ABOUT THE AUTHOR

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Dr. Marni C. Wiseman began her dermatology practice in Winnipeg, Manitoba in 2001. In addition to her teaching responsibilities as an Associate Professor and Section Head of Dermatology at the Faculty of Medicine at the University of Manitoba, Dr. Wiseman spends most of her days at her Private Medical Practice as the Medical Director of SKiNWISE DERMATOLOGY.

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Dr. Wiseman is a frequent supervisor and mentor for medical students and residents. She has published extensively in areas of inflammatory skin disease, photodermatosis, and cutaneous malignancy.

Dr. Wiseman's community commitments are extensive and include involvement with the Canadian Dermatology Association Sun Awareness program. She is an editor of the Journal of Cutaneous Medicine and Surgery and was the chair of the Skin Cancer Disease Site Group at CancerCare Manitoba for 15 years. Dr. Wiseman holds regular outreach skin cancer screening clinics in rural locations in Manitoba, has been featured in many news stories, and regularly presents at meetings and congresses nationally and internationally.

A RANDOMIZED WITHDRAWAL STUDY WITH RESCUE TREATMENT IN PATIENTS WITH PROTOCOL DEFINED FLARE: REVIEWING JADE REGIMEN

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disease, affecting 15-20% of people in developed countries.[1,2] It affects approximately 20% of the pediatric population and 5-10% of adults, as either adult-onset AD or as persistent AD from childhood.[3,4] It can significantly affect quality of life through its symptoms, the appearance of the skin, the impact of treatment, and secondary infections.[1,5] The management of AD may be complicated by its multifactorial and heterogeneous disease presentation that is affected by both genetic and environmental factors.[6-9] While there is a strong association between AD and other atopic conditions such as asthma, allergic rhinitis, and food allergies, which share similar pathophysiological pathways, this relationship is not yet fully understood.[7-10] A predisposition for immunoglobulin E (IgE)-mediated responses to environmental stimuli appears to be the common denominator between these conditions.[11]

A recent Delphi process identified unmet needs in three main areas of AD management: (i) diagnosis, (ii)

management and prognosis, and (iii) treatment.[12] Regarding diagnosis, it was determined that AD can be challenging to diagnose, particularly in adults or when confined only to the hands, and that validated diagnostic criteria are lacking. Regarding management and prognosis, the consensus panel noted that while AD was a clinical diagnosis, there were no standardized laboratory tests and reliable biomarkers to establish diagnosis in difficult cases, to stratify for severity or to monitor treatment efficacy. Highlighting the need for effective treatments for AD, the consensus panel developed fifteen statements in the area of treatment.
In summary, the expert panel stated that treatment of AD should be based on the severity of the disease, that valid and suitable severity indexes with a threshold for treatment choice should be identified and validated, that the Eczema Area and Severity Index (EASI 75) and itch NRS scale should be used to monitor response to systemic treatments, and therapeutic goals (endpoints, time points etc.) must be defined. The group also recommended the identification of subgroups of patients who are candidates for topical therapies with products other than steroids and noted that the long-term control of both skin lesions and symptoms is challenging, with some treatments losing efficacy over time.[12]

Given the relapsing-remitting nature of AD, intermittent treatment approaches may be suitable and continuous treatment may not be necessary, yet definitive protocols to address this approach have not been developed. The expert panel suggested that oral treatments, more suitable for on-off regimens, may be preferrable. Systemic treatments are often introduced at a later stage of disease and are not initiated in all patients who might benefit from them, likely because of variability in access and approved indications, as well as a lack of consensus on the appropriate timing of initiation of systemic treatments. In addition, current systemic conventional treatments may be poorly tolerated, contraindicated or ineffective in more medically complex patients, such as those with advanced age, those with comorbidities and those on polypharmacy. These constraints and the limited number of approved AD therapies has hindered the definition of a therapeutic algorithm.[12] Current management strategies in AD include basic emollient therapy, topical anti-inflammatory regimens, phototherapy, and systemic immunosuppressive drugs. For those patients requiring more advanced treatment for moderate-to-severe AD, biologics and small molecules, which can avoid the long-term use of systemic steroids and their potential side effects, are more recently available.[13]

Entering into this treatment landscape is abrocitinib, an oral, once-daily Janus kinase 1 (JAK1) selective inhibitor recently approved in July 2022 by Health Canada for the treatment of patients 12 years and older with refractory moderate-to-severe atopic dermatitis, including the relief of pruritus, who have had an inadequate response to other systemic drugs (e.g. steroids or biologics), or for whom these treatments are not advisable.[14] Janus kinase 1 inhibition modulates multiple downstream signaling pathways involved in the pathogenesis of AD, including interleukin (IL) 4, IL-13, IL-22, IL-31, and thymic stromal lymphopoietin.[15-19] Abrocitinib is a potent JAK1 inhibitor with half maximal inhibitory concentration (IC50) of 29 nM, 803 nM, > 10,000 nM, and 1259 nM for JAK1, JAK2, JAK3, and TYK2, respectively.[20]

The JAK1 Atopic Dermatitis Efficacy and Safety (JADE) global development program for abrocitinib encompasses the JADE MONO-1, JADE MONO-2, JADE TEEN, JADE COMPARE, JADE DARE and JADE REGIMEN studies, with additional data from other studies in the JADE program available in the future.[21] JADE MONO-1 and JADE MONO-2 both aimed to assess the efficacy and safety of abrocitinib monotherapy in adolescents and adults with moderate-to-severe atopic dermatitis.[22-24] The objective of JADE TEEN was to investigate the efficacy and safety of oral abrocitinib plus topical therapy in adolescents with moderate-to-severe AD.[25] JADE COMPARE evaluated the efficacy of abrocitinib, compared with placebo and dupilumab in patients with moderate-to-severe atopic dermatitis who were receiving background topical therapy.[26] The most recently published JADE program, JADE DARE, a randomised, double-blind, double-dummy, active-controlled, parallel-treatment, phase 3 trial was designed to assess the efficacy and safety of abrocitinib versus dupilumab in adults with moderate-to-severe atopic dermatitis who required systemic therapy or had inadequate response to topical medications.[27] The fifth trial in the program, the JADE REGIMEN trial, aimed to evaluate the maintenance of abrocitinib-induced response with continuous abrocitinib treatment, dose reduction or withdrawal, and response to treatment reintroduction following flare.[28] It is this trial that this article will focus on and review.

JADE REGIMEN was a Phase 3 multicenter, responder enriched, double blinded, placebo controlled, randomized withdrawal study with rescue treatment in patients with protocol defined flare. The study had three distinct periods, the first, following a screening visit, was a 12-week, open-label induction

period to determine response to once-daily abrocitinib 200 mg **(Figure 1)**. Only responders from this period, defined as those who achieved IGA 0/1 response [with ≥ 2-grade improvement] and EASI-75 response, moved on to the second period of the trial; a 40-week, double-blinded, randomized maintenance withdrawal period in which responders were randomly assigned in 1:1:1 ratio to receive once-daily monotherapy with abrocitinib 200 mg, abrocitinib 100 mg, or placebo. Randomization was stratified by age (<18 years of age and ≥18 years). While oral antihistamines and topical nonmedicated emollients were permitted throughout the study, no other treatments were permitted during the induction and maintenance periods. Those who did not achieve an IGA of 0/1 with 2 grades of improvement and an EASI 75 response at the end of the initial induction period had the opportunity to either enter a long-term extension safety study or discontinue treatment and enter a 4-week follow-up period.[28]

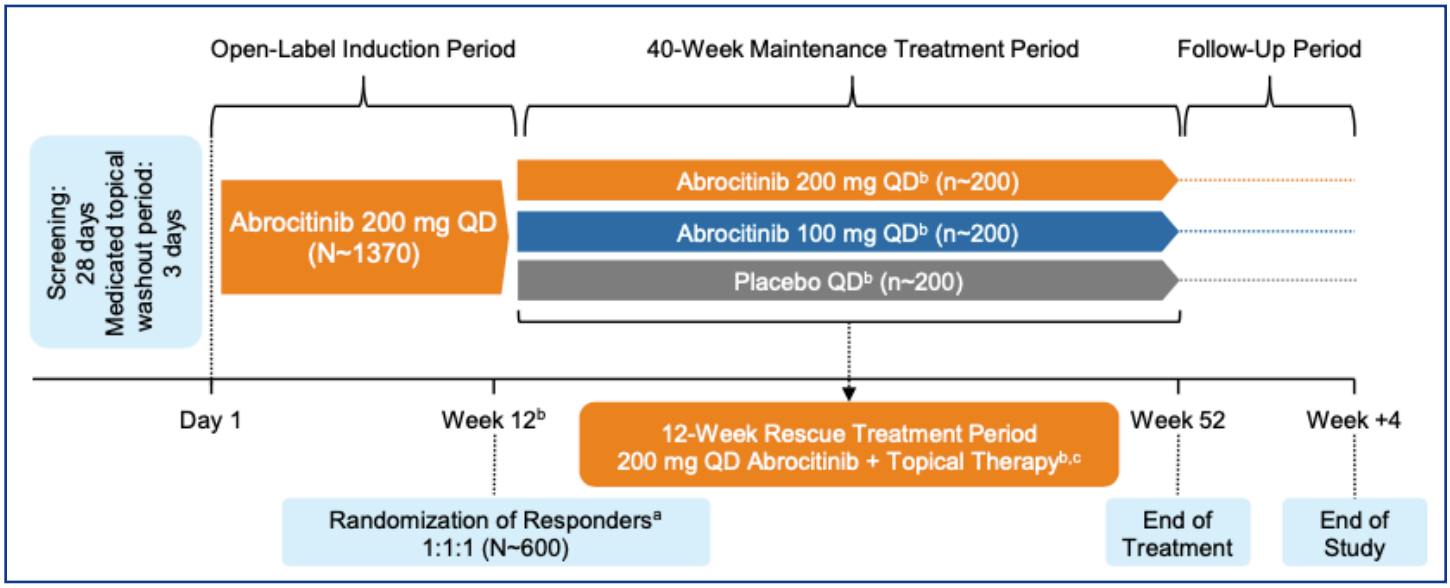
Those that experienced a flare (loss of response) requiring rescue during the maintenance period, entered the third period of the trial, a 12-week open-label rescue period with abrocitinib 200 mg and medicated topical therapy. Flare was defined as both a ≥ 50% loss of initial EASI response at week 12 and a new IGA score ≥ 2. Allowable topical therapies included corticosteroids, calcineurin inhibitors, and crisaborole, used as per the investigator's usual practice. Treatment could be interrupted for ≤ 28 consecutive days, at the investigator's discretion, for safety concerns, including observation of abnormal laboratory tests. **The intent of this study design was to provide a treatment and withdrawal situation that mimicked a real-world scenario, including the use of topicals and increasing systemic therapy dosing in the response to a flare, to provide insight on withdrawal and recapture that could help guide the clinician on the efficacy of intermittent dosing regimens.[28]**

The JADE REGIMEN enrolled patients 12 years of age or older with a body weight of 40 kg or greater, a confirmed diagnosis of AD per Hanifin and Rajka's diagnostic criteria, and moderate-to-severe AD (IGA ≥ 3; EASI ≥ 16; affected percentage of body surface area ≥ 10; and PP-NRS ≥ 4) at baseline. Patients had to have a documented history of inadequate response to topical treatment or systemic treatment of at least four consecutive weeks within the 6 months prior to screening.[28]

Patients with psychiatric conditions or with medical history of conditions associated with thrombocytopenia, coagulopathy, or platelet dysfunction were excluded. Prior dupilumab use was not an exclusion criterion, but all patients were required to wash out any prior AD treatments (e.g., biologic therapies, including dupilumab). Oral antihistamines and topical nonmedicated emollients were permitted throughout the study.[28]

The primary endpoint was the loss of response requiring rescue medication during the maintenance

Figure 1: *JADE REGIMEN Study Design; Gubelin et al, 2021*

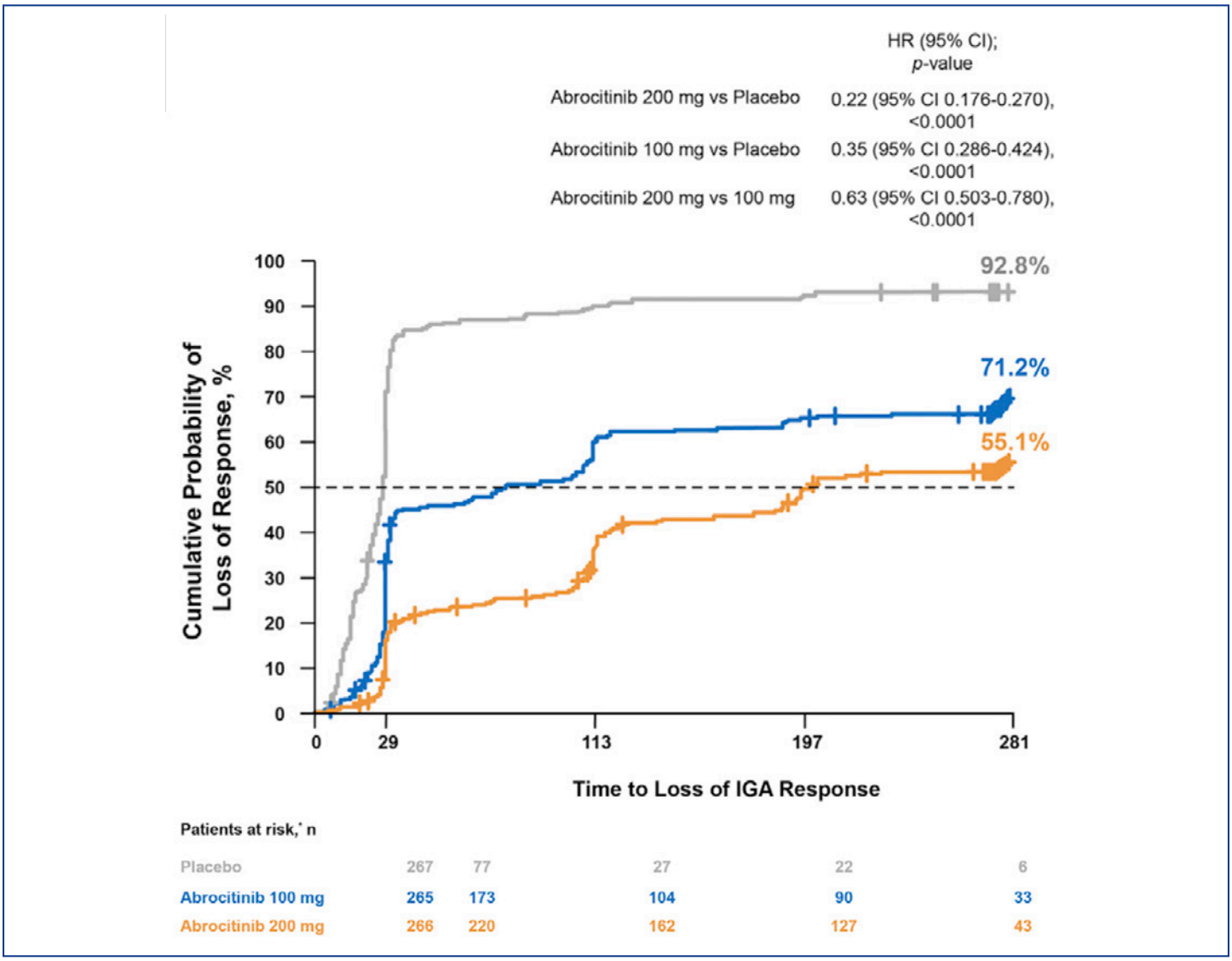


QD, once daily; Q2W, every 2 weeks.
a Responder criteria are defined as achieving an IGA 0/1 (clear [0] or almost clear [1] [on a 5-point scale], with reduction from IGA baseline of ≥2 points) and reaching an EASI-75.
bPatients who experience a flare will receive 12-week rescue treatment with open-label abrocitinib 200 mg QD plus topical therapy.
cDefinition of flare: loss of response associated with decrease of at least 50% in EASI response at week 12 and IGA score ≥2.

period and the key secondary endpoint was loss of IGA 0/1 response during the maintenance period. There were several additional efficacy assessments performed, including the proportion of patients who achieved IGA 0/1 response; ≥ 50%, ≥ 75%, ≥ 90%, and 100% EASI improvements; ≥ 4-point improvement in PP-NRS (PP-NRS-4 response); and change from baseline in SCORing atopic dermatitis subjective assessment of itch and sleep loss at all scheduled timepoints. These secondary efficacy assessments were also assessed during the rescue period. Multiple patient reported outcomes (PROs) were also recorded including quality of life assessments such as the dermatology life quality index (DLQI). Safety outcomes included the incidence of adverse events (AEs), serious AEs, AEs leading to discontinuation, and laboratory abnormalities.[28]

At 12 weeks, following the open-label induction period with abrocitinib 200 mg monotherapy, 64.7% (n=798) of patients met the protocol-defined response (IGA 0/1 and EASI-75), and were randomly assigned into the maintenance period. Of these, 266 patients were randomly assigned to receive abrocitinib 200 mg, 265 to receive abrocitinib 100 mg, and 267 to receive placebo. At the end of maintenance, the cumulative probability of experiencing a flare was 18.9% (95% CI, 14.2-24.9) in the abrocitinib 200 mg, 42.6% (95% CI, 36.3-49.5) in the abrocitinib 100 mg group, and 80.9% (95% CI, 75.8-85.6) in the placebo group. The Kaplan-Meier estimate of median time to protocol defined flare was not reached in either abrocitinib arm, and was 28 days (95% CI, 28-29) in the placebo arm **(Figure 2)**.[28]

Figure 2: *Time to protocol-defined flare; Blauvelt et al, 2021*



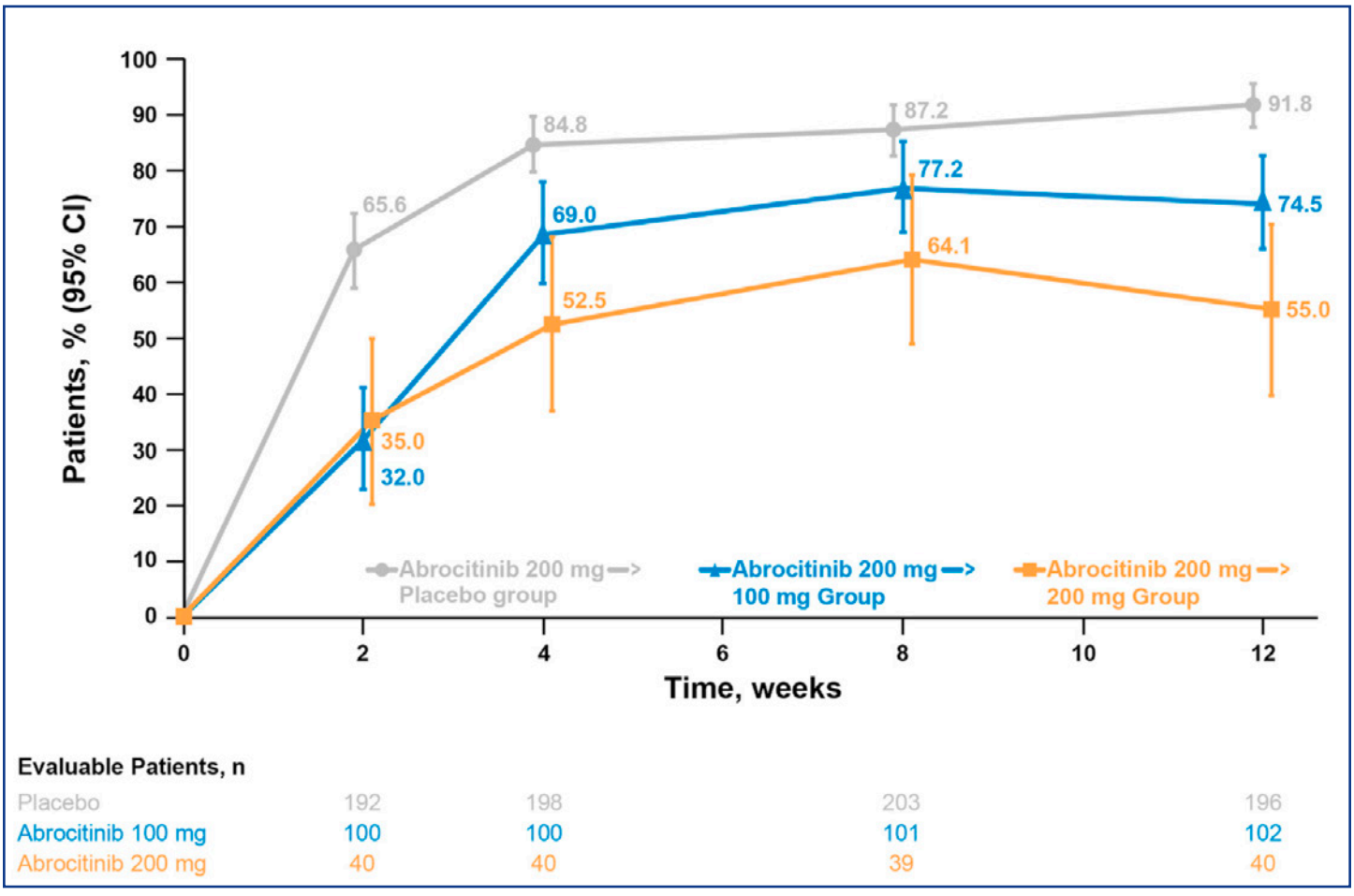
*Per study protocol, flare was defined as a ≥50% loss of initial eczema area and severity index response at week 12 with a new IGA score ≥2. HR, Hazard ratio; IGA, investigator global assessment. *Patients who did not have a flare and were continuing treatment.*

Results from the key secondary endpoint, loss of IGA 0/1 response, demonstrated that a higher proportion of patients in either abrocitinib group maintained IGA 0/1, EASI-75, EASI-90, and PP-NRS-4 responses compared with placebo at weeks 16, 28, 40 and 52.[28]

Regarding the key primary endpoint, the loss of response requiring rescue medication during the maintenance period, the majority of patients in the abrocitinib groups maintained response in contrast to the placebo group. A total of 44% (n = 351) entered the rescue period following disease flare: 43 (16.2%) in the abrocitinib 200 mg group, 104 (39.2%) in the abrocitinib 100 mg group, and 204 (76.4%) from the placebo group. Following rescue with abrocitinib 200 mg and topical corticosteroids, most, but not all patients were able to recapture response. The EASI-75 response recapture rates were 55.0% in the abrocitinib 200 mg, 74.5% in the abrocitinib 100 mg, and 91.8% in the placebo group. It should be noted that those in the abrocitinib 200 mg group are effectively recapturing response based on topical corticosteroids alone, given that they were already receiving the 200 mg dose prior to experiencing a flare **(Figure 3)**. As response was recaptured in over 50% of patients in the abrocitinib 200 mg group it may suggest that these patients were close to achieving EASI-75 when assessed. Increasing the dose of systemic therapy and using topical corticosteroid therapy simulates a real-world clinical experience. However, despite receiving standard rescue medication, there are some patients who do not recapture response, suggesting that continuous abrocitinib 200 mg monotherapy is the most effective option for maintaining disease control. However, given that approximately 60% of patients receiving the 100 mg abrocitinib dose did not relapse on the reduced dose for at least 40 weeks, and that 74.5% that flared were able to recapture response with dose escalation, an induction-maintenance approach might be a worthwhile strategy to consider in some patients.[28]

Patient-reported outcome measures improved in a dose response manner among abrocitinib treated patients who did not experience a protocol-defined flare, including the SCORing atopic dermatitis sleep subscale, patient-oriented eczema measure, and pruritus and symptoms assessment in atopic dermatitis.[28]

Figure 3: *Proportion of patients who recaptured ≥75% improvement in eczema area and severity index response during the rescue period; Blauvelt et al, 2021*



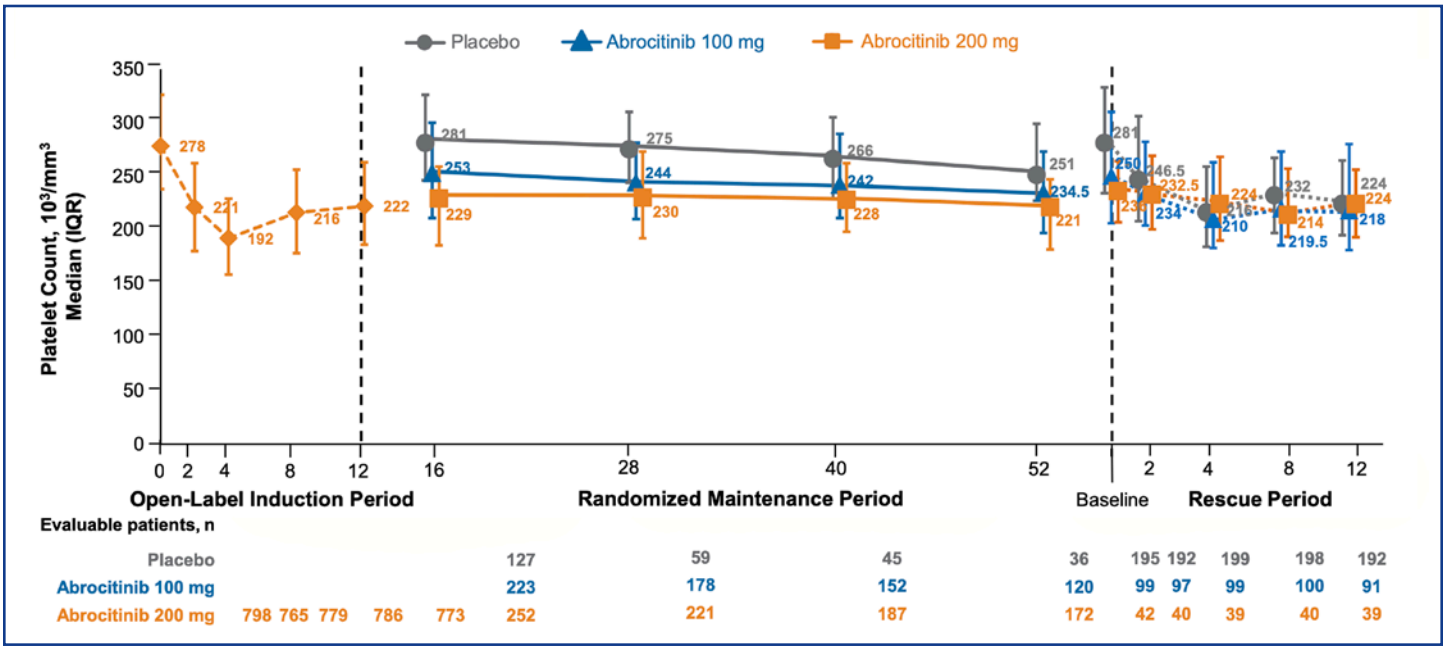
As patients had variable exposures to abrocitinib, adverse events were reported as incidence rates (patients per one hundred patient years). No new safety signals were observed in the trial. Treatment emergent adverse events (TEAEs) reported in > 2% were higher during the induction period than either the maintenance or rescue periods in the abrocitinib 200 mg group **(Table 1)**. Adverse events were dose dependent with fewer TEAEs reported in the abrocitinib 100 mg maintenance group versus the abrocitinib 200 mg maintenance group. Treatment discontinuation due to an AE was highest in the abrocitinib 200 mg group at 6.0% whereas the rates of discontinuation were similar in the abrocitinib 100 mg (1.9%) and placebo (1.5%) groups. There was one nonfatal case of retinal vein thrombosis leading to discontinuation in the abrocitinib 100 mg group during the maintenance period.[28]

In keeping with previous data, abrocitinib-treated patients demonstrated dose-related decreases in median platelet count.[23,24,28,29] Platelet levels dropped to their lowest level at week 4, returning to baseline levels and stabilizing throughout the maintenance and rescue periods. Importantly, no patients discontinued therapy due to reductions in platelet count. No clinically significant changes in hemoglobin, neutrophil, or lymphocytes counts were observed **(Figure 4)**.[28] These results are supported by those in the integrated safety analysis of the Phase II and Phase III clinical trial program.[22,28]

Table 1: *Incidence rates for treatment-emergent adverse events; Gubelin et al, 2021*

	Randomized Maintenance Period		
IR (95% CI)	**Placebo N=267**	**Abrocitinib 100 mg N=265**	**Abrocitinib 200 mg N=266**
IRs for TEAEs occurring in ≥2% of subjects (SAF-RA)	163.18 (130.70, 201.29)	51.44 (39.86, 65.32)	63.10 (50.87, 77.38)
Serious AEs excluding events of AD	3.18 (0.39, 11.49)	2.69 (0.73, 6.88)	7.77 (4.25, 13.04)
Discontinuations because of AEs	6.38 (1.74, 16.34)	3.36 (1.09, 7.85)	8.76 (5.01, 14.23)
TEAEs with IR ≥4 (excluding AD)			
Nausea	1.61 (0.04, 8.95)	1.35 (0.16, 4.87)	4.43 (1.91, 8.72)
Bronchitis	4.78 (0.99, 13.97)	2.03 (0.42, 5.92)	0.54 (0.01, 3.03)
Conjunctivitis	4.84 (1.00, 14.14)	2.02 (0.42, 5.91)	1.09 (0.13, 3.92)
Herpes zoster	1.59 (0.04, 8.84)	1.34 (0.16, 4.85)	4.40 (1.90, 8.67)
Nasopharyngitis	8.01 (2.60, 18.70)	6.98 (3.35, 12.84)	10.17 (6.03, 16.07)
Upper respiratory tract infection	9.80 (3.60, 21.34)	5.48 (2.37, 10.80)	4.42 (1.91, 8.71)
Blood creatine phosphokinase increased	1.59 (0.04, 8.84)	4.08 (1.50, 8.89)	7.85 (4.29, 13.18)
Asthma	4.77 (0.98, 13.95)	0.67 (0.02, 3.74)	2.19 (0.60, 5.60)
Acne	0.00 (0.00, 5.85)	3.42 (1.11, 7.97)	4.43 (1.91, 8.73)
Pruritus	6.44 (1.76, 16.49)	2.72 (0.74, 6.97)	1.64 (0.34, 4.78)

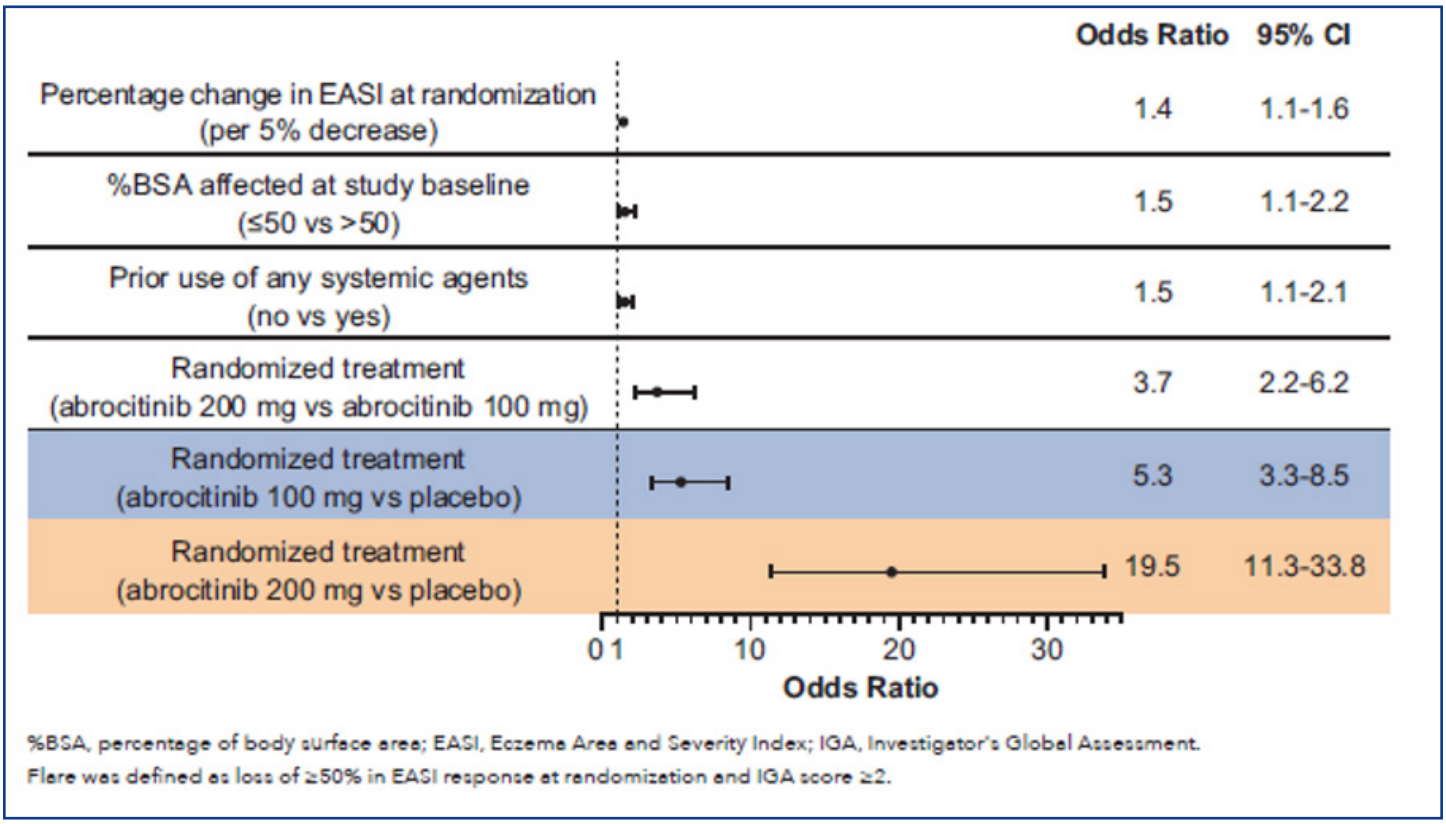
Figure 4: *Summary of Clinical Laboratory Evaluations Throughout the Study; Gubelin et al, 2021*



A post hoc analysis of the JADE REGIMEN data using a multivariable logistic regression model identified maintaining abrocitinib treatment as the primary factor associated with reducing the risk of experiencing a flare. Additional factors included the percentage change in EASI at randomization, the % BSA affected at baseline, and prior use of a systemic agent **(Figure 5)**.[30]

JADE REGIMEN presents a unique opportunity to provide clinical trial data to assess the potential performance of abrocitinib in the treatment of moderate-to-severe AD in a simulated real-world scenario. The majority of patients, 64.7%, responded, achieving IGA 0/1 and EASI-75, during the initial 12-week induction period with abrocitinib 200 mg once daily monotherapy. Notably, most of those who continued maintenance treatment with either dose of abrocitinib maintained their response over the 40-week maintenance period (83.8% in the abrocitinib 200 mg group and 60.8% in the abrocitinib 100 mg group), supporting the use of abrocitinib monotherapy in the treatment of moderate-to-severe AD. While abrocitinib 200 mg was the most effective option for maintaining disease control throught the entire study, an induction-maintenance approach with abrocitinib 200 mg followed by 100 mg may be a viable strategy in some patients, given that 60.8% of patients that dose reduced to receive abrocitinib 100 mg did not experience flare over the 44-week maintenance period, and 74.5% of those that subsequently flared with this dose reduction were able to recapture a response with dose escalation and topical therapy.

Figure 5: *Factors associated with not experiencing a flare; Thyssen JP, et al., 2021*



%BSA, percentage of body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment.
Flare was defined as loss of ≥50% in EASI response at randomization and IGA score ≥2.

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