16 (60%) and week 24 (50%), and about one third of all patients achieved a 20-point reduction in VAS pain at weeks 16 and 24 (30%; data not shown).

Safety

Overall, 9 (45%) patients who were treated with apremilast experienced a total of 19 AEs (Table 3). Apremilast was well tolerated among all patients. The most commonly reported AEs were diarrhea (20%), nausea (15%), and depression (10%). All other AEs, including abscess on chest, abdominal pain, fatigue, headache, and inflamed cyst, occurred in 1 patient each (Table 3). All AEs were mild or moderate in nature. Of the 20 patients who received apremilast, 4 (20%) discontinued therapy due to AEs. No serious AEs or deaths occurred in the study. No clinically meaningful abnormalities in laboratory measures or vital signs were observed.

Discussion

This small, open-label, pilot study found that apremilast improved HS disease activity, relieved pain, and improved QoL in patients with moderate HS. These improvements were observed as early as week 4 of treatment and were maintained up to week 16 (primary endpoint) and week 24. Approximately two thirds of patients achieved a HiSCR30 by week 16 of apremilast, and more than half achieved a HiSCR50. Clinical assessments of the total modified Sartorius, PGA,

VAS pain and DLQI scores also significantly improved with apremilast from baseline up to weeks 16 and 24. However, after 4 weeks of discontinuing apremilast therapy, HS clinical signs and symptoms began to reappear, including disease activity and pain, and the QoL measure began to deteriorate. In addition, apremilast also appeared to be well-tolerated, with no serious or unanticipated significant safety concerns reported.

The proportions of patients with mild-to-moderate HS who responded to apremilast were consistent with those having moderate-to-severe HS who responded to adalimumab, the only approved systemic, biologic treatment for HS to date.[13] We found HiSCR30 of 65% at weeks 16 and 24 and HiSCR50 of 55% and 60% at weeks 16 and 24, respectively. Kimball et al[13] reported in two phase 3 trials of adalimumab a HiSCR50 of 42% at week 12 in one study and 59% in another. We used the HiSCR30 as the primary endpoint in our study as a more conservative approach for treating patients with mild-to-moderate disease; however, the percentage of responders with the HiSCR50 was comparable to the HiSCR30 and the HiSCR50 reported for adalimumab.[13] The efficacy of apremilast in patients with mild-to-moderate HS demonstrated in this study suggests that prevention or delay of more aggressive disease should be considered as part of future clinical development programs in patients with less severe HS.

After discontinuation of apremilast for 4 weeks, patients experienced a recurrence of HS clinical signs and symptoms. Following significant improvement maintained over 24 weeks, this evidence of disease recurrence was rapid after discontinuation. Significant reversal of improvement was seen with modified Sartorius, PGA, and DLQI, and even though this response was not significant with the VAS pain score, the trend was similar. Relapse with adalimumab has

also been reported, however, at an average time of 9.5 months. Collectively, these findings suggest that recurrence of HS should not be considered treatment failure but rather a clinical feature of the disease indicating disease relapse progression, and the need for continued treatment.

Up to 24 weeks of apremilast was shown to be well tolerated with no new safety signals reported in this study. Diarrhea and nausea were the most commonly reported AEs among patients treated with apremilast, and most commonly caused treatment discontinuation. While AEs such as severe infections, reactivation of tuberculosis, and Epstein-Barr virus have been reported with adalimumab,[11] none of these AEs or any other serious AEs were reported with apremilast in our study. Treatment over longer periods of time is warranted to determine the safety of apremilast with longer-term use. Similar to psoriasis and psoriatic arthritis trials with apremilast, no significant laboratory abnormalities were found.

Although the mechanism of action of apremilast in HS is not fully understood, evidence suggests that HS is an inflammatory disease, as characterized by low CD3/CD8 lymphocytes and high natural killer (NK) cells,[14] and that apremilast may target inflammation in HS. A recent investigation of 24 patients (mean Hurley stage 2.25) with HS showed an increase in T helper 1- and T helper 17-associated cytokines in HS-lesion biopsies compared with healthy-tissue biopsies.[15] Other evidence comes from experimental studies. In a psoriasis model, apremilast significantly reduced cytokine and chemokine production by immune cells, inhibited TNF-α production by keratinocytes and NK cells, and reduced epidermal thickness and the proliferation index.[16] Similarly, apremilast inhibited T-cell proliferation and production of interferon-γ and

TNF-α in inflammatory arthritis models.[17] Further studies are needed to elucidate the exact mechanism by which apremilast treats the signs and symptoms of HS.

In conclusion, effective treatment options are still lacking for patients suffering from HS. Early detection and treatment of HS clinical symptoms may prevent aggressive disease progression. As shown in the current study, significant improvements in HS disease activity, pain relief, and QoL with apremilast were observed in patients with mild-to-moderate HS without any new safety signals. Thus, apremilast may offer a safe and effective treatment option for patients with less severe HS disease, which could delay further disease progression. Additional research is warranted to further characterize the efficacy and safety profile of apremilast in patients with HS.

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Table 1. Patient Disposition and Baseline Characteristics

Characteristic	(n = 20)
Age, years	
Mean ± SD	32.5 ± 10.0
Range	19-60
Gender, n (%)	
Female	14 (70%)
Male	6 (30%)
Body mass index, kg/m^2	
Mean ± SD	29.1 ± 7.7
Range	18.1-46.1
Baseline scores and characteristics, mean	
Nodules, number	8.8 ± 5.7
Fistulae, number	0.9 ± 1.3
Abscesses, number	0.3 ± 0.5
PGA	2.7 ± 0.5
VAS pain	26.3 ± 26.8
DLQI	11.6 ± 6.4
Modified Sartorius Score	
Total	35.6 ± 17.5
Region	10.4 ± 3.6
Nodules	17.5 ± 11.4
Fistulae	3.4 ± 5.1
Abscesses	0.3 ± 0.5
Distance	4.1 ± 3.4

DLQI, Dermatology Life Quality Index; PGA, physician global assessment; VAS, visual analogue scale.

Table 2: Changes from Baseline in Modified Sartorius Score with Apremilast in Patients with Mild-to-Moderate Hidradenitis Suppurativa

	Baseline	Week 16	Week 24	Week 28
Total score				
Mean ± SE	35.6 ± 3.9	16.8 ± 2.7	13.9 ± 3.1	18.4 ± 3.8
Change from BL		-18.9 ± 4.2	-21.7 ± 4.9	-19.0 ± 5.7
P-value vs BL		0.0002	0.0002	0.0020
Change from week 24				10.9 ± 3.6
P-value vs week 24				0.0352
Region score				
Mean ± SE	10.4 ± 0.8	6.2 ± 0.9	5.1 ± 1.1	6.0 ± 0.8
Change from BL		-4.2 ± 0.9	-5.3 ± 1.1	-4.4 ± 1.2
P-value vs BL		0.0001	0.0002	0.0078
Change from week 24				3.0 ± 0.9
P-value vs week 24				0.0234
Nodule score				
Mean ± SE	17.5 ± 2.6	7.7 ± 1.4	6.9 ± 1.7	9.3 ± 2.5
Change from BL		-9.8 ± 2.8	-10.6 ± 2.9	-9.6 ± 4.2
P-value vs BL		0.0002	0.0002	0.0127
Change from week 24				5.8 ± 2.3
P-value vs week 24				0.0391
Fistula score				
Mean ± SE	3.4 ± 1.1	1.0 ± 0.5	0.4 ± 0.3	0.7 ± 0.7
Change from BL		-2.4 ± 1.1	-3.0 ± 1.2	-2.5 ± 1.0
P-value vs BL		0.0313	0.0156	0.0625
Change from week 24				0.4 ± 0.9
P-value vs week 24				1.0000
Abscess score				
Mean ± SE	0.3 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1
Change from BL		-0.2 ± 0.1	-0.2 ± 0.1	-0.2 ± 0.1
P-value vs BL		0.1250	0.1250	0.5000
Change from week 24				0.1 ± 0.1
P-value vs week 24				1.0000

	Baseline	Week 16	Week 24	Week 28
Distance score				
Mean ± SE	4.1 ± 1.0	1.8 ± 0.4	1.4 ± 0.4	2.3 ± 0.7
Change from BL		-2.3 ± 1.0	-2.7 ± 0.9	-2.3 ± 0.9
P-value vs BL		0.0047	0.0011	0.0195
Change from week 24				1.6 ± 0.8
P-value vs week 24				0.0625

*Data are based on last observation carried forward.
BL, baseline; SE, standard error

Table 3. Number and Percentage of Patients Reporting Adverse Events

Adverse event	n (%)
Total Number of Patients Reporting AEs	**9 (45.0)**
Diarrhea	4 (20.0)
Nausea	3 (15.0)
Depression	2 (10.0)
Abscess on chest	1 (5.0)
Abdominal pain	1 (5.0)
Bronchitis	1 (5.0)
Common cold	1 (5.0)
Cough	1 (5.0)
Fatigue	1 (5.0)
Headache	1 (5.0)
Inflamed cyst	1 (5.0)
Suicidal thoughts	1 (5.0)
Urinary tract infection	1 (5.0)

Patients may have experienced ≥ 1 AE.

Figure Legends

Figure 1. Patient disposition. *Other includes conflicting schedule (n = 2), lost to follow up (n = 1), and relocation (n = 1). †For continuous variables. ITT, intention-to-treat population; LOCF, last observation carried forward.

Figure 2. Proportion of patients achieving (A) HiSCR30 and (B) HiSCR50 with apremilast at weeks 16 and 24. HiSCR30 and HiSCR50 were defined as a 30% and 50% reduction in abscesses and nodules, respectively. HiSCR, Hidradenitis Suppurativa Clinical Response.

Figure 3. Mean change from baseline in (A) modified Sartorius, (B) Physician's Global Assessment, (C) visual analog scale (VAS) for pain, and (D) Dermatology Life Quality Index scores. Change from baseline to week 24 and change from week 24 to week 28 were analyzed based on last observation carried forward (N = 20). $^{*}P < 0.05$, $^{\dagger}P < 0.01$, $^{\ddagger}P < 0.001$ versus baseline; $^{**}P < 0.05$, $^{\dagger\dagger}P < 0.01$ for week 24 versus week 28. BL, baseline; VAS pain, visual analog scale pain.

Figure 1. Patient disposition. *Other includes conflicting schedule (n = 2), lost to follow up (n = 1), and relocation (n = 1). †For continuous variables. ITT, intention-to-treat population; LOCF, last observation carried forward.

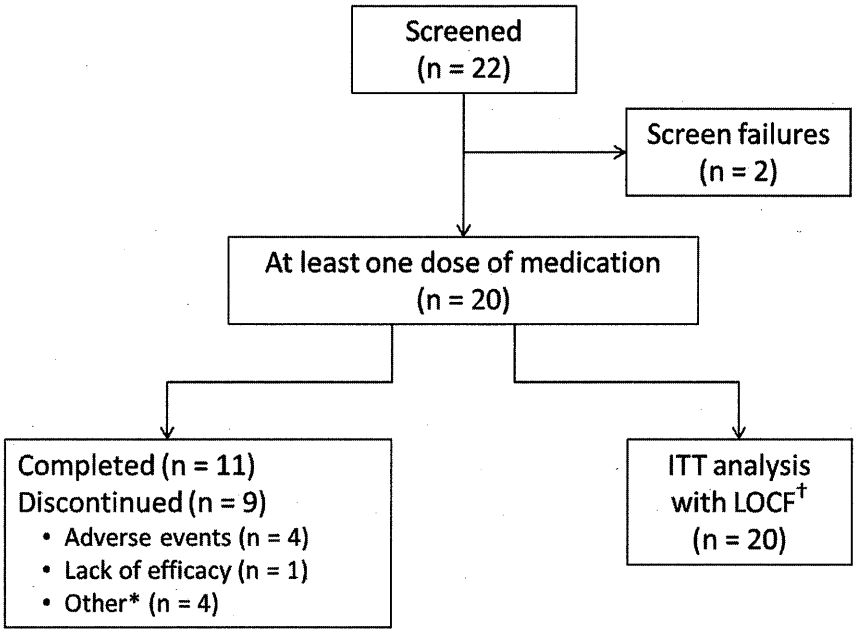
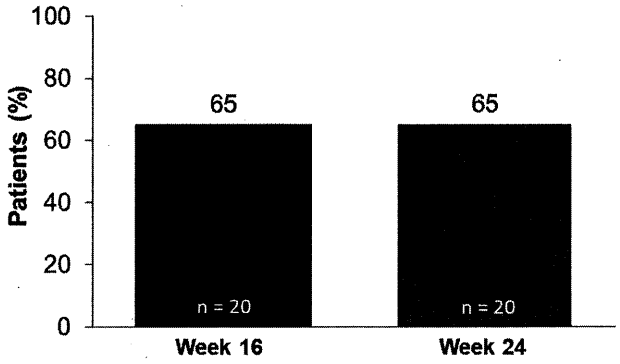


Figure 2. Proportion of patients achieving (A) HiSCR30 and (B) HiSCR50 with apremilast at weeks 16 and 24. HiSCR30 and HiSCR50 were defined as a ≥ 30% and ≥ 50% reduction in abscesses and nodules, respectively. HiSCR, Hidradenitis Suppurativa Clinical Response.

A. HiSCR30



B. HiSCR50

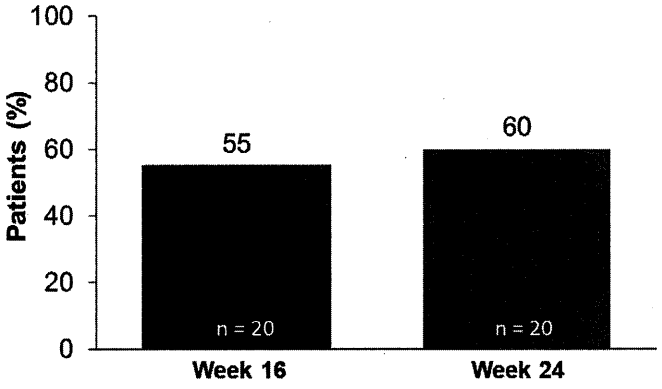
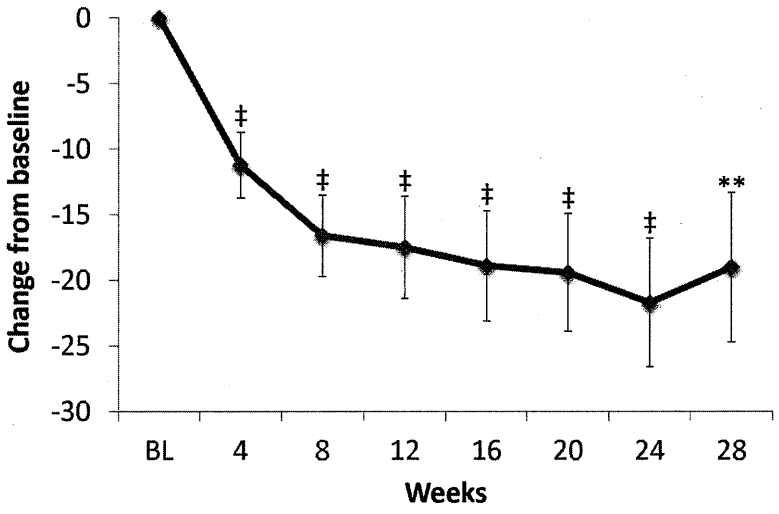
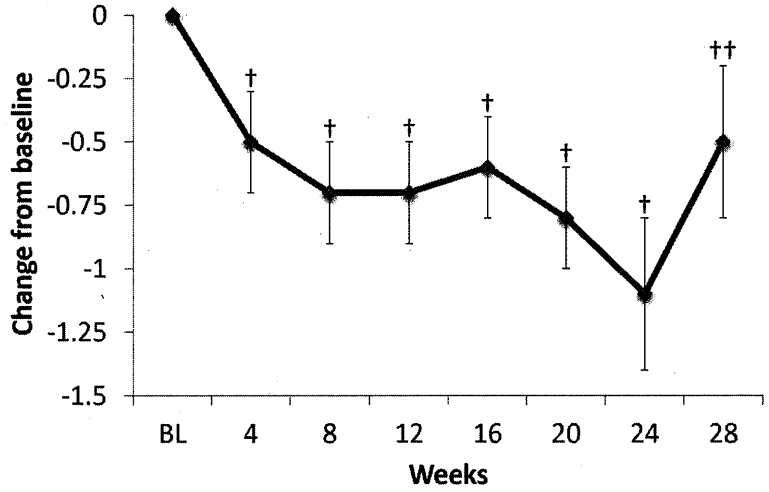


Figure 3. Mean change from baseline in (A) modified Sartorius, (B) Physician's Global Assessment, (C) visual analog scale (VAS) for pain, and (D) Dermatology Life Quality Index scores. Change from baseline to week 24 and change from week 24 to week 28 were analyzed based on last observation carried forward (N = 20). $^{*}P < 0.05$, $^{\dagger}P < 0.01$, $^{\ddagger}P < 0.001$ versus baseline; $^{**}P < 0.05$, $^{\dagger\dagger}P < 0.01$ for week 24 versus week 28. BL, baseline; VAS pain, visual analog scale pain.

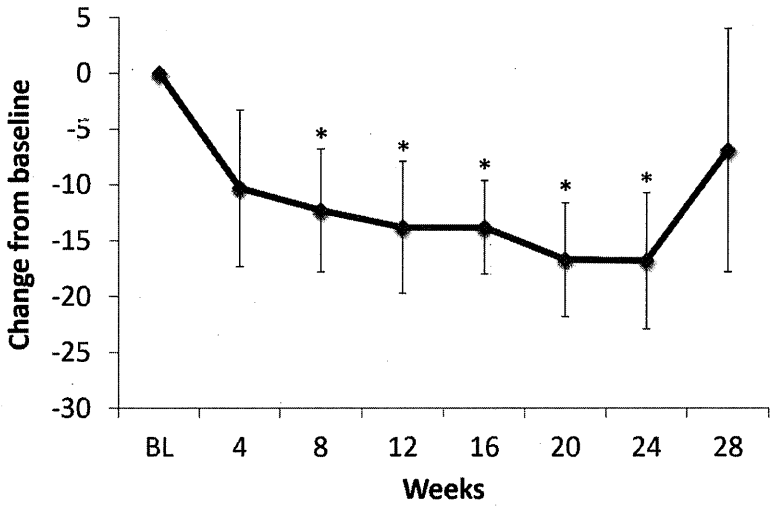
A. Modified Sartorius



B. Physician's Global Assessment



C. VAS for pain



D. Dermatology Life Quality Index