ORIGINAL RESEARCH ARTICLE

Interpreting the Relationship Among Itch, Sleep, and Work Productivity in Patients with Moderate-to-Severe Atopic Dermatitis: A Post Hoc Analysis of JADE MONO-2

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Abstract

Background Abrocitinib, an oral, once-daily Janus kinase 1-selective inhibitor, improved itch severity, sleep, and work productivity versus placebo in patients with moderate-to-severe atopic dermatitis.

Objective The aim of this study was to investigate relationships among itch, sleep, and work productivity in the phase III JADE MONO-2 clinical trial.

Methods A repeated-measures longitudinal model was used to examine relationships between itch (using the Peak Pruritus Numerical Rating Scale [PP-NRS] or Nighttime Itch Scale [NTIS]) and sleep disturbance/loss (using the Patient-Oriented Eczema Measure sleep item and SCORing AD Sleep Loss Visual Analog Scale) and, separately, between itch and work productivity (using the Work Productivity and Activity Impairment-Atopic Dermatitis Version 2.0 questionnaire). Mediation modelling was used to investigate the effect of treatment (abrocitinib vs placebo) on work impairment via improvements in itch and sleep.

Results The relationships between itch/sleep and itch/work productivity were approximately linear. PP-NRS scores of 0, 4–6, and 10 were associated with 0 days, 3–4 days, and 7 days per week of disturbed sleep, respectively. PP-NRS or NTIS scores of 0–1, 4–5, and 10 were associated with 0–10%, 20–30%, and >50% overall work impairment, respectively. Seventy-five percent of the effect of abrocitinib on reducing work impairment was indirectly mediated by improvement in itch, followed by sleep.

Conclusion These results quantitatively demonstrate that reducing itch severity is associated with improvements in sleep and work productivity. Empirical evidence for the mechanism of action of abrocitinib showed that itch severity is improved, which reduces sleep loss/sleep disruption and, in turn, improves work productivity.

Clinical Trial Registration NCT03575871

Plain Language Summary

Atopic dermatitis (AD), also called atopic eczema, is a common skin disease that is associated with itch and reduced quality of life. Abrocitinib, a recently approved medicine for AD, was shown in clinical trials to improve itch, which is considered the most bothersome symptom to people with AD. Abrocitinib also improved sleep outcomes and work productivity in people with moderate or severe AD. It is unknown if improvement in itch can lead to improvement in sleep and work productivity. We analyzed data from the JADE MONO-2 study, which included 391 people who received treatment with abrocitinib or placebo for 12 weeks. We used mathematical modelling to study relationships between itch and sleep or work productivity. We also wanted to study if the improvements in itch and sleep with abrocitinib treatment had an impact on work productivity. We found that a relationship existed between itch, sleep disturbance, and work impairment; as itch improved, so too

did sleep disturbance and work impairment. When people were treated with abrocitinib, they experienced relief from itch, which improved sleep, which in turn reduced work productivity loss. Larger and longer studies are needed to confirm these results. This analysis further informs the expectations of patients with moderate or severe AD as it relates to progression of symptom relief after treatment with abrocitinib.

Key Points

Atopic dermatitis (AD) is a chronic skin disease associated with intense itch and reduced quality of life.

This analysis demonstrated the association among itch severity, poor sleep, and reduced work productivity in patients with moderate-to-severe AD. Treatment with abrocitinib was shown to reduce itch, which in turn improved sleep outcomes, resulting in less work impairment.

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1 Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease that affects up to 20% of children and 5–10% of adults worldwide [1–6]. AD is typically characterized by intense pruritus (itch), eczematous lesions, and dry skin [5], of which itch is the most bothersome symptom [4, 7, 8]. Uncontrolled chronic itch is often worse at night and can lead to sleep disturbance/loss and decreased quality of life (QoL) [2, 9–13], which can in turn adversely impact function and productivity. Increasing disease severity augments the negative impact of AD on work productivity [3, 14–16].

The pathophysiology of itch in AD is influenced by extrinsic factors (i.e., allergens and irritants), genetic predisposition, and a type-2 immune response mediated via the signaling of pruritic and inflammatory cytokines (i.e., interleukin [IL]-31, IL-4, and IL-13) [17–20]. Itch likely contributes to sleep disturbance in patients with AD and other inflammatory diseases that involve upregulation of IL-4 and IL-13, given the significant increase in sleep impairment seen in patients with psoriasis and itch compared with those without pruritus [21–23]. As such, it is possible that systemic therapies targeting key pruritic cytokines in the itch pathway may also act to improve sleep quality and subsequently other aspects of daily life in patients with AD.

Abrocitinib is an oral, once-daily, selective Janus kinase 1 (JAK1) inhibitor approved for the treatment of moderate-to-severe AD in adults and adolescents [24–27]. Abrocitinib was shown to be a well-tolerated and effective treatment for moderate-to-severe AD in multiple clinical studies (phase IIb, JADE MONO-1, JADE MONO-2, JADE COMPARE, JADE TEEN, JADE REGIMEN, and JADE DARE) [28–34]. Significantly greater proportions of patients treated with abrocitinib (200 mg or 100 mg) achieved an Investigator Global Assessment (IGA) response of clear (0) or almost clear (1) with ≥2-grade improvement, a ≥75% improvement in Eczema Area and Severity Index score (EASI-75) response, and/or ≥4-point improvement from baseline in Peak Pruritus Numerical Rating Scale (PP-NRS4) response, than those treated with placebo [30]. In the phase III JADE MONO-1 and JADE MONO-2 trials, abrocitinib resulted in greater decreases from baseline in PP-NRS score compared with placebo [22, 23]. Additionally, in JADE MONO-2, greater decreases were observed with abrocitinib in Work Productivity and Activity Impairment Questionnaire-Atopic Dermatitis (WPAI-AD), Patient-Oriented Eczema Measure sleep item (POEM sleep item), and SCORing AD Sleep Visual Analog Scale (SCORAD Sleep Loss VAS) scores compared with placebo [30, 35].

The direct and indirect effects of abrocitinib on improving itch, sleep, and work productivity have not been evaluated [13]. This supplemental (post hoc) analysis used data from JADE MONO-2 to examine the relationships between itch and sleep disturbance and between itch and overall work impairment. In addition, a mediation model was developed to simultaneously evaluate interrelationships among treatment, itch, sleep, and work productivity. We thereby sought to quantify the direct and indirect effects of abrocitinib on work productivity through analysis of itch and sleep.

2 Methods

2.1 Study Design

JADE MONO-2 (NCT03575871) was a multicenter, international, phase III, randomized, placebo-controlled, parallel-group trial. Patients with moderate-to-severe AD were randomly assigned (2:2:1) to receive abrocitinib 200 mg, 100 mg, or placebo for 12 weeks. Full study details, including the primary efficacy and safety results, have been published previously [30]. The study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization Good Clinical Practice Guidelines. All local regulatory requirements were followed. This research was approved by institutional

review boards or ethics committees at each study site. An internal review committee monitored the safety of patients throughout the study. All patients provided written informed consent.

2.2 Patients

Eligible patients were aged ≥12 years with clinical diagnosis of moderate-to-severe AD (IGA ≥3, EASI ≥16, percentage of body surface area involvement [%BSA] ≥10, PP-NRS [defined as the worst itch experienced in the last 24 h; used with permission of Regeneron Pharmaceuticals, Inc. and Sanofi [36]] ≥4 on the day of the baseline visit) and a recent (within 6 months) history of inadequate response to topical corticosteroids or calcineurin inhibitors given for ≥4 weeks or an inability to receive topical treatment because it was medically inadvisable. Previous dupilumab use was permitted if it was discontinued >6 weeks before study initiation. Concomitant use of topical (corticosteroids, calcineurin inhibitors, tars, antibiotic creams, or antihistamines) or systemic therapies for AD was prohibited [30]. Rescue medication (including topical corticosteroids) was prohibited during the study. Full inclusion and exclusion criteria are published elsewhere [30].

2.3 Post Hoc Analysis

A repeated-measures longitudinal model [37, 38] was employed to estimate relationships between itch severity (PP-NRS or Night Time Itch Scale [NTIS], scored 0–10, higher scores indicating worse itch) as a predictor and sleep disturbance (POEM sleep item or SCORAD Sleep Loss VAS) as an outcome. The relationship between itch severity (PP-NRS or NTIS) as a predictor and work productivity (WPAI-AD) as an outcome was also investigated. In addition, the relationship between POEM sleep item and SCORAD Sleep Loss VAS was examined.

PP-NRS and NTIS were assessed daily during the 28-day screening period and the first 2 weeks after randomization, followed by single measurements at week 4, week 8, and week 12. As a result, in the analysis NTIS and PP-NRS values for baseline (week 0), week 1 and week 2 are represented by the mean of all available weekly measurements (if at least 4 observations were available). The POEM sleep item and SCORAD Sleep Loss VAS were collected at baseline and weeks 2, 4, 8, and 12.

WPAI-AD was assessed in adult patients at baseline and week 12 to measure the effect of AD on work productivity and regular activities during the previous 7 days. The activity impairment component of this questionnaire was completed by all adult patients, while the work impairment component was completed by only those adult patients who were employed during the study period and assessed the level of impairment in productivity while working. The WPAI-AD is designed in such a way that questions that are not applicable (i.e., impact of AD on work productivity) can be skipped by patients who are not employed and as such, for these patients, absenteeism, presenteeism, and overall work productivity were not calculated. As this omission is by design, these domains should not be considered as 'missing'.

To study the appropriateness of the linear approximation of the relationship between the predictor and the outcome, two models were investigated. The main model, with the predictor as a continuous variable, imposed a linear relationship between the predictor and the outcome. A model with the predictor as a categorical variable (sensitivity analysis) was also studied whereby a functional relationship between the outcome and the predictor is not imposed. The models assume that measurements from the same patient are not independent, which means that the error terms covary over time within a patient, and the error at one time point is allowed to covary with the error at another time point for any patient [38]. The covariance of the error terms for the same patient over time was modeled with a spatial power covariance structure that allows for time intervals that are not evenly spaced [38]. The models, which were fit in SAS with Prox Mixed and the Repeated statement, use all available data and assume that data were missing at random.

A mediation model, which can help elucidate the mechanism of action of a drug, was used to investigate the direct and indirect effects of the treatment (abrocitinib [200 mg and 100 mg] vs placebo) on overall work impairment (WPAI-AD), and how these effects were influenced by itch (PP-NRS and NTIS), and sleep (POEM sleep item and SCORAD Sleep Loss VAS), denoted as mediators [39]. The initial model included indirect causal paths from abrocitinib to overall work impairment through itch severity (latent variable F1) and sleep (latent variable F2) as well as direct effects of abrocitinib to overall work impairment (representing all other possible paths; Supplementary Fig. S1, see electronic supplementary material [ESM]). Variables e_ppnrs, e_ntis, e_poem, e_scrd, and e_wpai represent error terms, which reflect unexplained variation due to random measurement error (score unreliability). Variables e_itch and e_sleep represent disturbance terms, which reflect unexplained variation due to omitted (unmeasured) causes and score unreliability in the corresponding latent variables. Based on the results of the initial model, the mediation model can be re-specified to resolve any irregularities and contradictions.

3 Results

3.1 Patients

This post hoc analysis used data from the JADE MONO-2 study ($n = 391$), which included patients randomized to

treatment with abrocitinib 200 mg, abrocitinib 100 mg, or placebo. The baseline disease and demographic characteristics of these patients have been previously reported and were generally similar across treatment groups (Table 1) [30]. Patients from the JADE MONO-2 study were mostly male (59%) with a mean age of 35.1 years and an average PP-NRS score of 7 [30]. For this post hoc analysis, only those patients with at least one observation for each of the parameters assessed in the respective associations were included (Table 2).

3.2 Linearity Between Outcomes Through a Longitudinal Model

All available data from baseline to week 12 were included in a repeated-measures longitudinal model, with predictors as continuous or categorical variables. Similar results were observed in models in which the predictor was used as a continuous variable versus a categorical variable, supporting the linearity assumption for (a) the relationships between itch (PP-NRS and NTIS) and sleep (SCORAD sleep loss

Table 1 Demographic and baseline characteristics

Characteristic	Placebo n = 78	Abrocitinib		Total N = 391
		100 mg n = 158	200 mg n = 155	
Age, y				
Mean (SD)	33.4 (13.8)	37.4 (15.8)	33.5 (14.7)	35.1 (15.1)
<18, n (%)	8 (10.3)	17 (10.8)	15 (9.7)	40 (10.2)
Male sex, n (%)	47 (60.3)	94 (59.5)	88 (56.8)	229 (58.6)
Race, n (%)				
White	40 (51.3)	101 (63.9)	91 (58.7)	232 (59.3)
Asian	29 (37.2)	46 (29.1)	54 (34.8)	129 (33.0)
Black or African American	6 (7.7)	9 (5.7)	6 (3.9)	21 (5.4)
Multiracial	1 (1.3)	1 (0.6)	2 (1.3)	4 (1.0)
Not reported	2 (2.6)	1 (0.6)	2 (1.3)	5 (1.3)
Ethnicity, n (%)				
Not Hispanic or Latino	73 (93.6)	154 (97.5)	150 (96.8)	377 (96.4)
Hispanic or Latino	2 (2.6)	3 (1.9)	4 (2.6)	9 (2.3)
Not reported	3 (3.8)	1 (0.6)	1 (0.6)	5 (1.3)
Disease duration, mean (SD), years	21.7 (14.3)	21.1 (14.8)	20.5 (14.8)	21.0 (14.7)
PP-NRS score, mean (SD)	6.7 (1.9)	7.1 (1.6)	7.0 (1.6)	7.0 (1.7)
NTIS score, mean (SD)	6.2 (2.1)	6.8 (2.0)	6.8 (1.9)	6.7 (2.0)
SCORAD Sleep Loss VAS, mean (SD)	5.4 (2.3)	5.7 (2.5)	5.9 (2.5)	5.7 (2.5)
POEM Sleep item, mean (SD)	2.7 (1.3)	2.9 (1.3)	2.8 (1.3)	2.8 (1.3)
WPAI-AD, mean (SD)[a]				
Absenteeism[b]	n = 42 4.2 (10.3)	n = 93 4.6 (16.0)	n = 79 5.0 (19.5)	n = 214 4.7 (16.4)
Presenteeism[b]	n = 42 35.2 (24.3)	n = 92 35.4 (26.3)	n = 76 36.4 (26.3)	n = 210 35.8 (25.8)
Overall work productivity[b]	n = 42 37.3 (25.8)	n = 92 36.4 (27.4)	n = 76 36.9 (26.6)	n = 210 36.8 (26.7)
Activity impairment	n = 70 41.9 (27.2)	n = 139 41.0 (27.5)	n = 138 43.0 (25.6)	n = 347 42.0 (26.7)

AD atopic dermatitis, *NTIS* Night Time Itch Scale, *POEM* Patient-Oriented Eczema Measure, *PP-NRS* Peak Pruritus Numerical Rating Scale, *SCORAD Sleep Loss VAS* SCORing of Atopic Dermatitis Sleep Loss Visual Analog Scale, *SD* standard deviation, *WPAI-AD* Work Productivity and Activity Impairment-Atopic Dermatitis

[a]Adolescent patients did not respond to the WPAI-AD questionnaire

[b]Adult patients who were not employed at the time of the study did not answer WPAI-AD items related to employment

Table 2 Summary of patient numbers and individual patient-reported outcome observations included in analysis

	Patients included, n	Maximum observations per patient, n	Total observations used in analysis, n
PP-NRS vs NTIS	391	6	1966
PP-NRS vs POEM sleep item	390	5	1685
PP-NRS vs SCORAD Sleep Loss VAS	390	5	1691
PP-NRS vs WPAI[a]	220	2	357
NTIS vs POEM sleep item	389	5	1578
NTIS vs SCORAD Sleep Loss VAS	389	5	1583
NTIS vs WPAI[a]	219	2	341
SCORAD Sleep Loss VAS vs POEM sleep item	391	5	1842

NTIS Night Time Itch Scale, *POEM* Patient-Oriented Eczema Measure, *PP-NRS* Peak Pruritus Numerical Rating Scale, *SCORAD Sleep Loss VAS* SCORing of Atopic Dermatitis Sleep Loss Visual Analog Scale, *WPAI-AD* Work Productivity and Activity Impairment-Atopic Dermatitis

[a]WPAI overall work impairment

VAS and POEM sleep items) (Fig. 1); (b) the relationships between PP-NRS as a predictor and either POEM sleep item or SCORAD Sleep Loss VAS as the outcome, or WPAI as the outcome for work productivity (Fig. 2); and (c) the relationship between NTIS as a predictor and either POEM sleep item or SCORAD Sleep Loss VAS as the outcome, or WPAI as the outcome for work productivity (Fig. 3).

The relationship between itch and the POEM sleep item showed that PP-NRS ($N = 390$) scores of 0, 4–6, and 10 and NTIS ($N = 389$) scores of 0, 4–6, and 9–10 are associated with no days, 3–4 days per week, and every day of disturbed sleep, respectively (Fig. 4a): every 1-point improvement in

itch corresponded to an approximate 0.4-point improvement in the POEM sleep item. The relationship between itch and WPAI-AD showed that PP-NRS ($N = 220$) scores of 0–1, 4–5, and 10 and NTIS ($N = 219$) scores of 0–1, 4–5, and 10 are associated with 0–10%, 20–30%, and >50% overall work impairment, respectively (Fig. 4b): every 1-point improvement in itch corresponded to an approximate 5% improvement in WPAI-AD overall work impairment. With the interpretations of the relationships between outcomes found in the longitudinal model, further investigation of specific paths between outcomes was evaluated through mediation modeling.
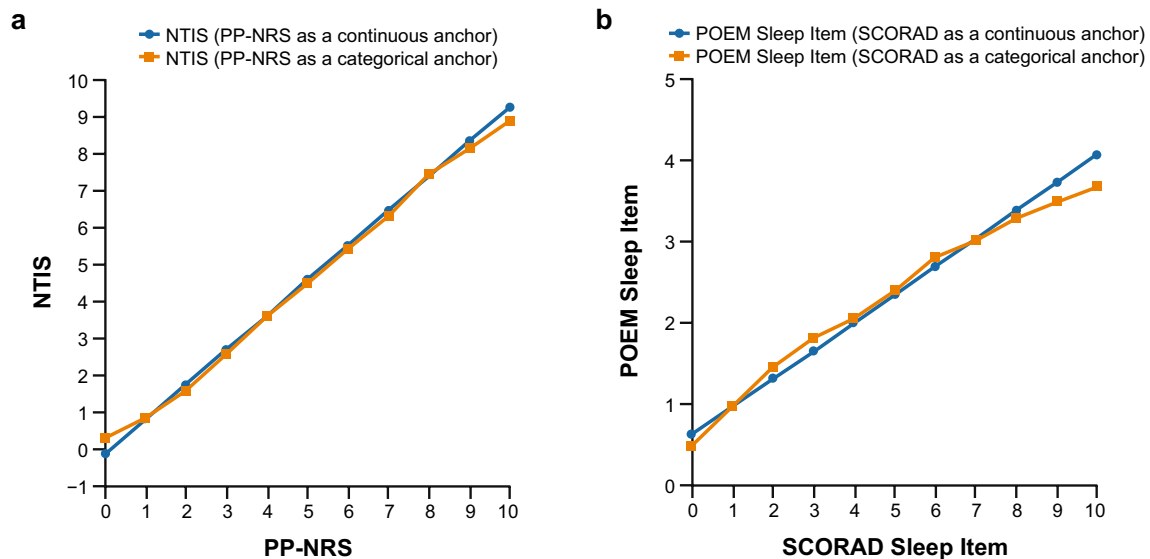
Fig. 1 Relationships between **a** PP-NRS and NTIS and **b** SCORAD and POEM sleep items. *NTIS* Night Time Itch Scale, *POEM* Patient-Oriented Eczema Measure, *PP-NRS* Peak Pruritus Numerical Rating Scale, *SCORAD Sleep Loss VAS* SCORing of Atopic Dermatitis Sleep Loss Visual Analog Scale, *WPAI-AD* Work Productivity and Activity Impairment-Atopic Dermatitis
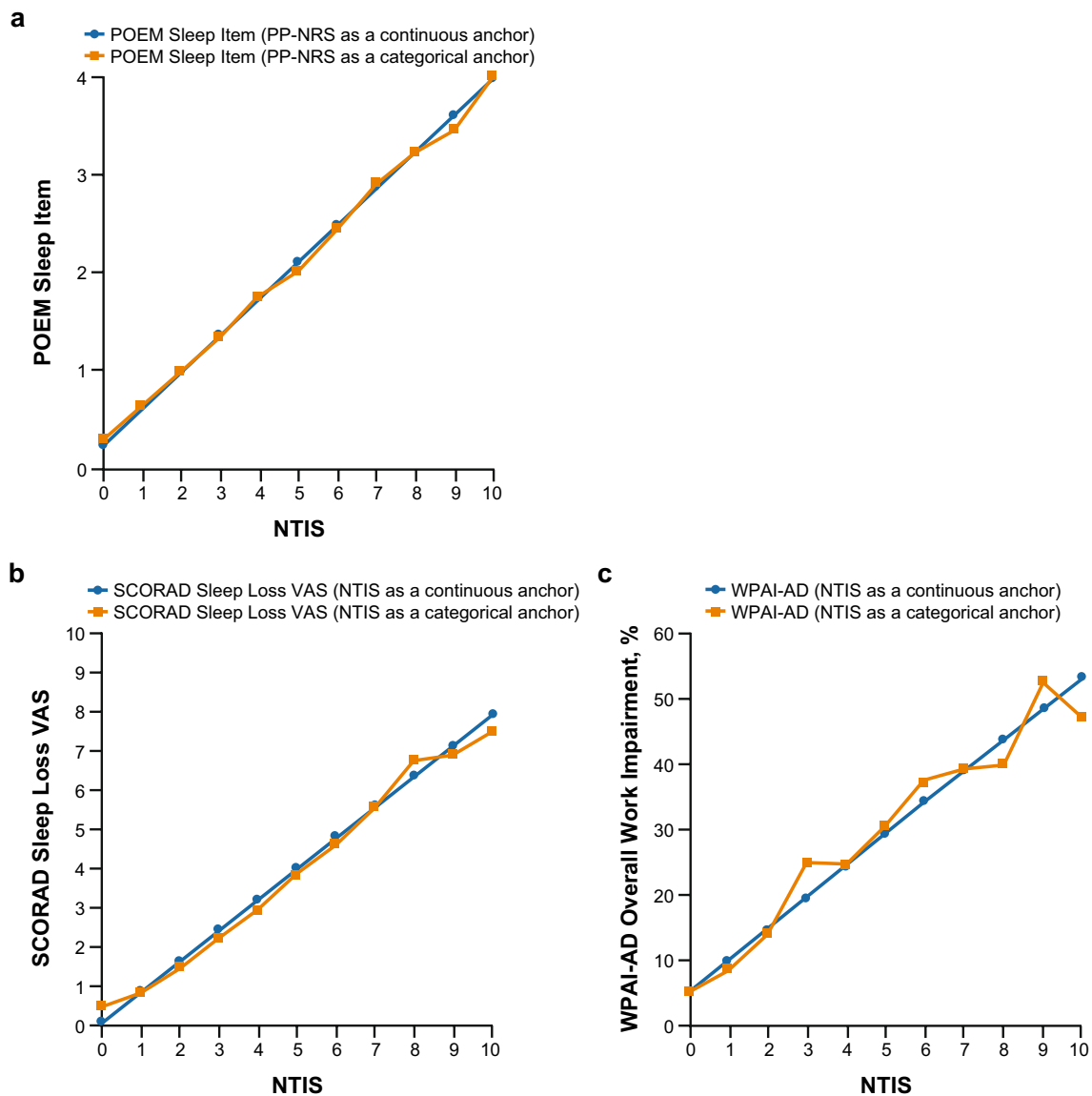
a

b

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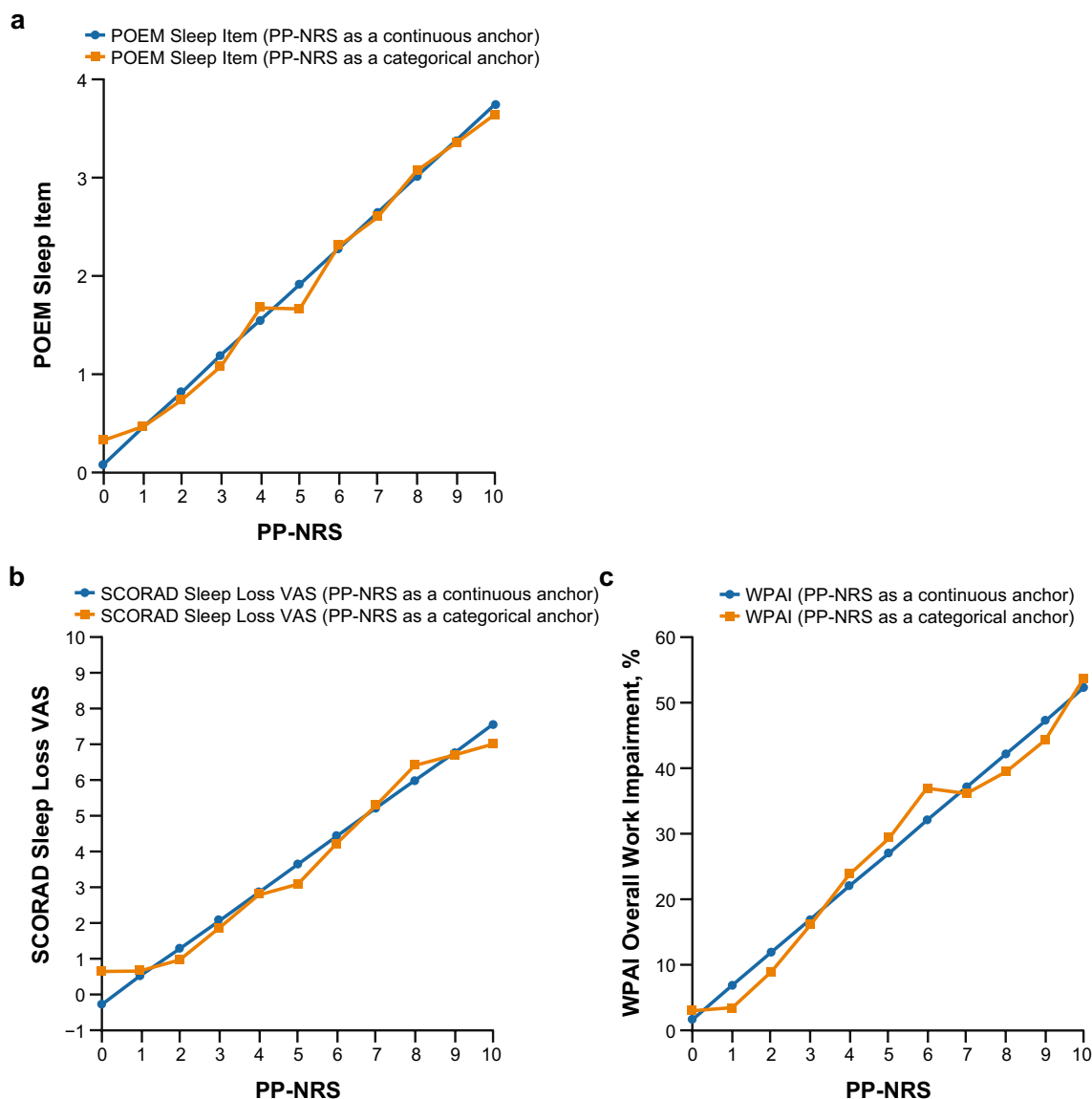
Fig. 2 Relationships between outcomes and PP-NRS as the anchor (continuous predictor or categorical predictor): **a** PP-NRS and POEM Sleep item, **b** PP-NRS and SCORAD Sleep Loss VAS, and **c** PP-NRS and WPAI overall work impairment. *NTIS* Night Time Itch Scale, *POEM* Patient-Oriented Eczema Measure, *PP-NRS* Peak Pruritus Numerical Rating Scale, *SCORAD Sleep Loss VAS* SCORing of Atopic Dermatitis Sleep Loss Visual Analog Scale, *WPAI* Work Productivity and Activity Impairment questionnaire
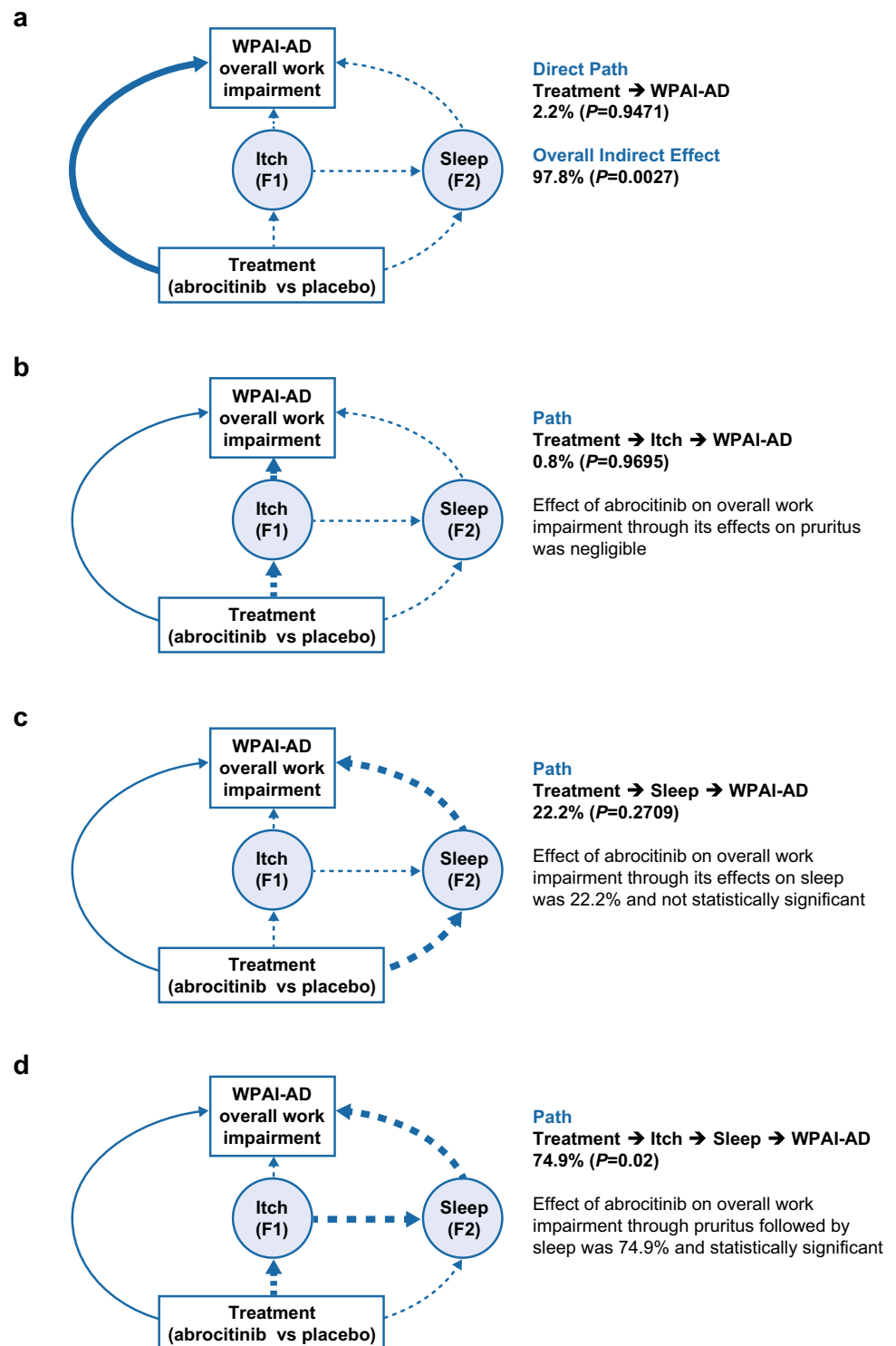
3.3 Mediation Modeling

The mediation model investigated the effect of abrocitinib on work productivity with itch and sleep as mediators. Data from 148 patients at week 12 were available for analysis. The direct effect of abrocitinib on overall work impairment was found to be 2.2% and not statistically significant ($p = 0.95$); the overall indirect effect was 97.8% and statistically significant ($p = 0.0027$), indicating that abrocitinib affects overall work impairment predominantly indirectly (Fig. 5a).

Furthermore, the path from abrocitinib to overall work impairment through itch was 0.8% ($p = 0.97$) and through sleep was 22.2% ($p = 0.27$) (Fig. 5b & c, respectively).

Finally, the effect of treatment on overall work impairment via itch and sleep (i.e., treatment improves itch, improved itch improves sleep, and improved sleep improves overall work impairment) was 74.9% and statistically significant ($p = 0.02$) (Fig. 5d).

Based on the above results, the mediation model was re-specified: (a) the direct path from treatment to WPAI was excluded, (b) the path from itch (Factor 1) to WPAI was excluded, and (c) the path from treatment to sleep

Fig. 3 Relationships between outcomes and NTIS as the anchor (continuous predictor or categorical predictor): **a** NTIS and POEM sleep item, **b** NTIS and SCORAD Sleep Loss VAS, and **c** NTIS and WPAI overall work impairment. *NTIS* Night Time Itch Scale, *POEM* Patient-Oriented Eczema Measure, *PP-NRS* Peak Pruritus Numerical Rating Scale, *SCORAD Sleep Loss VAS* SCORing of Atopic Dermatitis Sleep Loss Visual Analog Scale, *WPAI* Work Productivity and Activity Impairment questionnaire

(Factor 2) was also excluded from the model (Supplementary Fig. S2, see ESM). In this re-specified model, treatment affects WPAI overall work impairment only indirectly, first via improving itch, followed by improved sleep outcomes, which in turn reduces work impairment.

4 Discussion

Itch is the most common symptom for patients with AD and affects several aspects of everyday life [40]. Itch, particularly at night, interferes with sleep and the normal cycle of physical and mental relaxation and thus can adversely affect daytime physical and mental function and alertness [13, 41–44]. This analysis systematically establishes relationships among the patient-reported assessments of itch, sleep, and work productivity and identifies the path that best models the effects of treatment on work productivity through itch and sleep outcomes, evaluating their relative contributions. The relationships between itch and sleep and between itch and work productivity were approximately linear and indicate that greater itch severity is strongly associated with greater sleep disturbance/loss and has a notable impact on work impairment. Severe PP-NRS or NTIS (≥7)

Fig. 4 Interpretation of the association between itch and **a** sleep and **b** overall work impairment. *NTIS* Night Time Itch Scale, *POEM* Patient-Oriented Eczema Measure, *PP-NRS* Peak Pruritus Numerical Rating Scale, *SCORAD Sleep Loss VAS* SCORing of Atopic Dermatitis Sleep Loss Visual Analog Scale, *WPAI-AD* Work Productivity and Activity Impairment-Atopic Dermatitis questionnaire version 2.0
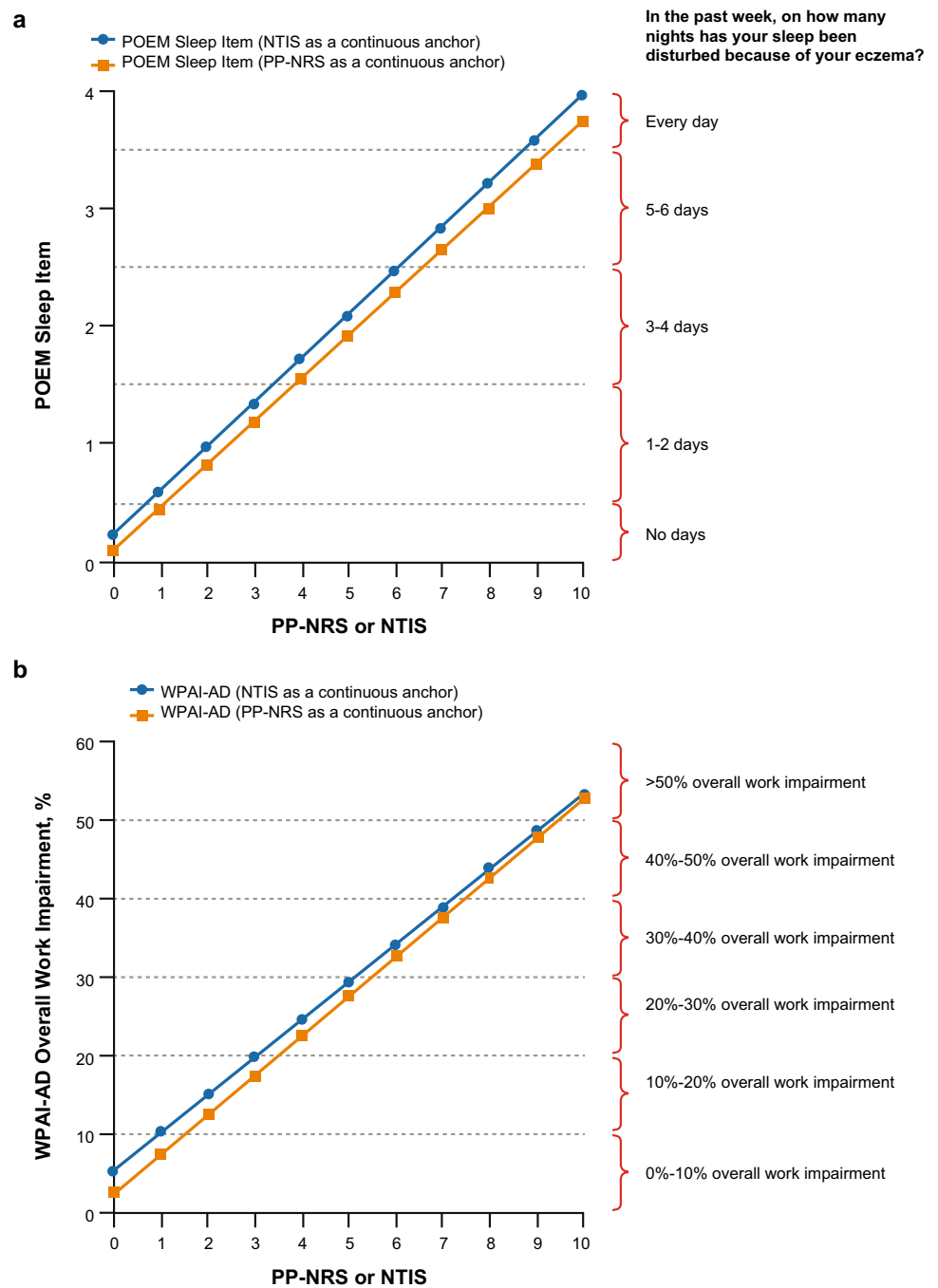
is associated with ≥5 days/week of sleep disturbance and ≥30% overall work impairment, with each 1-point reduction in itch severity reducing overall work impairment by 5%.

Intense itch, sleep disturbances, and poor work productivity are all bothersome impacts of AD that have an adverse effect on patients' QoL [13, 44]. Improvements in these symptoms can provide substantial changes in a patient's daily life. The mediation model quantitatively shows that, in patients with moderate-to-severe AD, abrocitinib improves

overall work productivity in a sequential process beginning with treatment effects on itch, which translate into improvement in sleep that eventually manifests as lesser impairment in work productivity.

This analysis was limited by its post hoc nature and the relatively small and varied number of observations for employed patients in the mediation model (53.7%–98.5% of total sample size). In addition, the contribution of factors (other than itch) to sleep disturbance, such as

Fig. 5 Mediation modeling: **a** direct and overall indirect effects, **b** path via itch, **c** path via sleep, and **d** path via itch and sleep. *WPAI-AD* Work Productivity and Activity Impairment—Atopic Dermatitis questionnaire version 2.0. Solid, single-headed arrows indicate direct paths; Dashed, single-headed arrows, indicate indirect paths

a

Direct Path
Treatment → WPAI-AD
2.2% (*P*=0.9471)

Overall Indirect Effect
97.8% (*P*=0.0027)

b

Path
Treatment → Itch → WPAI-AD
0.8% (*P*=0.9695)

Effect of abrocitinib on overall work impairment through its effects on pruritus was negligible

c

Path
Treatment → Sleep → WPAI-AD
22.2% (*P*=0.2709)

Effect of abrocitinib on overall work impairment through its effects on sleep was 22.2% and not statistically significant

d

Path
Treatment → Itch → Sleep → WPAI-AD
74.9% (*P*=0.02)

Effect of abrocitinib on overall work impairment through pruritus followed by sleep was 74.9% and statistically significant

increased monoamine and cytokine dysregulation, and decreased melatonin and skin temperature [44], were not considered, although one may argue that at least some of the effects mediated by these additional variables may be accounted for within itch. Furthermore, this model does not explore dose relationships.

5 Conclusions

In JADE MONO-2, the relationships between itch and sleep outcomes and between itch and work productivity were approximately linear, demonstrating that reduction in itch severity was associated with improved sleep and work

productivity [45]. Empirical evidence for the mechanism of action of abrocitinib suggests that the effect of abrocitinib on work productivity is predominantly mediated by an indirect path wherein treatment with abrocitinib improves itch severity, which reduces sleep loss/sleep disturbance that, in turn, improves work productivity. Future research using data from clinical studies with longer duration of treatment may expand these observations.

Declarations

Author Contributions Andrew G. Bushmakin, Joseph C. Cappelleri, and Daniela E. Myers contributed to study concept and design. Andrew G. Bushmakin and Joseph C. Cappelleri conducted the statistical analysis of the data. Gil Yosipovitch, Melinda J. Gooderham, Sonja Ständer, Luz Fonacier, Jacek C. Szepietowski, Mette Deleuran, Giampiero Girolomoni, John C. Su, Andrew G. Bushmakin, Joseph C. Cappelleri, Claire Feeney, Gary Chan, Andrew J. Thorpe, Hernan Valdez, Pinaki Biswas, Ricardo Rojo, Marco DiBonaventura, and Daniela E. Myers interpreted the data, provided critical feedback on the manuscript, approved the final manuscript for submission, and are accountable for the accuracy and integrity of the manuscript.

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