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Efficacy and Safety of Brodalumab, an Anti–interleukin-17 Receptor A Monoclonal Antibody, for Palmoplantar Pustulosis: 16-Week Results of a Randomized Clinical Trial

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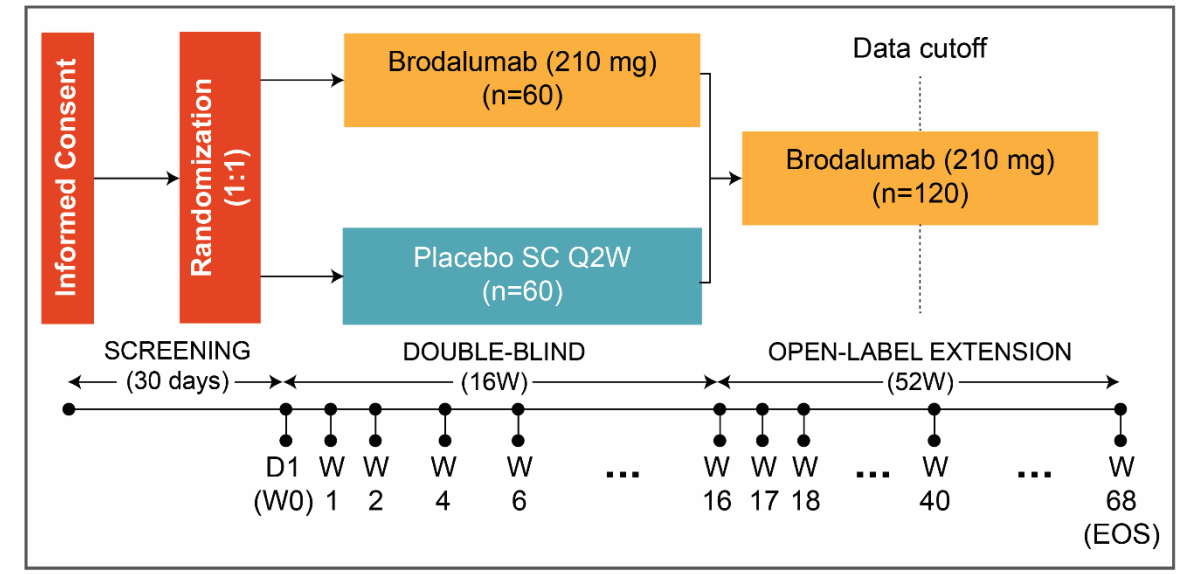
Supplementary Material

Online Resource 1 Study design



At week 17, the patients in the brodalumab group during the double-blind period received placebo and those in the placebo group received brodalumab to maintain the blinding in the double-blind period

D1, day 1; EOS, end-of-study; Q2W, every 2 weeks; SC, subcutaneous; W, week

Online Resource 2:

Patients had to meet all the following criteria for diagnosis of palmoplantar pustulosis PPP: (1) pustules on the palms, soles, or both, (2) progression from vesicles to pustules, and (3) repeated occurrence of lesions at the same sites. Also, for eligibility, patients had to have an inadequate response to any 1 or combination of the following therapies, viz., topical corticosteroids, topical vitamin D3, phototherapy, and etretinate. Patients meeting any of the following criteria were excluded: (1) patients with a diagnosis of plaque psoriasis, pustular psoriasis, drug-induced PPP, or pompholyx; (2) patients with PPP demonstrating an improvement in PPP Area Severity Index (PPPASI) total score of ≥4 points during the screening period; (3) patients with a known focal infection at the time of informed consent who had not received appropriate treatment or patients who had received treatment for focal infection (e.g., tonsillectomy and dental treatment) or treatment for metal allergy (e.g., change of dental materials) within 6 months before the start of intervention; (4) substantial concurrent diseases and substantial laboratory abnormalities at pre-examination; (5) past or present history of suicidal ideation or any suicidal behavior at enrollment; (6) severe depression with Personal Health Questionnaire Depression Scale (PHQ-8) total score of ≥15 at enrollment; (7) use of a topical agent or an emollient or change in the dosage of an emollient that may affect efficacy evaluation on the palmoplantar areas within 2 weeks before the start of the intervention; (8) use of any of the following within 4 weeks before the start of the intervention: systemic treatment that may affect efficacy evaluation, systemic immunosuppressants or immunomodulators, systemic antibiotics, phototherapy, class I (strongest) topical corticosteroids, and intraarticular, intramuscular, or epidural injection of corticosteroids; these were also prohibited during the conduct of the study.

PPP-SI Scoring:

For PPP Severity Index (PPP-SI) scoring, the same 4 body areas as those used for PPPASI scoring were taken into consideration for assessing the severity of the 3 symptoms, erythema (E), pustule/vesicle, including crusts, i.e., dried pustules (P), and desquamation/scales (D). However, the more severely affected site at baseline was identified as the evaluation location. The evaluation location was evaluated for the 3 symptoms listed above, each on a 5-point scale of none (0) to very severe (4). Thus, the total score (ranging from 0 to 12) was calculated as the PPP-SI total score=(E+P+D).

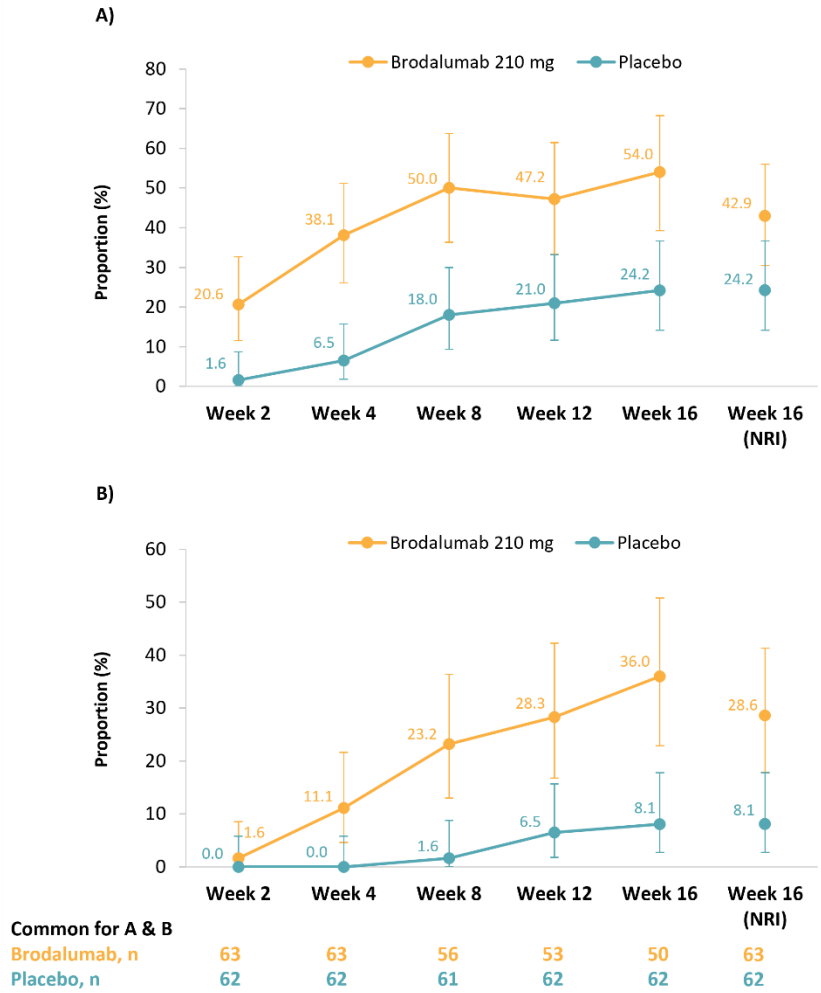
Details of Discontinuations:

Discontinuations due to treatment-emergent adverse events (TEAEs) were reported in 6 of 126 patients, all 6 patients were from the brodalumab group:

- Exacerbation of extrapalmoplantar lesions of palmoplantar pustulosis (n=1)
- Malaise, fever, phlyctenular (frictenic) keratoconjunctivitis, and neutrophil count increased (n=1)
- Pneumonia (n=1)
- Apical periodontitis and pyoderma (scalp, lower legs, back) (n=1)
- Cellulitis (right foot) (n=1)
- Depressed mood, bone erosion (n=1)

Tables and Figures

Online Resource 3 Proportion of patients who achieved (a) PPPASI-50 response and (b) PPPASI-75 response by NRI



Treatment Difference	
Week	**% [95% CI]**
2	19.0 [7.6, 31.3]
4	31.6 [16.6, 45.5]
8	32.0 [13.0, 47.9]
12	26.2 [6.6, 42.8]
16	29.8 [9.9, 47.1]
16 (NRI)	18.7 [1.6, 34.7]

Treatment Difference	
Week	**% [95% CI]**
2	1.6 [-4.7, 8.7]
4	11.1 [3.9, 21.6]
8	21.6 [10.0, 34.8]
12	21.9 [6.6, 36.5]
16	27.9 [11.5, 43.9]
16 (NRI)	20.5 [6.4, 34.3]

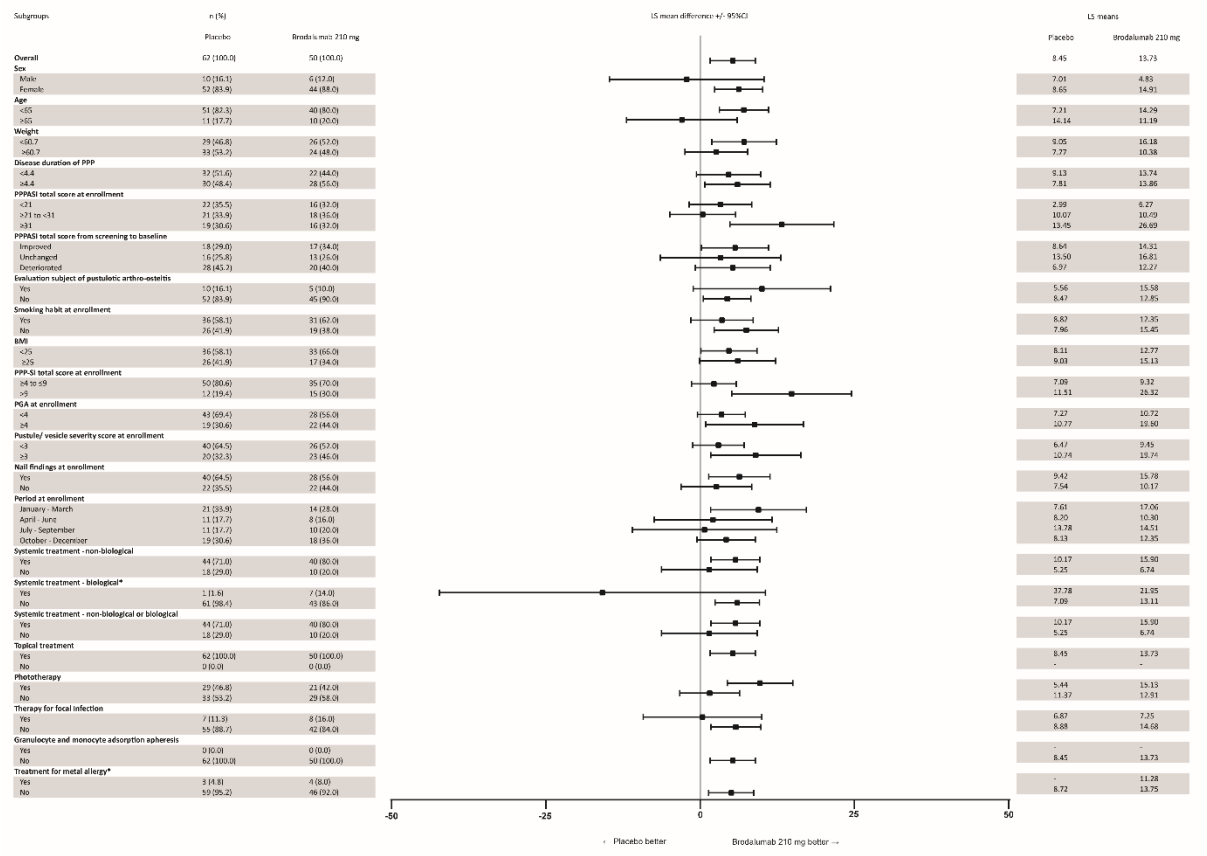
Error bars in the figures indicate 95% CI by Clopper-Pearson confidence interval.
95% CI in the tables are exact confidence interval.
CI, confidence interval; NRI, nonresponder imputations; PPPASI, PPP Area and Severity Index

Online Resource 4 Major secondary efficacy endpoints: Change from baseline at week 16 (NRI and BOCF approach)

Endpoint	**Brodalumab (210 mg) n=63**	**Placebo n=62**	**Treatment Difference**
PPPASI-50 response, %[§]	42.9 (30.5, 56.0)	24.2 (14.2, 36.7)	18.7 (1.6, 34.7)
PPPASI-75 response, %[§]	28.6 (17.9, 41.3)	8.1 (2.7, 17.8)	20.5 (6.4, 34.3)
PPPASI-90 response, %[§]	12.7 (5.6, 23.5)	0.0 (0.0, 5.8)	12.7 (5.1, 23.6)
PPP-SI total score, change from baseline, mean (SD)[†]	–3.1 (3.05)	–1.8 (2.21)	NA
PPP-SI-50 response, %[§]	38.1 (26.1, 51.2)	14.5 (6.9, 25.8)	23.6 (6.4, 38.8)
PPP-SI-75 response, %[§]	14.3 (6.7, 25.4)	1.6 (0.0, 8.7)	12.7 (3.3, 23.8)
PPP-SI-90 response, %[§]	6.3 (1.8, 15.5)	0.0 (0.0, 5.8)	6.3 (0.1, 15.8)
PPP-SI Component score, change from baseline, mean (SD)			
Erythema[†]	–1.1 (1.23)	–0.7 (0.99)	NA
Pustules/vesicle[†]	–1.1 (1.21)	–0.4 (0.86)	NA
Desquamation/scale[†]	–0.9 (1.17)	–0.7 (0.86)	NA
Pustule/vesicle Severity Score, change from baseline, mean (SD)[†]	–1.0 (1.12)	−0.4 (0.82)	NA
DLQI, change from baseline, mean (SD)[†]	–2.3 (5.88)	–2.7 (4.88)	NA
PGA 0/1 response, %[†]	25.4 (15.3, 37.9)	9.7 (3.6, 19.9)	15.7 (2.0, 29.7)
NRS-PPP Pain score, change from baseline, mean (SD)[a†]	−1.4 (3.22)	−2.2 (3.18)	NA
NRS-PPP Itch score, change from baseline, mean (SD)[b†]	−1.1 (3.26)	−1.6 (2.90)	NA

Data are presented as % (95% CI) unless specified otherwise
[†]BOCF approach was used
[§]NRI were performed
[a]For those with NRS Score at baseline ≥1, n=51 for brodalumab group, n=46 for placebo group
[b]n=61 for brodalumab group, n=61 for placebo group
BOCF, baseline observation carried forward; CI, confidence interval; DLQI, Dermatology Life Quality Index; NA, not available; NRI, nonresponder imputations; NRS, Numerical Rating Scale; PGA, Physician's Global Assessment; PPP, palmoplantar pustulosis; PPPASI, PPP Area and Severity Index; PPP-SI, PPP Severity Index; SD, standard deviation

Online Resource 5 Subgroup analysis



*compound symmetry was used. When using compound symmetry, the sandwich variance was applied
BMI, body mass index; CI, confidence interval; LS mean, least-square mean; PGA, Physician's Global Assessment PPP, palmoplantar pustulosis; PPPASI, PPP Area and Severity Index; PPP-SI, PPP Severity Index

Online Resource 6 Change from Baseline in DLQI, NRS-PPP Itch, and NRS-PPP Pain Scores at Week 16 by PPPASI Response Groups

Endpoint	**Brodalumab (210 mg)**	**Placebo**	**Brodalumab (210 mg)**	**Placebo**
PPPASI-50 response	Yes		No	
n, for DLQI change	27	15	23	47
DLQI change, mean (SD)	–5.0 (6.22)	–3.7 (2.85)	–0.3 (6.00)	–2.4 (5.36)
n, for NRS-PPP Itch change	26	15	22	46
NRS-PPP Itch change, mean (SD)	–2.7 (4.00)	–4.1 (2.63)	0.1 (2.44)	–0.8 (2.53)
n, for NRS-PPP Pain change	19	11	21	35
NRS-PPP Pain change, mean (SD)	–3.9 (3.05)	–3.8 (2.04)	0.2 (2.79)	–1.7 (3.34)
PPPASI-75 response	Yes		No	
n, for DLQI change	18	5	32	57
DLQI change, mean (SD)	–6.4 (6.38)	–4.0 (3.08)	–0.8 (5.69)	–2.6 (5.01)
n, for NRS-PPP Itch change	18	5	30	56
NRS-PPP Itch change, mean (SD)	–3.7 (3.94)	–3.6 (1.52)	0.0 (2.64)	–1.4 (2.93)
n, for NRS-PPP Pain change	12	4	28	42
NRS-PPP Pain change, mean (SD)	–4.3 (3.08)	–4.5 (2.08)	–0.6 (3.22)	–2.0 (3.20)
PPPASI-90 response	Yes		No	
n, for DLQI change	8	0	42	62
DLQI change, mean (SD)	–6.8 (4.50)	-	–2.1 (6.58)	–2.7 (4.88)
n, for NRS-PPP Itch change	8	0	40	61
NRS-PPP Itch change, mean (SD)	–5.1 (3.09)	-	–0.6 (3.26)	–1.6 (2.90)
n, for NRS-PPP Pain change	5	0	35	46
NRS-PPP Pain change, mean (SD)	–6.6 (1.67)	-	–1.0 (3.19)	–2.2 (3.18)

DLQI, Dermatology Life Quality Index; NRS, Numerical Rating Scale; PPP, palmoplantar pustulosis; PPPASI, PPP Area and Severity Index; SD, standard deviation