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APREMILAST LONG-TERM SAFETY UP TO 5 YEARS FROM 15 POOLED RANDOMIZED, PLACEBO-CONTROLLED STUDIES OF PSORIASIS, PSORIATIC ARTHRITIS, AND BEHÇET'S SYNDROME

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Online Resource 1. Summary of Study Designs

Study and Trial Dates	Clinical Trial Registration	Study Design	Study Drugs	Treatment Duration	Main Eligibility Criteria	Sample Size
PSOR-005 [1] Start: September 1, 2008 Completion: May 20, 2015	NCT00773734	Phase 2b, multicenter, randomized (1:1:1:1), double-blind, placebo-controlled study	APR 10 mg BID, APR 20 mg BID, APR 30 mg BID, or PBO	PBO-controlled: Weeks 0 to 16 APR extension: Weeks 16 to 24	Adults (≥18 years) with moderate to severe chronic plaque psoriasis	APR 30 mg BID, n=88 PBO, n=88
ESTEEM 1 [2] Start: September 9, 2010 Completion: November 22, 2016	NCT01194219 EudraCT: 2010-019991-55	Phase 3, multicenter, randomized (2:1), double-blind, placebo-controlled study	APR 30 mg BID or PBO	PBO-controlled: Weeks 0 to 16 APR extension: Weeks 16 to 32 Randomized withdrawal phase: Weeks 32 to 52 Long-term extension	Adults (≥18 years) with moderate to severe chronic plaque psoriasis	APR 30 mg BID, n=562 PBO, n=282

				phase: Weeks 52 to 260		
ESTEEM 2 [3] Start: November 22, 2010 Completion: November 30, 2016	NCT01232283 EudraCT: 2010-019992-30	Phase 3, multicenter, randomized (2:1), double-blind, placebo-controlled study	APR 30 mg BID or PBO	PBO-controlled: Weeks 0 to 16 APR extension: Weeks 16 – 32 Randomized withdrawal phase: Weeks 32 to 52 Long-term extension phase: Weeks 52 to 260	Adults (≥18 years) with moderate to severe chronic plaque psoriasis	APR 30 mg BID, n=274 PBO, n=137
LIBERATE [4] Start: October 1, 2012 Completion: April 4, 2016	NCT01690299 EudraCT: 2012-000859-14	Phase 3b, multicenter, randomized (1:1:1), placebo-controlled, double-blind, double-dummy study with 2	APR 30 mg BID, etanercept 50 mg SC QW, or PBO	PBO-controlled: Weeks 0 to 16 APR extension: Weeks 16 to 104	Adults (≥18 years) with moderate to severe chronic plaque psoriasis	APR 30 mg BID, n=83 PBO, n=84

		active-treatment groups				
PSOR-011 [5] Start: July 9, 2013 Completion: December 15, 2015	NCT01988103	Phase 2b, multicenter, randomized (1:1:1), double-blind, placebo-controlled study with 2 active-treatment groups	APR 30 mg BID, APR 20 mg BID, or PBO	PBO-controlled: Weeks 0 to 16 APR extension: Weeks 16 to 68	Japanese adults with moderate to severe chronic, stable plaque psoriasis	APR 30 mg BID, n=85 PBO, n=84
UNVEIL [6] Start: April 20, 2015 Completion: November 22, 2016	NCT02425826	Phase 4, multicenter, randomized (2:1), placebo-controlled, double-blind study	APR 30 mg BID or PBO	PBO-controlled: Weeks 0 to 16 APR extension: Weeks 16 to 52	Adults (≥18 years) with moderate chronic plaque psoriasis	APR 30 mg BID, n=148 PBO, n=73
ADVANCE[a] [7] Start: March 11, 2019 Completion: July 24, 2020	NCT03721172	Phase 3, multicenter, randomized (1:1), placebo-controlled,	APR 30 mg BID or PBO	PBO-controlled: Weeks 0 to 16 APR extension:	Adults (≥18 years) with mild to moderate chronic plaque psoriasis	APR 30 mg BID, n=297 PBO, n=298

		double-blind study		Weeks 16 to 32		
STYLE [8] Start: May 16, 2017 Completion: January 9, 2019	NCT03123471	Phase 3, multicenter, randomized (2:1), placebo-controlled, double-blind study	APR 30 mg BID or PBO	PBO-controlled: Weeks 0 to 16 APR extension: Weeks 16 to 32	Adults (≥18 years) with moderate to severe plaque psoriasis and moderate to severe plaque psoriasis of the scalp	APR 30 mg BID, n=201 PBO, n=102
PALACE 1 [9] Start: June 2, 2010 Completion: October 27, 2016	NCT01172938 EudraCT: 2010-018385-23	Phase 3, randomized (1:1:1) double-blind, placebo-controlled, parallel-group study with 2 active-treatment groups.	APR 20 mg BID, APR 30 mg BID, or PBO	PBO-controlled: Weeks 0 to 24 APR extension: Weeks 24 to 260	Adults (≥18 years) with psoriatic arthritis inadequately controlled by DMARDs	APR 30 mg BID, n=168 PBO, n=168
PALACE 2 [10] Start: September 27, 2010 Completion: January 25, 2017	NCT01212757 EudraCT: 2010-018386-32	Phase 3, randomized (1:1:1), double-blind, placebo-controlled, parallel-group study with 2 active-	APR 20 mg BID, APR 30 mg BID, or PBO	PBO-controlled: Weeks 0 to 24 APR extension: Weeks 24 to 260	Adults (≥18 years) with psoriatic arthritis inadequately controlled by DMARDs	APR 30 mg BID, n=162 PBO, n=159

		treatment groups				
PALACE 3 [11] Start: September 30, 2010 Completion: February 9, 2017	NCT01212770 EudraCT: 2010-019941-24	Phase 3, randomized (1:1:1), double-blind, placebo-controlled, parallel-group study with 2 active-treatment groups	APR 20 mg BID, APR 30 mg BID, or PBO	PBO-controlled: Weeks 0 to 24 APR extension: Weeks 24 to 260	Adults (≥18 years) with psoriatic arthritis ≥6 months of duration, who met CASPAR, were inadequately controlled by DMARDs, had ≥1 plaque psoriasis lesion ≥2 cm; stable doses of NSAIDs, narcotics, and/or low-dose oral corticosteroids allowed	APR 30 mg BID, n=167 PBO, n=169
PALACE 4 [12] Start: December 9, 2010 Completion: August 16, 2017	NCT01307423	Phase 3, randomized (1:1:1), double-blind, placebo-controlled, parallel-group study with 2 active-treatment groups	APR 20 mg BID, APR 30 mg BID, or PBO	PBO-controlled: Weeks 0 to 24 APR extension: Weeks 24 to 260	Adults (≥18 years) with psoriatic arthritis ≥3 months of duration, ≥3 swollen joints and ≥3 tender joints, who met CASPAR and had no history of treatment with csDMARDs or biologics	APR 30 mg BID, n=176 PBO, n=176

ACTIVE [13] Start: September 4, 2013 Completion: November 17, 2016	NCT01925768	Phase 3b, multicenter, randomized (1:1), double-blind, placebo-controlled, parallel-group study	APR 30 mg BID or PBO	PBO-controlled: Weeks 0 to 24 APR extension: Weeks 24 to Week 104	Adults (≥18 years) with psoriatic arthritis ≥3 months of duration, ≥3 swollen joints and ≥3 tender joints, who met CASPAR, had CRP ≥0.2 mg/dL, had prior treatment with ≤1 csDMARD, and were biological DMARD-naive; stable doses of NSAIDs, narcotics and low-dose oral corticosteroids allowed	APR 30 mg BID, n=110 PBO, n=109
BCT-001 [14] Start: August 1, 2009 Completion: May 1, 2012	NCT00866359 EudraCT: 2008-002722-11	Phase 2, multicenter, randomized (1:1), double-blind, placebo-controlled, parallel-group study	APR 30 mg BID or PBO	PBO-controlled: Weeks 0 to 12 APR extension: Weeks 12 to 24	Adults (≥18 years) with Behçet's syndrome meeting ISG criteria, ≥1 oral or genital ulcer within 28 days before screening, and ≥2 oral ulcers at time of randomization	APR 30 mg BID, n=55 PBO, n=56

RELIEF[a] [15] Start: December 30, 2014 Completion: July 17, 2020	NCT02307513 EudraCT: 2014-002108-25	Phase 3, multicenter, randomized (1:1), double-blind, placebo-controlled, parallel group study	APR 30 mg BID or PBO	PBO-controlled: Weeks 0 to 12 APR extension: Weeks 12 to 64	Adults (≥18 years) with Behçet's syndrome meeting ISG criteria, ≥2 oral ulcers at screening, and ≥2 oral ulcers at randomization despite at least one previous medication for oral ulcers	APR 30 mg BID, n=104 PBO, n=103

[a]Part of study was conducted during COVID-19 pandemic.

APR, apremilast; BID, twice daily; CASPAR, Classification Criteria for Psoriatic Arthritis; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DMARD, disease-modifying antirheumatic drug; ISG, International Study Group for Behçet's Disease; NSAIDs, nonsteroidal anti-inflammatories; PBO, placebo; QW, once weekly; SC subcutaneous.

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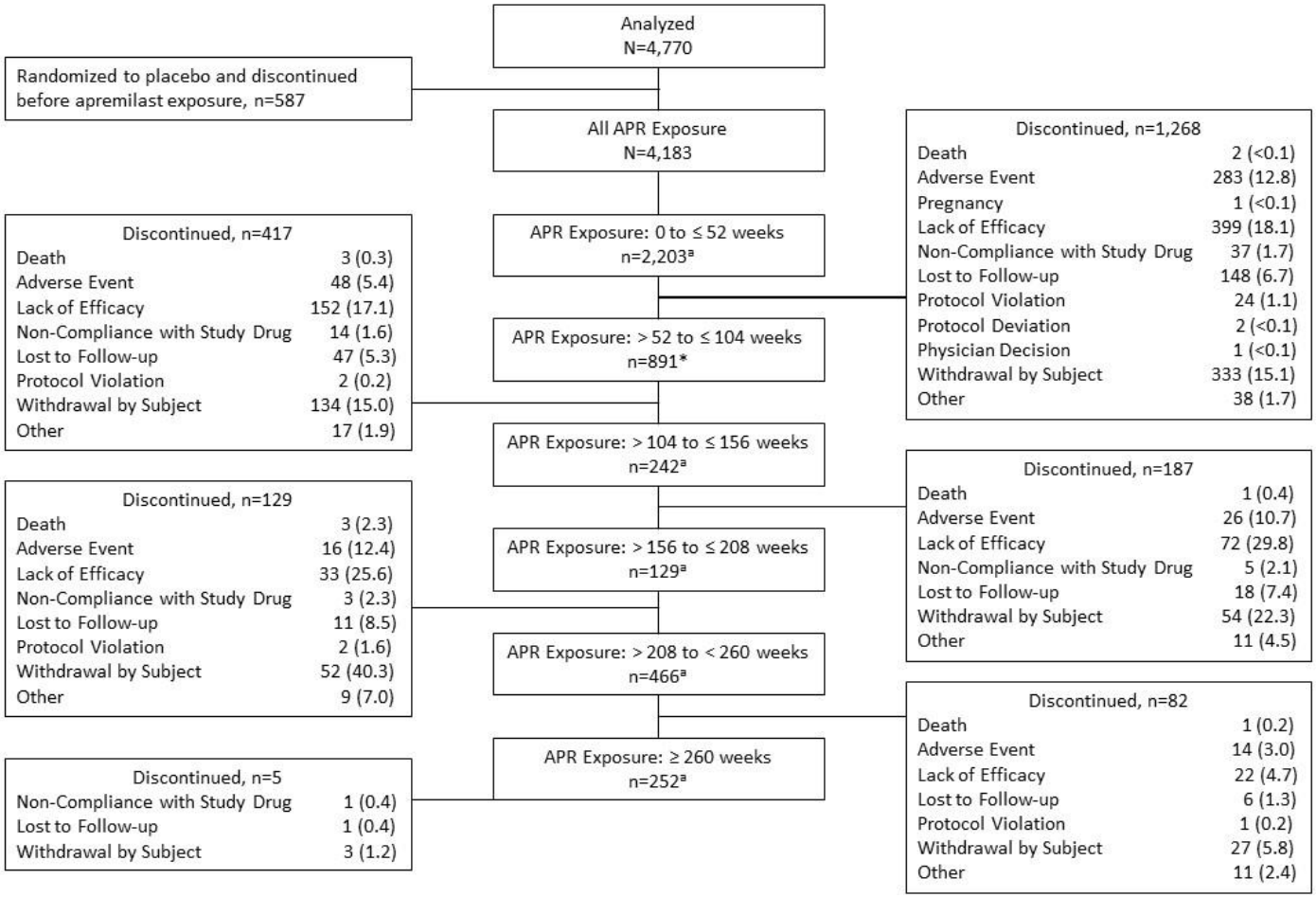
Online Resource 2. Patient Disposition in the Pooled Studies



[a]Number of patients with length of apremilast exposure within specified interval.

APR, apremilast.

Online Resource 3. Medical History by Indication

	Placebo	Apremilast 30 mg BID
Psoriatic Arthritis	**N=780** **n (%)**	**N=781** **n (%)**
Hypertension	315 (40.4)	278 (35.6)
Hypercholesterolemia	90 (11.5)	112 (14.3)
Gastroesophageal reflux disease	81 (10.4)	110 (14.1)
Depression	94 (12.1)	102 (13.1)
Menopause	77 (9.9)	99 (12.7)
Osteoarthritis	96 (12.3)	99 (12.7)
Obesity	88 (11.3)	96 (12.3)
Neoplasms (benign, malignant, unspecified)	98 (12.6)	93 (11.9)
Postmenopause	96 (12.3)	92 (11.8)
Seasonal allergy	60 (7.7)	87 (11.1)
Drug hypersensitivity	79 (10.1)	82 (10.5)
Hysterectomy	62 (7.9)	69 (8.8)
Insomnia	58 (7.4)	65 (8.3)
Hyperlipidemia	74 (9.5)	58 (7.4)
Asthma	46 (5.9)	53 (6.8)
Cholelithiasis	34 (4.4)	53 (6.8)
Cholecystectomy	38 (4.9)	50 (6.4)
Anxiety	37 (4.7)	49 (6.3)
Hypothyroidism	51 (6.5)	48 (6.1)

Diabetes mellitus (type 2)	58 (7.4)	45 (5.8)
Appendicitis	42 (5.4)	42 (5.4)
Spinal osteoarthritis	39 (5.0)	41 (5.2)
Appendicectomy	39 (5.0)	40 (5.1)
Back pain	35 (4.5)	40 (5.1)
Migraine	32 (4.1)	40 (5.1)
Tonsillectomy	45 (5.8)	38 (4.9)
Myocardial infarction	8 (1.0)	9 (1.2)
Cardiac failure congestive	5 (0.6)	3 (0.4)
Angina, unstable	1 (0.1)	1 (0.1)
Cerebrovascular accident	1 (0.1)	1 (0.1)
Psoriasis	**N=1,145** **n (%)**	**N=1,733** **n (%)**
Hypertension	323 (28.2)	527 (30.4)
Seasonal allergy	147 (12.8)	240 (13.8)
Depression	125 (10.9)	224 (12.9)
Gastroesophageal reflux disease	143 (12.5)	202 (11.7)
Hyperlipidemia	133 (11.6)	202 (11.7)
Obesity	124 (10.8)	202 (11.7)
Drug hypersensitivity	129 (11.3)	190 (11.0)
Diabetes mellitus (type 2)	93 (8.1)	159 (9.2)
Hypercholesterolemia	80 (7.0)	157 (9.1)
Neoplasms (benign, malignant, unspecified)	105 (9.2)	156 (9.0)

Asthma	76 (6.6)	145 (8.4)
Osteoarthritis	83 (7.2)	143 (8.3)
Anxiety	76 (6.6)	140 (8.1)
Postmenopause	77 (6.7)	127 (7.3)
Hypothyroidism	63 (5.5)	113 (6.5)
Arthralgia	76 (6.6)	104 (6.0)
Back pain	64 (5.6)	104 (6.0)
Insomnia	76 (6.6)	87 (5.0)
Myocardial infarction	18 (1.6)	39 (2.3)
Cerebrovascular accident	7 (0.6)	10 (0.6)
Cardiac failure congestive	3 (0.3)	3 (0.2)
Angina, unstable	0 (0)	1 (0.1)
Suicidal ideation/attempt	2 (0.2)	1 (0.1)
Behçet's Syndrome	**N=159** **n (%)**	**N=159** **n (%)**
Headache	15 (9.4)	28 (17.6)
Migraine	9 (5.7)	12 (7.5)
Back pain	7 (4.4)	10 (6.3)
Menopause	11 (6.9)	10 (6.3)
Neoplasms (benign, malignant, unspecified)	9 (5.7)	10 (6.3)
Gastroesophageal reflux disease	8 (5.0)	9 (5.7)
Hypertension	16 (10.1)	9 (5.7)
Asthma	17 (10.7)	8 (5.0)

Depression	8 (5.0)	9 (5.7)
Osteoarthritis	7 (4.4)	8 (5.0)
Insomnia	11 (6.9)	7 (4.4)
Hyperlipidemia	6 (3.8)	6 (3.8)
Anxiety	9 (5.7)	5 (3.1)
Fibromyalgia	16 (10.1)	5 (3.1)
Cerebrovascular accident	0 (0)	1 (0.6)
Diabetes mellitus (type 2)	2 (1.3)	1 (0.6)
Acute myocardial infarction	1 (0.6)	0 (0.0)
Obesity	1 (0.6)	0 (0)

Medical histories shown were reported by ≥5% of patients in one or both groups or are histories of special interest.

Online Resource 4. Adverse Events by Exposure Period

Patients, n (%)	Week 0 to ≤Week 52 (m=2,203)	Week >52 to ≤Week 104 (m=891)	Week >104 to ≤Week 156 (m=242)	Week >156 to ≤Week 208 (m=129)	Week >208 to <Week 260 (m=466)	Up to Week 260 (m=252)
Any TEAE	1,559 (70.8)	715 (80.2)	207 (85.5)	119 (92.2)	426 (91.4)	239 (94.8)
Common TEAEs (≥5%)						
Diarrhea	414 (18.8)	159 (17.8)	47 (19.4)	15 (11.6)	74 (15.9)	50 (19.8)
Headache	266 (12.1)	84 (9.4)	20 (8.3)	11 (8.5)	54 (11.6)	35 (13.9)
Nasopharyngitis	150 (6.8)	132 (14.8)	38 (15.7)	22 (17.1)	86 (18.5)	63 (25.0)
Nausea	377 (17.1)	114 (12.8)	36 (14.9)	27 (20.9)	70 (15.0)	41 (16.3)
URTI	170 (7.7)	115 (12.9)	44 (18.2)	38 (29.5)	98 (21.0)	72 (28.6)

TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

Patient incidence is 100 times the number (n) of patients reporting the event divided by (m) the number of patients with treatment duration ≥ the lower bound of the exposure interval.

Online Resource 5. Serious Adverse Events by Exposure Period

Patients, n (%)	Week 0 to ≤Week 52 (m=2,203)	Week >52 to ≤Week 104 (m=891)	Week >104 to ≤Week 156 (m=242)	Week >156 to ≤Week 208 (m=129)	Week >208 to <Week 260 (m=466)	Up to Week 260 (m=252)
Any serious TEAE	110 (5.0)	61 (6.8)	41 (16.9)	36 (27.9)	90 (19.3)	54 (21.4)
Serious TEAEs						
Abdominal pain	2 (0.1)	2 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)
Angina pectoris	1 (<0.1)	2 (0.2)	2 (0.8)	1 (0.8)	1 (0.2)	0 (0)
Atrial fibrillation	3 (0.1)	0 (0)	0 (0)	1 (0.8)	1 (0.2)	2 (0.8)
Congestive cardiac failure	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)
Cholelithiasis	3 (0.1)	2 (0.2)	0 (0)	0 (0)	2 (0.4)	1 (0.4)
Non-cardiac chest pain	0 (0)	2 (0.2)	1 (0.4)	0 (0)	2 (0.4)	1 (0.4)
Acute pancreatitis	1 (<0.1)	1 (0.1)	0 (0)	0 (0)	2 (0.4)	0 (0)
Pneumonia	5 (0.2)	0 (0)	1 (0.4)	2 (1.6)	3 (0.6)	1 (0.4)
Pregnancy	2 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Psoriatic arthropathy	3 (0.1)	0 (0)	2 (0.8)	1 (0.8)	7 (1.5)	1 (0.4)
Syncope	1 (<0.1)	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)

A TEAE is an adverse event with a start date on or after the date of the first dose of investigational product and no later than 28 days after the last dose of investigational product. Each patient is counted once for each applicable category.

Patient incidence is 100 times the number (n) of patients reporting the event divided by (m) the number of patients with treatment duration less than or equal to the lower bound of the exposure interval.

TEAE, treatment-emergent adverse event.

Online Resource 6. Deaths During Studies

Study	Patient Demographics	Treatment Received	Study Day	Cause of Death	Relationship With Study Drug
PALACE 1	36 y White male	APR 30 mg BID	695	Trauma due to motorcycle accident	Not suspected
PALACE 1	41 y Asian male	APR 30 mg BID	1692	Necrotizing fasciitis, acute kidney injury, shock	Not suspected
PALACE 2	64 y White male	Placebo and APR 30 mg BID	1330	Cerebrovascular accident	Not suspected
PALACE 2	55 y White female	APR 30 mg BID	1224	Cerebral infarction	Not suspected
ACTIVE	49 y White male	APR 30 mg BID	386	Atherosclerosis	Not suspected
PSOR-005	63 y White male	Placebo	84	Sudden death	Not suspected
ESTEEM 1	28 y White female	Placebo	55	Completed suicide	Not suspected
ESTEEM 1	55 y White female	Placebo and APR 30 mg BID	979	Cardiac arrest	Not suspected
ESTEEM 1	69 y White male	Placebo and APR 30 mg BID	777	Cerebrovascular accident	Not suspected
ESTEEM 2	30 y White female	APR 30 mg BID	111	Lung congestion and bilateral edema	Suspected

				consistent with cardiac failure	
ESTEEM 2	28 y White male	APR 30 mg BID	1433	Alcoholism	Not suspected
ESTEEM 2	51 y White female	Placebo and APR 30 mg BID	353	Intracranial hemorrhage	Not suspected

APR, apremilast; BID, twice daily.

Online Resource 7. TEAEs Leading to Discontinuation

	Placebo Controlled		Apremilast Exposure					
Patients, n (%)	**Placebo (N=2,084)**	**Apremilast 30 mg BID (N=2,673)**	**Week 0 to ≤Week 52 (m=2,203)**	**Week >52 to ≤Week 104 (m=891)**	**Week >104 to ≤Week 156 (m=242)**	**Week >156 to ≤Week 208 (m=129)**	**Week >208 to <Week 260 (m=466)**	**Up to Week 260 (m=252)**
Any TEAE leading to discontinuation	91 (4.4)	154 (5.8)	280 (12.7)	47 (5.3)	27 (11.2)	19 (14.7)	14 (3.0)	0 (0)
Abdominal discomfort	2 (0.1)	4 (0.1)	5 (0.2)	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)
Upper abdominal pain	0 (0)	8 (0.3)	10 (0.5)	0 (0)	0 (0)	1 (0.8)	0 (0)	0 (0)
Behçet's syndrome	5 (0.2)	1 (<0.1)	4 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Depression	0 (0)	5 (0.2)	7 (0.3)	1 (0.1)	1 (0.4)	0 (0)	1 (0.2)	0 (0)
Diarrhea	9 (0.4)	36 (1.3)	53 (2.4)	2 (0.2)	0 (0)	1 (0.8)	1 (0.2)	0 (0)
Dizziness	3 (0.1)	6 (0.2)	7 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Fatigue	3 (0.1)	7 (0.3)	8 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Headache	6 (0.3)	24 (0.9)	31 (1.4)	1 (0.1)	2 (0.8)	0 (0)	0 (0)	0 (0)
Migraine	1 (<0.1)	5 (0.2)	7 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Nausea	10 (0.5)	42 (1.6)	54 (2.5)	2 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)
Pruritus	3 (0.1)	2 (0.1)	2 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Psoriasis	11 (0.5)	8 (0.3)	16 (0.7)	6 (0.7)	2 (0.8)	2 (1.6)	1 (0.2)	0 (0)
Vomiting	3 (0.1)	15 (0.6)	23 (1.0)	0 (0)	0 (0)	1 (0.8)	0 (0)	0 (0)

Includes TEAEs that led to discontinuation in ≥5 patients in the placebo-controlled period. A TEAE is an adverse event with a start date on or after the date of the first dose of investigational product and no later than 28 days after the last dose of investigational product. Each patient is counted once for each applicable category. Patient incidence is 100 times the number (n) of patients reporting the event divided by (m) the number of patients with treatment duration ≥ the lower bound of the exposure interval.

BID, twice daily; TEAE, treatment-emergent adverse event.