Impact of dupilumab on SNOT-22 sleep and function scores in CRSwNP

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Clinical Implications

Chronic rhinosinusitis with nasal polyps (CRSwNP) frequently affects patients' sleep and functioning. Patients with CRSwNP receiving dupilumab reported less impairment in sleep and functioning scores versus placebo after 24 weeks of treatment, with benefits maintained at week 52.

Chronic rhinosinusitis with nasal polyps (CRSwNP) is an inflammatory disease of the upper airways.[1] Symptoms of CRSwNP are burdensome and impact patients' health-related quality of life (HRQoL), often impairing sleep quality,[1-3] resulting in daytime sleepiness and compromising ability to function and work.[2,4] The condition is often nonresponsive to standard treatments including systemic corticosteroids (SCS), which may drive patients to seek more intense disease management (eg, surgery).[5] Despite the frequency of sleep disturbance, awareness may be lacking among patients and caregivers of the impact of CRSwNP on sleep quality and the consequences of disturbed sleep. As a result, sleep is often overlooked in diagnosis and as a target for treatment.

Dupilumab is a monoclonal antibody that inhibits signaling of IL-4 and IL-13, which are key drivers of type 2 inflammation in multiple diseases including CRSwNP.[6] In 2 randomized, placebo-controlled, phase 3 studies, SINUS-24 (NCT02912468) and SINUS-52 (NCT02898454), in patients with CRSwNP, dupilumab treatment was associated with a significant reduction in nasal polyp score and nasal congestion compared with placebo, improved smell, and was generally well tolerated.[7]

As CRSwNP symptoms frequently impact patients' sleep and functioning, we assessed the effect of dupilumab on the 22-Item Sinonasal Outcome Test (SNOT-22) sleep and function (fatigue, productivity, and concentration) domain scores in SINUS-24 and SINUS-52.

Full details of SINUS-24 and SINUS-52 have been published previously.[7] This *post hoc* analysis included data for patients who received subcutaneous dupilumab (300 mg) or placebo to week 24 in SINUS-24 and to week 52 in SINUS-52.

Outcome measures included the sleep and fatigue domains based on SNOT-22, validated in the CRSwNP population,[8] which were assessed to week 24 (SINUS-24) and week 52 (SINUS-52). The sleep domain of SNOT-22 comprises 4 items: "difficulty falling asleep," "wake up at night," "lack of a good night's sleep," and "wake up tired." The function domain of SNOT-22 comprises 3 items: "fatigue," "reduced productivity," and "reduced concentration." Item level scores for both the sleep and the function domains range from 0 to 5 (0 = no problem; 5 = problem as bad as can be), with higher scores indicating greater disease severity. Individual item scores were summed, and an average domain score was derived.

Analyses were conducted in the intent-to-treat population and in subgroups: patients with/without comorbid asthma, nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD), SCS use in the previous 2 years, allergic rhinitis, and prior sinonasal surgery for nasal polyps, and patients reporting 1 SNOT-22 sleep or function domain item as most important at baseline.

Mean changes in average SNOT-22 sleep and function domain scores from baseline up to week 24 (SINUS-24) and week 52 (SINUS-52) were determined, and least-squares (LS) mean differences (95% confidence interval [CI]) for dupilumab versus placebo were calculated. Data were analyzed using the worst observation carried forward and multiple imputation methods followed by an analysis of covariance model. The analysis is *post hoc* and *P* values are nominal.

Baseline characteristics, including average SNOT-22 sleep and function domain scores, were balanced across treatment arms (Table I). The baseline average SNOT-22 sleep and function domain scores ranged from 2.25 to 2.50 for placebo and from 2.00 to 2.25 for dupilumab.

Improvements in average SNOT-22 sleep domain scores were greater with dupilumab versus placebo at week 24 in the SINUS-24 study (−1.38 vs −0.41; LS mean difference vs placebo: −0.97; 95% CI: −1.24, −0.71; $P < .0001$) and at week 52 in the SINUS-52 study (−1.27 vs −0.34; LS mean difference vs placebo: −0.93; 95% CI: −1.18, −0.68; $P < .0001$). Differences were observable as early as week 8 ($P < .0001$; Figure 1 and Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). The corresponding LS mean percent change in sleep domain score from baseline with dupilumab and placebo was −53.03% and −3.76%, respectively, at week 24 (SINUS-24; $P < .0001$), and −27.23% and 13.82%, respectively, at week 52 (SINUS-52; $P = .0023$).

Improvements in average SNOT-22 function domain scores were greater with dupilumab versus placebo at week 24 in the SINUS-24 study (−1.31 vs −0.44; LS mean difference vs placebo: −0.86; 95% CI: −1.11, −0.61; $P < .0001$) and at week 52 in the SINUS-52 study (−1.08 vs −0.32; LS mean difference vs placebo: −0.76; 95% CI: −1.01, −0.51; $P < .0001$). Differences were observable as early as week 8 ($P < .0001$; Figure 1 and Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). The corresponding LS mean percent change in function domain score from baseline with dupilumab and placebo was −50.92% and −6.47%, respectively, at week 24 (SINUS-24; $P < .0001$), and −41.19% and −5.27%, respectively, at week 52 (SINUS-52; $P < .0001$).

Changes in sleep and function item scores were also assessed by change in nasal polyp score (groups assessed: improvement <1 point, ≥1 but <2 points, and ≥3 points). Improvements

TABLE I. Demographics and baseline characteristics of patients with CRSwNP (ITT population)

	SINUS-24		SINUS-52	
Demographic/Characteristic	**Placebo (n = 133)**	**Dupilumab (n = 143)**	**Placebo (n = 153)**	**Dupilumab (n = 150)**
Age (y), median (IQR)	50 (41-60)	52 (39-61)	53 (44-61)	51 (42-61)
Men, n (%)	70 (53)	88 (62)	95 (62)	97 (65)
Women, n (%)	63 (47)	55 (39)	58 (38)	53 (35)
Nasal polyp duration (y)	10.8 (8.6)	11.4 (9.7)	10.9 (9.4)	11.3 (10.4)
Nasal polyp score* (scale 0-8)	5.86 (1.31)	5.64 (1.23)	5.96 (1.21)	6.07 (1.22)
Asthma, n (%)*	77 (58)	78 (55)	91 (59)	83 (55)
NSAID-ERD, n (%)*	37 (28)	43 (30)	44 (29)	34 (23)
Any prior nasal polyp surgery, n (%)*	98 (74)	96 (67)	88 (58)	85 (57)
≥1 previous surgery	99 (74)	99 (69)	88 (58)	88 (59)
≥3 previous surgeries	29 (22)	33 (23)	18 (12)	22 (15)
Allergic rhinitis history, n (%)*	65 (49)	75 (52)	88 (58)	89 (59)
SCS use in the preceding 2 y, n (%)*	85 (64)	90 (63)	122 (80)	119 (79)
Nasal congestion or obstruction score (scale 0-3)	2.45 (0.55)	2.26 (0.57)	2.38 (0.54)	2.48 (0.62)
SNOT-22				
Total score (scale 0-110)	50.9 (20.2)	48.0 (20.2)	53.5 (21.9)	50.2 (19.7)
Average sleep domain score (scale 0-5)*	2.25 (1.35)	2.25 (1.41)	2.50 (1.45)	2.25 (1.33)
Average function domain score (scale 0-5)*	2.10 (1.32)	2.12 (1.38)	2.33 (1.44)	2.00 (1.36)

Data are mean (SD), unless specified.

CRSwNP, Chronic rhinosinusitis with nasal polyps; *IQR*, interquartile range; *ITT*, intent-to-treat; *NSAID-ERD*, nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; *SCS*, systemic corticosteroid; *SD*, standard deviation; *SNOT-22*, 22-Item Sinonasal Outcome Test.

*Descriptive statistics include patients after worst observation carried forward at each visit; patients whose values at each visit were imputed by multiple imputation methods were excluded from the analysis.

versus placebo were observed in dupilumab-treated patients for all sleep and function item scores at week 24 (SINUS-24) and week 52 (SINUS-52), regardless of change in nasal polyp score (data not shown).

The beneficial effect of dupilumab versus placebo on SNOT-22 sleep and function domain scores was also observed in all predefined patient subgroups at week 24 (SINUS-24) and at week 52 (SINUS-52) (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Although the reduced sleep and function domain scores with dupilumab were statistically significant versus placebo in all subgroups, some numerical differences were apparent at week 52. For example, numerically greater improvements in function were seen in patients with asthma versus those without asthma and in patients with prior nasal polyp surgery versus those without surgery. Although the reduced sleep and function domain scores with dupilumab were statistically significant versus placebo in all subgroups, some differences were apparent at week 52 (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

In this analysis, patients with CRSwNP receiving dupilumab reported less impairment in sleep and functioning as measured by SNOT-22 sleep and function domain scores versus placebo after 24 weeks of treatment, with benefits maintained at week 52. The positive effect of dupilumab occurred irrespective of comorbid asthma, NSAID-ERD, allergic rhinitis, prior surgery, and/or SCS use.

Patients showed improved outcomes in fatigue, productivity, and concentration as measured by SNOT-22 function domain scores. As impaired sleep is known to have a detrimental impact on HRQoL and functioning,[9] our results suggest a broader impact for dupilumab on HRQoL beyond symptomatic relief from CRSwNP. However, data were not collected using standard sleep scales (eg, Pennsylvania Sleep Inventory) during SINUS-24 and SINUS-52. Hence, although demonstrating a beneficial effect of dupilumab compared with placebo on sleep and functioning, our data do not permit evaluation of how this might translate into overall improvements in general health and functioning. Any potential contribution of obstructive sleep apnea was also beyond the scope of the current analysis.

Despite these limitations, this analysis suggests a reduction in daily CRSwNP symptoms (eg, congestion/rhinorrhea) with dupilumab[7] may be responsible for the improvement in sleep scores, which in turn may be responsible for the observed improvement in function scores.

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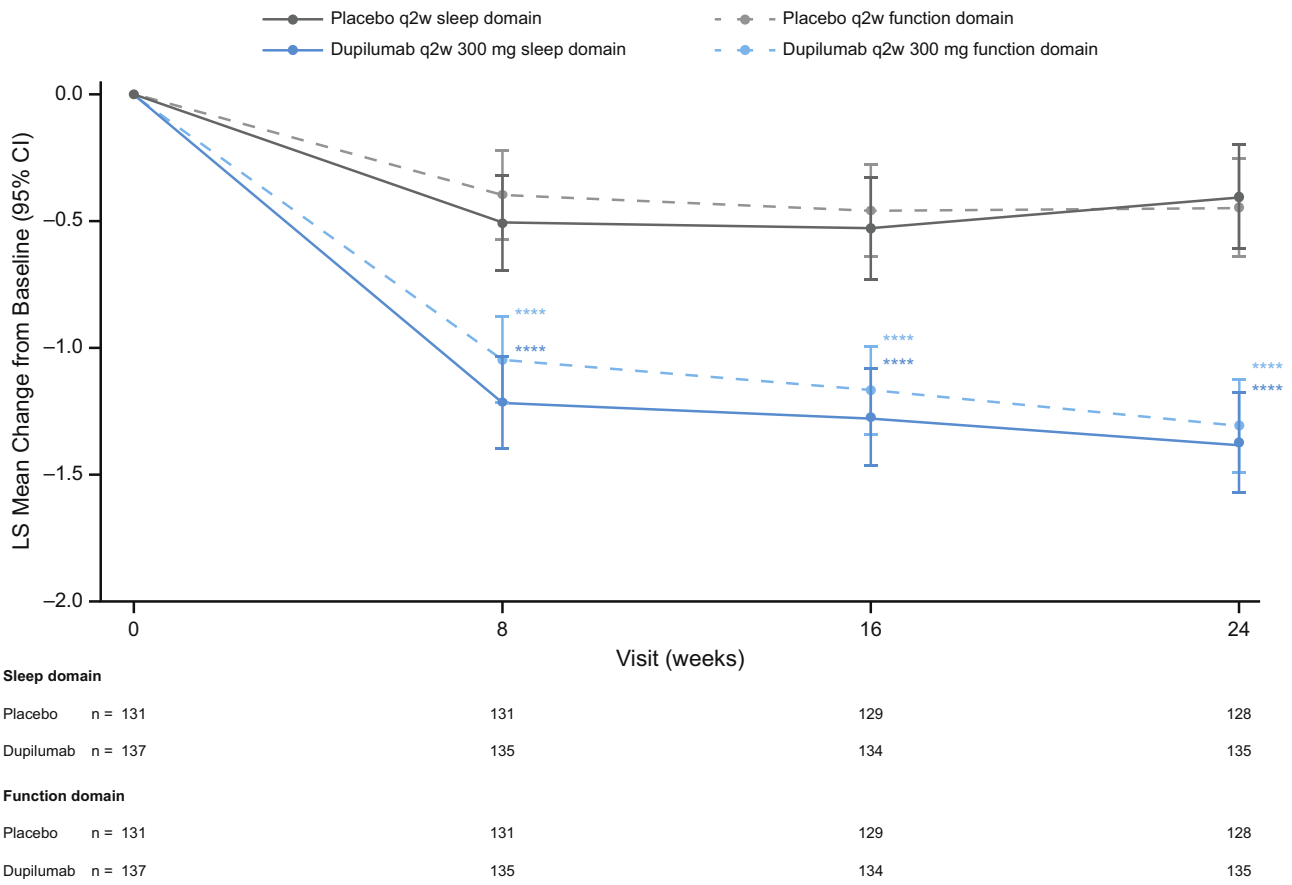

FIGURE 1. Change from baseline in average sleep and function domain scores up to Week 24 (SINUS-24 ITT population). The sleep domain of SNOT-22 includes the items "difficulty falling asleep," "wake up at night," "lack of a good night's sleep," and "wake up tired." The function domain of SNOT-22 includes the items "fatigue," "reduced productivity," and "reduced concentration." *CI*, Confidence interval; *ITT*, intent-to-treat; *LS*, least squares; *q2w*, every 2 weeks; *SNOT-22*, 22-Item Sinonasal Outcome Test.

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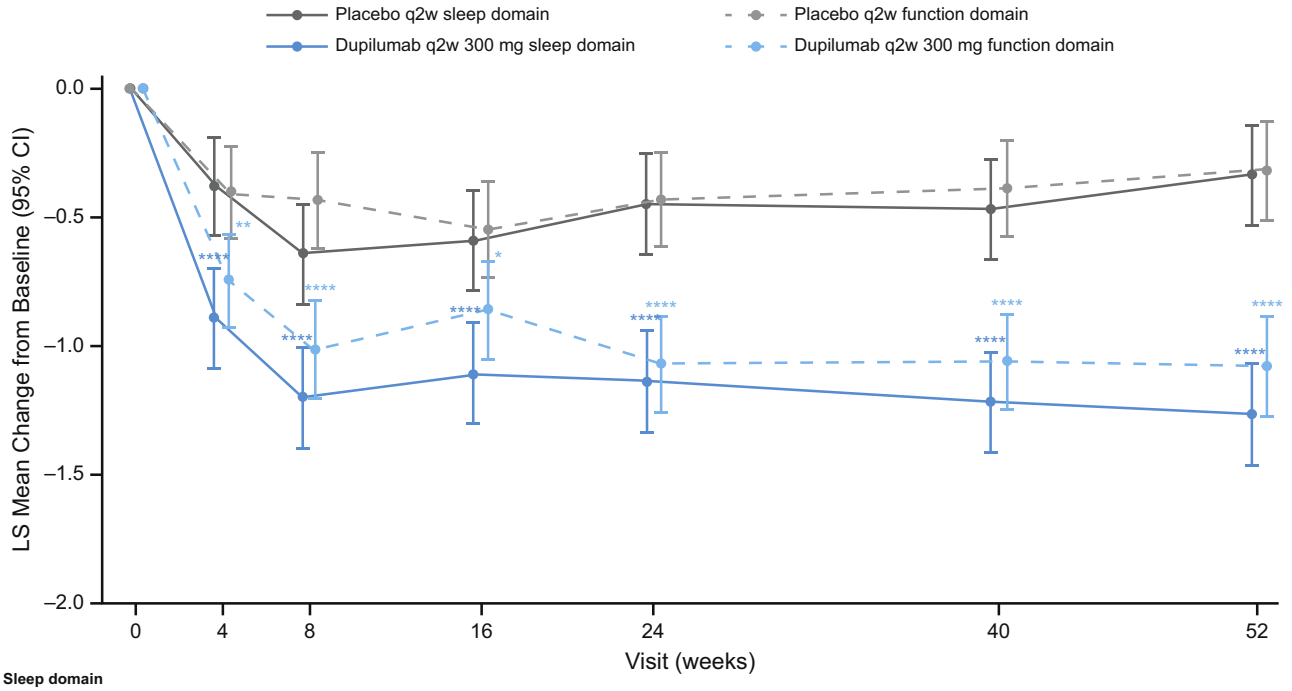

Sleep domain							
Placebo	n = 152	149	146	147	145	140	143
Dupilumab	n = 147	144	143	140	141	140	143
Function domain							
Placebo	n = 152	149	146	147	145	140	143
Dupilumab	n = 147	144	143	140	141	140	143

FIGURE E1. Change from baseline in average sleep and function domain scores up to week 52 (SINUS-52 intent-to-treat population). The sleep domain of SNOT-22 includes the items "difficulty falling asleep," "wake up at night," "lack of a good night's sleep," and "wake up tired." The function domain of SNOT-22 includes the items "fatigue," "reduced productivity," and "reduced concentration." *CI*, Confidence interval; *LS*, least squares; *q2w*, every 2 weeks; *SNOT-22*, 22-Item Sinonasal Outcome Test.

TABLE E1. Change from baseline in average SNOT-22 sleep and function domain scores for dupilumab versus placebo at week 24 (SINUS-24) and week 52 (SINUS-52) by patient subgroup

	Average SNOT-22 sleep domain score*					Average SNOT-22 function domain score†				
		Change from baseline LS mean (standard error)		LS mean difference			Change from baseline LS mean (standard error)		LS mean difference	
Subgroup	n/n‡	Placebo	Dupilumab	(95% CI) vs placebo	*P* value	n/n‡	Placebo	Dupilumab	(95% CI) vs placebo	*P* value
Week 24 (SINUS-24)										
History of asthma										
Yes	74/77	−0.50 (0.14)	−1.62 (0.14)	−1.12 (−1.48, −0.77)	<.0001	74/77	−0.49 (0.13)	−1.48 (0.13)	−0.99 (−1.33, −0.65)	<.0001
No	54/58	−0.32 (0.17)	−1.09 (0.15)	−0.77 (−1.17, −0.37)	.0002	54/58	−0.39 (0.15)	−1.05 (0.14)	−0.66 (−1.02, −0.29)	.0005
NSAID-ERD history										
Yes	37/42	−0.52 (0.22)	−1.56 (0.21)	−1.03 (−1.55, −0.52)	<.0001	37/42	−0.48 (0.20)	−1.47 (0.19)	−0.99 (−1.47, −0.51)	<.0001
No	91/93	−0.35 (0.12)	−1.34 (0.11)	−0.99 (−1.30, −0.68)	<.0001	91/93	−0.42 (0.11)	−1.26 (0.11)	−0.84 (−1.13, −0.55)	<.0001
History of surgery										
Yes	95/94	−0.35 (0.12)	−1.37 (0.12)	−1.03 (−1.34, −0.71)	<.0001	95/94	−0.47 (0.11)	−1.35 (0.11)	−0.88 (−1.18, −0.59)	<.0001
No	33/41	−0.51 (0.19)	−1.35 (0.17)	−0.84 (−1.36, −0.33)	.0017	33/41	−0.45 (0.17)	−1.25 (0.16)	−0.80 (−1.26, −0.33)	.0011
History of allergic rhinitis										
Yes	62/73	−0.43 (0.16)	−1.36 (0.14)	−0.93 (−1.31, −0.54)	<.0001	62/73	−0.40 (0.16)	−1.31 (0.14)	−0.91 (−1.29, −0.53)	<.0001
No	66/62	−0.44 (0.15)	−1.43 (0.15)	−0.99 (−1.37, −0.62)	<.0001	66/62	−0.53 (0.13)	−1.30 (0.13)	−0.78 (−1.11, −0.44)	<.0001
SCS use during past 2 y										
Yes	84/88	−0.44 (0.13)	−1.53 (0.12)	−1.09 (−1.43, −0.75)	<.0001	84/88	−0.51 (0.12)	−1.45 (0.11)	−0.94 (−1.26, −0.62)	<.0001
No	44/47	−0.41 (0.28)	−1.22 (0.30)	−0.81 (−1.23, −0.40)	.0001	44/47	−0.59 (0.26)	−1.33 (0.27)	−0.74 (−1.13, −0.36)	.0002
Patients reporting 1 SNOT-22 sleep or function domain item as most important at baseline	80/87	−0.56 (0.13)	−1.49 (0.12)	−0.94 (−1.27, −0.60)	<.0001	53/48	−0.62 (0.16)	−1.59 (0.16)	−0.97 (−1.39, −0.55)	<.0001
Week 52 (SINUS-52)										
History of asthma										
Yes	84/81	−0.23 (0.13)	−1.18 (0.14)	−0.95 (−1.29, −0.61)	<.0001	84/81	−0.08 (0.13)	−1.07 (0.13)	−0.99 (−1.33, −0.65)	<.0001
No	59/62	−0.39 (0.15)	−1.28 (0.15)	−0.89 (−1.26, −0.52)	<.0001	59/62	−0.56 (0.15)	−1.01 (0.15)	−0.44 (−0.82, −0.07)	.0201
NSAID-ERD history										
Yes	42/34	−0.22 (0.20)	−1.35 (0.21)	−1.12 (−1.65, −0.60)	<.0001	42/34	0.08 (0.19)	−1.16 (0.20)	−1.24 (−1.74, −0.74)	<.0001
No	101/109	−0.34 (0.12)	−1.22 (0.12)	−0.88 (−1.16, −0.59)	<.0001	101/109	−0.44 (0.12)	−1.03 (0.12)	−0.59 (−0.88, −0.30)	<.0001
History of surgery										
Yes	82/83	−0.30 (0.13)	−1.37 (0.13)	−1.07 (−1.40, −0.74)	<.0001	82/83	−0.22 (0.13)	−1.20 (0.13)	−0.97 (−1.29, −0.66)	<.0001
No	61/60	−0.37 (0.15)	−1.13 (0.15)	−0.76 (−1.13, −0.38)	<.0001	61/60	−0.46 (0.16)	−0.92 (0.16)	−0.46 (−0.86, −0.06)	.0238
History of allergic rhinitis										
Yes	83/88	−0.45 (0.14)	−1.55 (0.14)	−1.10 (−1.43, −0.78)	<.0001	83/88	−0.39 (0.14)	−1.30 (0.14)	−0.90 (−1.24, −0.57)	<.0001
No	60/55	−0.27 (0.15)	−0.96 (0.16)	−0.70 (−1.09, −0.30)	.0005	60/55	−0.25 (0.14)	−0.82 (0.15)	−0.57 (−0.95, −0.19)	.0034
SCS use during past 2 y										
Yes	117/117	−0.32 (0.12)	−1.24 (0.12)	−0.92 (−1.20, −0.64)	<.0001	117/117	−0.42 (0.12)	−1.10 (0.12)	−0.68 (−0.96, −0.39)	<.0001
No	26/26	−0.52 (0.23)	−1.44 (0.24)	−0.92 (−1.46, −0.38)	.0009	26/26	−0.02 (0.23)	−1.12 (0.24)	−1.11 (−1.65, −0.57)	<.0001

Patients reporting 1 SNOT-22 sleep or function domain item as most important at baseline	105/98	−0.44 (0.13)	−1.42 (0.13)	−0.98 (−1.29, −0.67)	<.0001	57/55	−0.66 (0.17)	−1.57 (0.17)	−0.91 (−1.35, −0.47)	<.0001

CI, Confidence interval; *LS*, least squares; *NSAID-ERD*, nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; *SCS*, systemic corticosteroid; *SNOT-22*, 22-Item Sinonasal Outcome Test.
*The sleep domain of SNOT-22 includes the items "difficulty falling asleep," "wake up at night," "lack of a good night's sleep," and "wake up tired."
†The function domain of SNOT-22 includes the items "fatigue," "reduced productivity," and "reduced concentration."
‡Placebo/dupilumab.