Article Type: Original article

Title: AD-REAL: A prospective, multinational, observational cohort study of clinical effectiveness and treatment discontinuation of oral systemics for moderate-to-severe atopic dermatitis

Authors:

Matthias Augustin[1], Andreas Pinter[2], Silvia Sabatino[7], Louis P. Sanden[7], Pablo Chicharro[3], Esther Serra-Baldrich[4], Mahreen Ameen[5], Anthony Bewley[6], Walid Fakhouri[7], Inmaculada de la Torre[7], Julien Seneschal[8]

[1]Institute for Health Services Research in Dermatology and Nursing (IVDP), University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany.

[2]Department for Dermatology, Venereology and Allergology, University Hospital Frankfurt, Frankfurt am Main, Germany.

[3]Hospital Universitario de la Princesa, Madrid, Madrid, Spain

[4]Department of Dermatology, Cutaneous Allergy Unit, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain.

[5]Department of Dermatology, Royal Free London NHS Foundation Trust, London, UK

[6]Department of Dermatology, Barts Health NHS Trust & Queen Mary University of London, London, UK.

[7]Eli Lilly and Company, Indianapolis, Indiana, USA.

[8]CHU de Bordeaux, Dermatology and Pediatric Dermatology, National Reference Center for Rare Skin Disorders, Hôpital Saint-André, UMR 5164, F-33000 Bordeaux, France.

Corresponding author:

Julien Seneschal

CHU de Bordeaux, Dermatology and Pediatric Dermatology, National Reference Center for Rare Skin Disorders, Hôpital Saint-André, UMR 5164, F-33000 Bordeaux, France.

Email address: julien.seneschal@chu-bordeaux.fr
Phone number: +33 (0)5 56 79 47 05

Supplementary Table 1: Patient demographics at baseline for all treatment cohorts

Baseline characteristics	Baricitinib (N=87)	Conventional systemics (N=113)	Other JAKi (N=92)[a]	Abrocitinib (N=33)	Upadacitinib (N=59)	Systemic corticosteroids (N=12)	Others (N=9)
Countries, n (%)							
France	17 (19.5)	34 (30.1)	20 (21.7)	7 (21.2)	13 (22.0)	0 (0.0)	0 (0.0)
Germany	37 (42.5)	2 (1.8)	39 (42.4)	20 (60.6)	19 (32.2)	0 (0.0)	1 (11.1)
Spain	12 (13.8)	33 (29.2)	18 (19.6)	5 (15.2)	13 (22.0)	6 (50.0)	4 (44.4)
UK	21 (24.1)	44 (38.9)	15 (16.3)	1 (3.0)	14 (23.7)	6 (50.0)	4 (44.4)
Disease characteristics at baseline, n (%)							
Systemic treatment experienced	61 (70.1)	35 (31.0)	73 (79.3)	23 (69.7)	50 (84.7)	7 (58.3)	7 (77.8)
Failure of previous systemic therapy	39 (44.8)	12 (10.6)	44 (47.8)	14 (42.4)	30 (50.8)	3 (25.0)	2 (22.2)
Use of topical steroids							
Monotherapy	36 (41.4)	53 (46.9)	42 (45.7)	17 (51.5)	25 (42.4)	5 (41.7)	3 (33.3)
Concomitant use of topical steroids	51 (58.6)	60 (53.1)	50 (54.3)	16 (48.5)	34 (57.6)	7 (58.3)	6 (66.7)

JAKi = Janus-kinase inhibitor; N = Total population; n= number of patients in each cohort; % = percentage of patients in the category

[a]Other JAKi includes abrocitinib and upadacitinib.

Supplementary Table 2: Overall patient population discontinuation at Week 24 for all treatments

Discontinuation up to Week 24[a]	Baricitinib (N=87)	Conventional systemics (N=113)	Other JAKi (N=92)[b]	Abrocitinib (N=33)	Upadacitinib (N=59)	Systemic corticosteroids (N=12)	Others (N=9)
Kaplan-Meier cumulative incidence of initial treatment discontinuation, % (95% CI)[c]	29.0 (19.8, 38.8)	50.8 (40.9, 59.8)	18.8 (11.5, 27.5)	30.3 (15.6, 46.4)	12.2 (5.3, 22.1)	91.7 (32.6, 99.3)	55.6 (17.5, 82.0)
Patients with initial treatment discontinued, n (%)[d]	25 (28.7)	55 (48.7)	17 (18.5)	10 (30.3)	7 (11.9)	11 (91.7)	5 (55.6)
Primary lack of effectiveness	7 (8.0)	4 (3.5)	6 (6.5)	3 (9.1)	3 (5.1)	0 (0.0)	0 (0.0)
Secondary loss of effectiveness	5 (5.7)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events	3 (3.4)	13 (11.5)	1 (1.1)	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lack of compliance	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patient/physician decision[e]	5 (5.7)	9 (8.0)	4 (4.3)	2 (6.1)	2 (3.4)	8 (66.7)	4 (44.4)
AD remission	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment interruption ≥30 days[f]	2 (2.3)	2 (1.8)	3 (3.3)	2 (6.1)	1 (1.7)	2 (16.7)	1 (11.1)
Data cutoff after interruption[g]	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Addition of a concomitant systemic treatment[h]	2 (2.3)	17 (15.0)	1 (1.1)	0 (0.0)	1 (1.7)	1 (8.3)	0 (0.0)
Other	1 (1.1)	5 (4.4)	2 (2.2)	2 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)

AD = atopic dermatitis; CI = confidence interval; CRF = case report form; JAKi = Janus-kinase inhibitor; N = Total population in each cohort, n (%) = number (percentage) of patients in the category

[a]Baseline visit date is designated as study Day 1. Week 24 corresponds to Day 169.
[b]Other JAKi include abrocitinib and upadacitinib.
[c]Confidence intervals are estimated by Kaplan-Meier method.
[d]Sustained clinical response will be considered as a cause of treatment discontinuation in this analysis.

[e]In accordance to CRF guidance, the use of "patient/physician decision" was selected when none of the other selections were applicable: a position, opinion, or judgment reached after consideration by a physician with reference to the patient.
[f]Treatment interruption included initiation, stopping, and re-initiation of the same systemic treatment.
[g]Cut-off was based on clinical protocols from phase 3 trials of systemic treatments in AD, which excluded patients exposed to systemic immunosuppressive/immunomodulating drugs within 4 weeks prior to baseline, consistent with treatment discontinuation [20,34].
[h]Patients were considered as non-responders from the point in time concomitant systemic treatment commenced and were censored.

45 **Supplementary Table 3: EASI outcomes for all treatment cohorts at Week 24 from baseline**

EASI Score	Baricitinib (N=87)	Conventional systemics (N=113)	Other JAKi (N=92)[a]	Abrocitinib (N=33)	Upadacitinib (N=59)	Systemic corticosteroids (N=12)	Other (N=9)
EASI total score[a]							
Baseline, n	80	98	83	28	55	11	8
Mean (SD)	15.8 (10.6)	19.8 (10.8)	16.4 (9.2)	14.2 (7.1)	17.5 (10.0)	19.5 (14.9)	19.7 (10.6)
Week 24, n	68	74	70	27	43	9	6
Mean (SD)	5.2 (6.1)	10.1 (11.0)	5.3 (8.7)	6.1 (9.6)	4.8 (8.2)	20.3 (16.0)	17.8 (12.3)
EASI 75 [b]							
Week 24, n	68	74	66	25	41	9	7
n (%)[c]	28 (41.2)	17 (23.0)	41 (62.1)	14 (56.0)	27 (65.9)	0 (0.0)	1 (14.3)
EASI ≤7[a]							
Baseline							
Overall[d], nx	64	84	64	22	42	11	6
n (%)[e]	14 (21.9)	11 (13.1)	11 (17.2)	3 (13.6)	8 (19.0)	3 (27.3)	1 (16.7)
BSA and Itch NRS subgroups[f]							
BSA ≤ 40% and Itch NRS ≥7, nx	30	23	27	12	15	4	2
n (%)	6 (20.0)	4 (17.4)	4 (14.8)	1 (8.3)	3 (20.0)	2 (50.0)	1 (50.0)
BSA ≤ 40% and Itch NRS <7, nx	27	25	19	5	14	4	0
n (%)	8 (29.6)	6 (24.0)	7 (36.8)	2 (40.0)	5 (35.7)	1 (25.0)	0 0 (0.0)
BSA > 40% and Itch NRS ≥7, nx	4	22	0	0	0	0	0
n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
BSA > 40% and Itch NRS <7, nx	3	14	0	0	0	0	0
n (%)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Week 24							
Overall, nx	58	65	57	23	34	9	4
n (%)[c]	47 (81.0)	41 (63.1)	48 (84.2)	18 (78.3)	30 (88.2)	3 (33.3)	2 (50.0)

BSA and Itch NRS subgroups							
BSA ≤ 40% and Itch NRS ≥7, nx	25	19	25	12	13	4	0
n (%)	20 (80.0)	15 (78.9)	21 (84.0)	10 (83.3)	11 (84.6)	2 (50.0)	0 (0.0)
BSA ≤ 40% and Itch NRS <7, nx	25	16	16	5	11	4	1
n (%)	20 (80.0)	10 (62.5)	15 (93.8)	4 (80.0)	11 (100.0)	1 (25.0)	1 (100.0)
BSA > 40% and Itch NRS ≥7, nx	4	18	11	5	6	0	2
n (%)	3 (75.0)	12 (66.7)	7 (63.6)	3 (60.0)	4 (66.7)	0 (0.0)	1 (50.0)
BSA > 40% and Itch NRS <7, nx	4	12	5	1	4	0	0
n (%)	4 (100.0)	4 (33.3)	5 (100.0)	1 (100.0)	4 (100.0)	0 (0.0)	0 (0.0)

BSA = body surface area; EASI = Eczema area and Severity Index; JAKi = Janus kinase inhibitor; LOCF = last observation carried forward; N = Total population; n= number of patients in each cohort; nx = number of patients with this outcome at baseline; NRI = non-responder imputation; NRS = numerical rating scale; % = percentage of patients

[a]Missing data was imputed using LOCF for Week 24 outcomes.

[b]Missing data was imputed using NRI for Week 24 outcomes.

[c]The percentage of patients at Week 24 is calculated as the number of patients with a response and available outcome data at Week 24.

[d]Overall nx includes patients with evaluable EASI data regardless of available BSA or itch NRS data. Patients with missing BSA and itch NRS were included.

[e]The percentage of patients at baseline is based on the number of patients with a response and available outcome data at baseline.

[f]Subgroup nx is restricted to patients with evaluable EASI, BSA, and itch NRS data. Patients with missing BSA or itch NRS data were excluded from the subgroup.

Supplementary Table 4: Patient-reported outcomes for all treatment cohorts at baseline and Week 24

Baseline characteristics and outcome measures	Baricitinib (N=87)	Conventional systemics (N=113)	Other JAKi (N=92)[a]	Abrocitinib (N=33)	Upadacitinib (N=59)	Systemic corticosteroids (N=12)	Others (N=9)
Itch NRS							
Patients with baseline Itch NRS ≥ 4, n (%)[b]	59 (80.8)	81 (87.1)	63 (85.1)	25 (92.6)	38 (80.9)	11 (91.7)	7 (100.0)
Patients with available itch NRS at Week 24[c], n	50	56	39	19	20	9	6
Itch NRS ≥ 4-point improvement, n (%)[d]	21 (42.0)	8 (14.3)	15 (38.5)	7 (36.8)	8 (40.0)	0 (0.0)	1 (16.7)
Pain NRS							
Patients with baseline Pain NRS ≥ 4, n (%)[b]	53 (60.9)	67 (59.3)	52 (56.5)	22 (66.7)	30 (50.8)	9 (75.0)	7 (77.8)
Patients with available Pain NRS at at Week 24[c], n	42	48	34	16	18	7	6
Pain NRS ≥ 4-point improvement, n (%)[d]	16 (38.1)	8 (16.7)	13 (38.2)	6 (37.5)	7 (38.9)	0 (0.0)	2 (33.3)

Janus-kinase inhibitor; N = Total population; n= number of patients in each cohort; NRI =non-responder imputation; NRS = numerical rating scale; % = percentage

[a]Other JAKi includes abrocitinib and upadacitinib.
[b]The percentage of patients at baseline is calculated as the number of patients with a response and available outcome data at baseline.
[c]Missing data were imputed using NRI.
[d]The percentage of patients at Week 24 is calculated as the number of patients with a response and available outcome data at Week 24.