Supplementary Online Content

Silverberg JI, Simpson EL, Wollenberg A, et al. Long-term efficacy of baricitinib in adults with moderate to severe atopic dermatitis who were treatment responders or partial responders: an extension study. *JAMA Dermatol*. Published online May 12, 2021. doi:10.1001/jamadermatol.2021.1273

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Supplementary Methods

Study Population

Patients were eligible for enrollment in BREEZE-AD3 if they completed the final active treatment visit in BREEZE-AD1 (NCT03334396), BREEZE-AD2 (NCT03334422), or BREEZE-AD7 (NCT03733301). The eligibility criteria and other key details for these originating studies have been previously described.[9,10] Results for patients originating from BREEZE-AD7 are not reported in this manuscript as the 68-week efficacy follow-up data are not yet available.

Treatment Protocol

BREEZE-AD3 comprises a screening and baseline period, treatment period 1, treatment period 2, a substudy, and a post-treatment follow-up period (eFigure 1).

Screening and Baseline Period

The last treatment visit of the originating study was the screening/baseline visit for BREEZE-AD3 (week 16 of continuous therapy); however, if patients were still completing washout from systemic therapies from the originating study, this period could be extended for a maximum of 8 weeks.

Treatment Period 1 (BREEZE-AD3 Weeks 0-52 [Weeks 16-68 of Continuous Therapy])

Responders and partial responders receiving placebo or baricitinib, 1 mg, 2 mg, or 4 mg at completion of the originating study remained on their assigned treatment. If a patient who received placebo or baricitinib, 1 mg, worsened during BREEZE-AD3 to a validated Investigator Global Assessment for AD (vIGA-AD) score ≥3 (moderate disease) during treatment period 1, they were provided TCS if not currently receiving and rerandomized in a blinded fashion 1:1 to baricitinib, 4 mg or 2 mg. Patients receiving baricitinib, 4 mg or 2 mg at the start of BREEZE-AD3 were not eligible for dose increases.

Treatment Period 2 (BREEZE-AD3 Weeks 52-104 [Weeks 68-120 of Continuous Therapy])

At BREEZE-AD3 week 52 (week 68 of continuous therapy), all patients were assessed for eligibility for a randomized withdrawal and downtitration substudy. Patients with vIGA-AD (0,1,2) at week 52 who were assigned baricitinib, 4 mg or 2 mg, at the start of BREEZE-AD3, who were not on a study treatment interruption, and had not used high-potency TCS for the last 14 days were eligible for enrollment in the substudy. Patients receiving baricitinib, 4 mg, were rerandomized 1:1:1 to placebo or baricitinib, 2 mg or 4 mg. Patients receiving baricitinib, 2 mg, were rerandomized 1:1:1 to placebo or baricitinib, 1 mg or 2 mg. Patients enrolled in the substudy were automatically retreated with their original baricitinib dose if their vIGA-AD score became ≥3.

Patients not eligible for the randomized withdrawal and downtitration substudy continued on their assigned treatment.

Post-treatment Follow-up Period

A post-treatment follow-up visit was carried out approximately 28 days after the last dose of investigational product, either at the end of the study or after early termination.

Baricitinib, 2 mg, Open-Label Addendum

An addendum to the study protocol allowed patients to directly enter BREEZE-AD3 without completing an originating study. All patients enrolled under the addendum received open-label baricitinib, 2 mg, for 52 weeks. At week 52, patients meeting the eligibility criteria could participate in the randomized withdrawal and downtitration substudy; otherwise, they continued to be treated with open-label baricitinib, 2 mg.

Randomization and Blinding

Randomization was carried out via a computer-generated random sequence using an interactive web-response system (IWRS). Patients randomized on study entry were stratified by disease severity at baseline (vIGA-AD [0,1,2] vs vIGA-AD [3] vs vIGA-AD [4]). Patients rerandomized at week 52 (week 68 of continuous therapy) were stratified by disease severity (vIGA-AD [0,1] vs vIGA-AD [2]).

The IWRS was used to assign blister packs, each containing double-blind investigational product tablets, including identical matching placebo tablets in the randomized withdrawal and downtitration substudy.

eTable 1. End Points Evaluated in Responders and Partial Responders[a]

End point	BREEZE-AD3 week	Week of continuous therapy[b]
Primary		
vIGA-AD (0,1)	Weeks 16, 36, and 52	Weeks 32, 52, and 68
Secondary		
EASI75	Weeks 16, 36, and 52	Weeks 32, 52, and 68
Itch NRS ≥4-point improvement from baseline[c]	Week 16	Week 32
Exploratory		
Skin Pain NRS ≥4-point improvement from baseline[c]	Week 16	Week 32
ADSS item 2 ≥1.5-point improvement from baseline[c]	Week 16	Week 32

Abbreviations: ADSS, Atopic Dermatitis Sleep Scale; EASI75, 75% improvement in Eczema Area and Severity Index; NRS, numeric rating scale; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis.

[a] Responders and partial responders had vIGA-AD (0,1) or (2), respectively, at entry into BREEZE-AD3 and were never rescued during originating study (BREEZE-AD1/BREEZE-AD2).

[b] Includes 16-week treatment period in the originating studies (BREEZE-AD1/BREEZE-AD2).

[c] Baseline of originating study.

eTable 2. Mean Change From Baseline Responses in Patient-Reported Harmonizing Outcome Measures for Eczema (DLQI, POEM) at Weeks 16, 32, and 68 of Continuous Treatment for Patients Who Entered BREEZE-AD3 as Responders or Partial Responders[a]

	BARI, 2 mg (N=54)				BARI, 4 mg (N=70)		
End point	**Week 16[a]**	**Week 32[a]**	**Week 68[a]**		**Week 16[a]**	**Week 32[a]**	**Week 68[a]**
DLQI	–8.0 (6.8)	–6.7 (8.1)	–7.9 (7.9)		–9.6 (6.7)	–7.7 (6.7)	–7.1 (6.7)
POEM	–10.5 (8.4)	–8.4 (8.8)	–9.0 (8.1)		–12.5 (6.8)	–9.3 (7.8)	–8.8 (7.6)

Data are mean change from baseline (SD). Missing data were imputed using LOCF.

Abbreviations: BARI, baricitinib; DLQI, Dermatology Life Quality Index; LOCF, last observation carried forward; POEM, Patient Oriented Eczema Measure; SD, standard deviation; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis.

[a] Responders and partial responders had vIGA-AD (0,1) or (2), respectively, at entry into BREEZE-AD3 and were never rescued during originating study (BREEZE-AD1/BREEZE-AD2).

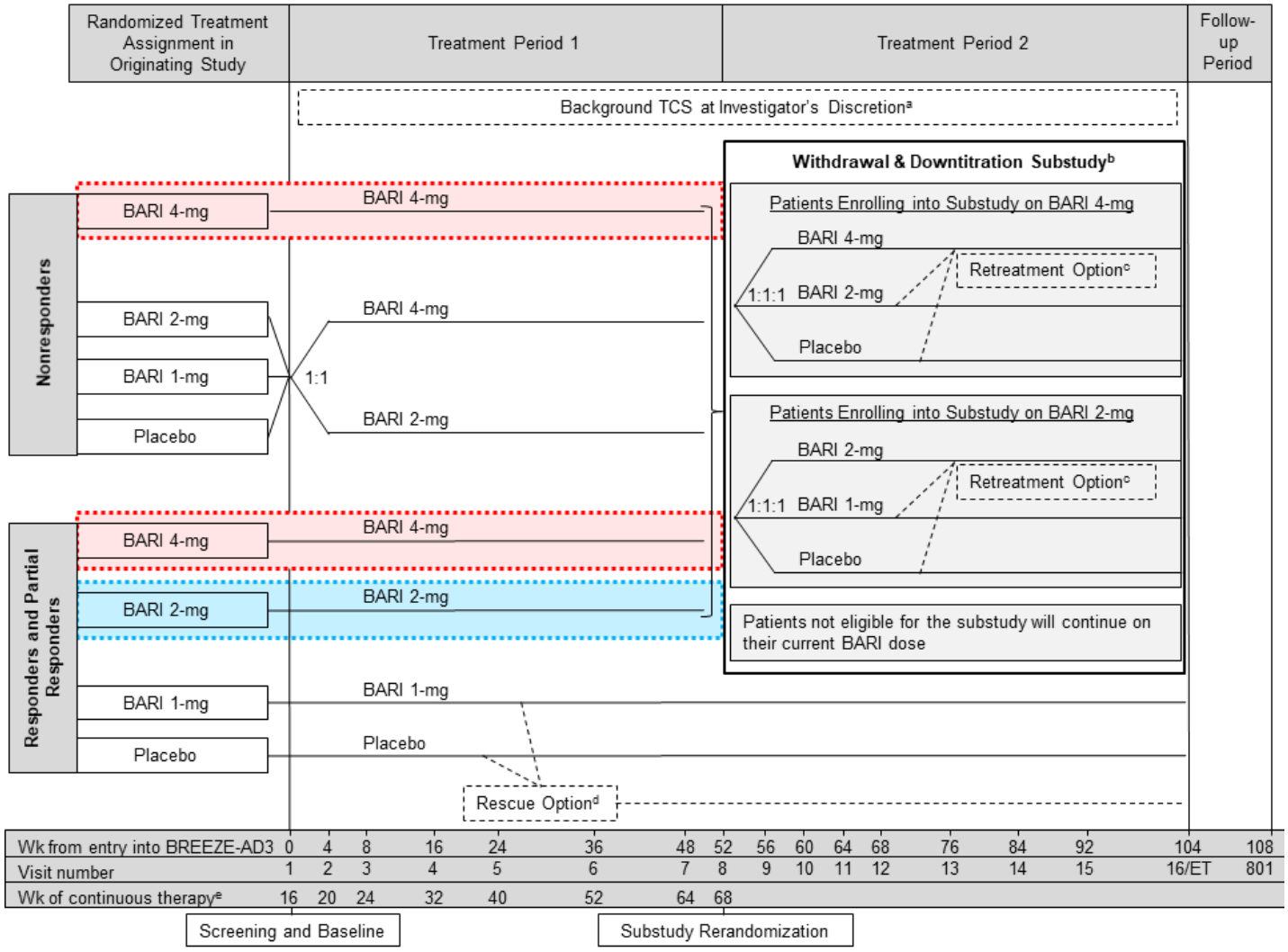
[b] Data for the modified intention-to-treat population are shown as weeks of continuous therapy, which includes the 16-week treatment period in the originating studies.

eTable 3. Topical Corticosteroid Use During the 52-Week Treatment Period of BREEZE-AD3 for Patients Who Entered BREEZE-AD3 as Responders or Partial Responders[a]

Topical corticosteroid	BARI, 2 mg (N=54)	BARI, 4 mg (N=70)
Low and moderate potency use		
n (%)	22 (41)	37 (53)
Low potency[b]		
Mean, g	14	15
Median, g	0	0
IQR, g	0-0	0-5
Moderate potency[c]		
Mean, g	31	53
Median, g	0	0
IQR, g	0-33	0-48

Abbreviations: IQR, interquartile range; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis.
[a] Responders and partial responders had vIGA-AD (0,1) or (2), respectively, at entry into BREEZE-AD3 and were never rescued during originating study (BREEZE-AD1/BREEZE-AD2).
[b] Hydrocortisone 2.5% ointment.
[c] Triamcinolone 0.1% cream.

eFigure. BREEZE-AD3 Study Design



Red and blue shading indicates data that are reported in this manuscript; responders and partial responders were patients who had a vIGA-AD (0,1) or (2) and were never rescued during the originating study (BREEZE-AD1/BREEZE-AD2); all patients who received continuous baricitinib, 4 mg, through BREEZE-AD1/BREEZE-AD2 and BREEZE AD3.
Abbreviations: BARI, baricitinib; ET, early termination; TCS, topical corticosteroids; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis; Wk, week.
[a] Background TCS may have been initiated or reinitiated at any time during the study and were to be provided as part of rescue or re-treatment any time a patient's vIGA-AD score became ≥3.
[b] Eligible patients were rerandomized in the withdrawal and downtitration substudy. Patients who did not enroll in the substudy remained on their assigned treatment.
[c] Patients enrolled in the substudy were automatically re-treated if their vIGA-AD score became ≥3.
[d] Rescue to baricitinib, 4 mg or 2 mg, was available if their vIGA-AD score became ≥3.
[e] Applicable for patients who received the same treatment in the originating study (BREEZE-AD1/BREEZE-AD2) through BREEZE-AD3.

