The Journal of Rheumatology

POMALIDOMIDE (CC-4047) IN PATIENTS WITH INTERSTITIAL LUNG DISEASE DUE TO SYSTEMIC SCLEROSIS: A PHASE II, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY

Journal:	*The Journal of Rheumatology*
Manuscript ID	2016-1040
Manuscript Type:	Brief Communication
Date Submitted by the Author:	19-Aug-2016

Complete List of Authors:	Hsu, Vivien; Rutgers-RWJ Medical School, Medicine Denton, Christopher; Royal Free and University College, Rheumatology Domsic, Robyn; University of Pittsburgh, Medicine, Division of Rheumatology Furst, Daniel; UCLA Medical School, Rischmueller, Maureen; The Queen Elizabeth Hospital and University of Adelaide, Rheumatology Stanislav, Marina; Research Rheumatology Institute n.a. V.A., Rheumatology Steen, Virginia; Georgetown University, Rheumatology Hough, Douglas; Celgene Corporation, I&I Clinical Research Korish, Shimon; Celgene Corporation, I&I Clinical Research and Development Cooper, Alyse; Celgene Corporation, I&I Clinical Research Choi, Suktae; Celgene Corporation, Biostatistics

Keywords:	Systemic sclerosis, Interstitial lung disease, Clinical trials, Disease activity, Disease modifying antirheumatic drugs

Running head: Hsu, et al: Pomalidomide in systemic sclerosis

POMALIDOMIDE (CC-4047) IN PATIENTS WITH INTERSTITIAL LUNG DISEASE DUE TO SYSTEMIC SCLEROSIS: A PHASE II, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY

Vivien J. Hsu,[1] Christopher P. Denton,[2] Robyn T. Domsic,[3] Daniel Furst,[4] Maureen Rischmueller,[5] Marina Stanislav,[6] Virginia Steen,[7] Douglas R. Hough,[8] Shimon Korish,[8] Alyse Cooper,[8] Suktae Choi,[8]

[1]Vivien Hsu, MD: RWJ Medical School Scleroderma Program, New Brunswick, New Jersey; [2]Christopher P. Denton, MBBS, MRCP: Center of Rheumatology and Connective Tissue Disease, London, United Kingdom; [3]Robyn T. Domsic, MD, MPH: Department of Rheumatology, University of Pittsburgh, Pittsburgh, Pennsylvania; [4]Daniel E. Furst, MD: David Geffen School of Medicine at UCLA, Los Angeles, California; [5]Maureen Rischmueller, MD, FRACP: The Queen Elizabeth Hospital and University of Adelaide, Adelaide, Australia; [6]MarinaStanislav, MD, PhD, DMSc: Research Rheumatology Institute n.a. V.A. Nassonova, Moscow, Russia; [7]Virginia D. Steen, MD: Georgetown University Medical Center, Washington, DC; [8]Douglas R. Hough, MD, Shimon Korish, MD, Alyse Cooper, and Suktae Choi, PhD: Celgene Corporation, Summit, New Jersey.

Address correspondence to Vivien Hsu, MD, RWJ Medical School Scleroderma Program, 51 French St, PO Box 19, New Brunswick, NJ 08903 USA.

Tel: 732-418-8484. Fax: 732-418-8463. E-mail: hsuvm@rwjms.rutgers.edu.

ABSTRACT

Objectives To evaluate the safety and efficacy of pomalidomide (POM) on forced vital capacity (FVC), modified Rodnan Skin Score (mRSS), and gastrointestinal (GI) symptomatology over 52 weeks of treatment in patients with interstitial lung disease due to systemic sclerosis (SSc-ILD).

Methods 23 SSc-ILD adult patients diagnosed with SSc[1,2] were randomized 1:1 POM:placebo (PBO).

Results: Mean change at Week 52 from baseline in predicted FVC% -5.2 and -2.8; mRSS -2.7 and -3.7; and UCLA SCTC GIT 2.0 score 0.1 and 0.0, with POM and placebo, respectively.

Conclusions The study did not meet its Week 52 primary endpoints. POM was generally well-tolerated.

Funding Celgene Corporation

Clinical Trials number NCT01559129

Lung involvement has become the leading cause of deaths directly attributable to SSc-ILD.[3] Progressive SSc-ILD is associated with inexorable deterioration in lung function with associated debility and death, resulting in 5- and 10-year mortality of 30% and 50%, respectively.[4]

Pomalidomide (POM) is an IMiDs® compound, structurally similar to thalidomide. POM binds to cereblon and facilitates Ikaros and Aiolos degradation, resulting in immune-modulation of myeloid and lymphocyte cells. POM exhibits anti-fibrotic activity in preclinical models of dermal fibrosis.[5] Thalidomide has demonstrated beneficial effects in eleven SSc patients treated in an open-label, dose-escalating, 12-week study.[6] Skin biopsies demonstrated changes in skin fibrosis and an increase in epidermal and dermal infiltrating CD8+ T cells with thalidomide treatment. Plasma levels of IL-12 and TNF α increased, while IL-5 and IL-10 remained unchanged. These changes were associated with beneficial clinical effects, including decreased gastroesophageal reflux symptoms, and healing of digital ulcers. Non-clinical studies demonstrated that POM has potential anti-fibrotic effects in SSc patients through the inhibition of Th2 cytokines and enhanced production of anti-fibrotic Th1 cytokines such as IFN-γ, GM-CSF and IL-2.[7] These results suggested that POM had potential therapeutic benefit as an anti-fibrotic agent to improve pulmonary and dermal fibrosis in SSc.

METHODS

Study design. This phase II, multicenter, randomized, double-blind, parallel-group study comprised 2 treatment phases, 52 weeks blinded treatment and a two-year open-label treatment extension, which was followed by a 4 year long-term follow-up phase. The study was conducted in accordance with the general ethical principles outlined in the Declaration of Helsinki and following protocol CC-4047-SSC-001 as approved by Western IRB, number 20111970. All patients provided their written informed consent before starting any study-related procedures.

Patients. Eligible patients between 18 and 80 years of age, met the diagnosis of limited cutaneous SSc(lSSc) or diffuse cutaneous SSc (dSSc) based on the 2013 classification criteria for systemic sclerosis, with onset of the first non-Raynaud's SSc symptoms within 7 years prior to screening date. Eligible patients met at least one of the following pulmonary-related criteria: (1) FVC readings ≥ 45% and < 70% of predicted value at screening and baseline (Visit 2) (2) FVC readings ≥ 70% and ≤ 80% of predicted value at screening and baseline (Visit 2) with a documented history of either or both (a) a ≥ 5% decrease in FVC in the 24-month period prior to Baseline (based on 3 or more assessments) or (b) an HRCT fibrosis score > 20%.[8] Baseline FVC readings within 5% of screening FVC readings were required. Diffusion lung capacity for carbon monoxide (DLco) ≥ 35% and ≤ 80% of predicted value was required at screening in addition to abnormalities on high resolution computed tomography (HRCT) consistent with SSc-related interstitial lung disease, including: honeycombing or reticular changes with or without ground glass.[9]

In the 52-week placebo-controlled phase, approximately 88 patients were to be randomized 1:1 to placebo or POM 1 mg QD, stratified based on their type of SSc, either ([lSSc] or [dSSc]). At week 52, all patients receiving placebo were transitioned to POM 1 mg QD in a blinded fashion for up to an additional 2 years; patients receiving POM 1 mg QD continued this assigned treatment. Patients were permitted to continue other supportive medications at stable doses to treat SSc disease-related symptoms, including proton pump inhibitors, angiotensin converting enzyme inhibitors / angiotensin receptor blockers, and cough medications. No other Immunosuppressive therapy was permitted, except low-dose systemic corticosteroids (≤ 10 mg prednisone or equivalent/day).

Efficacy assessments. Co-primary efficacy assessments included spirometry testing of FVC and forced expiratory volume in 1 second (FEV_1), mRSS, and the UCLA SCTC GIT V2.0. Secondary efficacy assessments included baseline and transition dyspnea indexes (BDI/TDI), and pulse oximetry (SpO2).

Safety analysis. At scheduled clinic visits, safety was evaluated based on adverse events (AEs), weight, vital signs, physical examination, electrocardiograph recordings and clinical laboratory studies. An independentData Monitoring Board was implemented for external safety monitoring as an additional safety feature for this study.

Statistical analysis. An estimated sample size of 88 patients was needed to yield 80% power to detect ≥ 5% difference between POM treatment and placebo, with 8% of common standard deviation and a 25% discontinuation assumption, using a two-sample t-test with a 2-sided significance level of 0.1. Efficacy was evaluated based on the full analysis set, which consisted of all randomized patients. Safety was evaluated

based on the safety population, which consisted of all randomized patients who received at least 1 dose of study drug, and safety outcomes were analyzed and summarized descriptively.

RESULTS

Patients. A total of 59 patients were screened, 23 were randomized and 22 received study drug. Eleven patients were randomized in the POM arm and 12 in the placebo arm. One patient, who was ineligible for the study, was randomized in the POM arm but did not receive study drug. Of these patients, 11 (50.0%) completed 52 weeks, with more placebo patients (7 [58.3%]) completing treatment versus (4 [36.4%]) POM patients.

The demographic and disease characteristics of patients at baseline were comparable across treatment groups (**Table 1**).The mean age was 49.8 years (range 31 to 69 years) in the POM arm and 44.8 years (range 25 to 68 years) in the placebo arm. Ninety percent of patients in the POM arm and 83.3% in the placebo arm were female. Seventy percent of patients in the POM arm and 83.3% of patients in the placebo arm were white. Mean (min, max) body mass index at Screening was 26.67 kg/m^2 (17.4, 49.8) and 30.64 kg/m^2 (22.0, 40.9) in the POM and placebo arms, respectively. The majority of patients had dSSc: eight (80%) and nine (75%) in the POM and placebo arms, respectively.

Efficacy. Observed changes in all co-primary efficacy endpoints favored placebo. In the POM and placebo arms, the mean change at Week 52 from Baseline in predicted FVC% was -5.2 and -2.8, for the mRSS was -2.7 and -3.7, and for the UCLA SCTC GIT 2.0 instrument total score was 0.1 and 0.0, respectively.[10] The only mean

decrease (-0.1) from Baseline in the UCLA SCTC GIT 2.0 instrument total score was at Week 24 in the POM arm (**Table 2**). Statistical significance was not achieved for any of the three primary endpoints.

For the secondary efficacy endpoints, improvement in the POM arm was reported for the mean change in the UCLA SCTC GIT 2.0 instrument subscale scores of Diarrhea (-0.2, -0.3, -0.5, -0.8 at Weeks 12, 24, 76, 156, respectively), and Emotional Well-being (-0.4, -0.3, -0.1 at Weeks 12, 24, 52, respectively).[11] The change from Baseline in dyspnea (as measured by the TDI) regarding Functional Impairment, Magnitude of Task, and Magnitude of Effort at Weeks 12, 24 and 52 favored placebo.

Safety and tolerability. The safety profile of POM through the placebo-controlled period and through study termination was comparable. In the 52-week placebo-controlled period, adverse events (AEs) were reported by 12 (100.0%) patients receiving placebo, and 9 (90.0%) receiving POM 1 mg QD (**Table 3**). AEs occurring in ≥10% in either treatment group during this phase included constipation, diarrhea, nausea, bronchitis, upper respiratory tract infection, influenza, urinary tract infection, ligament sprain, arthralgia, headache, dyspnea, oro-pharyngeal pain, rash, and skin ulcer (**Table 3**). Overall, four POM patients (40%) discontinued due to treatment-emergent adverse events (TEAEs); one POM patient discontinued due to TEAEs during the Open-Label Extension Phase(**Table 3**). There were four POM patients (40%) with serious AE's (SAEs) compared to one placebo patient (8.3%) during the treatment phase; one POM patient had an SAE during the Open-Label Extension Phase (**Table 3**).

DISCUSSION

Due to difficulties in recruiting patients for this study related to restrictive inclusion and exclusion criteria, the Sponsor prematurely terminated enrollment. Based upon interim analysis data, the study did not demonstrate a statistically significant improvement in any of the three co-primary efficacy endpoints (changes from Baseline in FVC, mRSS or UCLA SCTC GIT 2.0 instrument total score at Weeks 24, or 52 for patients who completed blinded treatment. Patients in both the placebo and active treatment arms demonstrated disease progression consistent with the natural history of SSc-ILD. The study was terminated early due to lack of clinical efficacy of POM over 52 weeks. At week 52, no trends were noted for the secondary end points over time or by treatment group.

In this study, POM was well tolerated with an AE profile consistent with the known safety profile for POM in other diseases. There were no new safety findings from this study. Overall TEAEs were comparable across both treatment arms. TEAEs leading to discontinuation in the POM arm occurred in four (40%) of the 10 patients.

Although thalidomide has been shown in an open-label study to have beneficial effects in SSC, POM did not improve the clinical measurements in this small, placebo-controlled SSC-ILD population. There were too few patients to make meaningful conclusions.

CONCLUSIONS

The current study did not demonstrate efficacy of POM therapy in patients with SSC-ILD. POM demonstrated an acceptable safety profile and was generally well-

tolerated. The safety profile was similar to previous investigations of POM for other conditions.

ACKNOWLEDGMENTS

The authors wish to acknowledge the contributions of Will Smith, MD, who served as a medical monitor for this study. The authors, however, directed and are fully responsible for all content and editorial decisions for this manuscript.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Hsu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Hsu, Cooper

Acquisition of data. Hsu, Denton, Domsic, Furst, Rischmueller, Stanislav, Steen, Cooper, Hough, and Choi

Analysis and interpretation of data. Hsu, Choi, Hough, Korish, and Cooper

Funding: Celgene Corporation

REFERENCES

1. van den Hoogen FVD, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 Classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2013;65:2737-47.
2. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2013;72:1747-55.
3. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis 2007;66:940-4.
4. Mayes MD, Lacey JV Jr, Beebe-Dimmer J, Gillespie BW, Cooper B, Liang TJ, Schottenfeld D. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum 2003;48:2246-55.
5. Weingärtner S, Zerr P, Tomcik M, Palumbo-Zerr K, Distler A, Dees C, et al. Pomalidomide is effective for prevention and treatment of experimental skin fibrosis. Ann Rheum Dis 2012;71:1895-9.
6. Marriott JB, Clarke IA, Dredge K, Muller G, Stirling D, Dalgleish AG. Thalidomide and its analogues have distinct and opposing effects on TNF-alpha and TNFR2

during co-stimulation of both CD4(+) and CD8(+) T cells. Clin Exp Immunol 2002;130:75-84.

7. Oliver SJ, Moreira A, Kaplan G. Immune stimulation in scleroderma patients treated with thalidomide. Clin Immunol 2000;97:109-20.
8. Goh NSL, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med 2008;177:1248-54.
9. Khanna D, Brown KK, Clements PJ, Elashoff R, Furst DE, Golding J, et al. Systemic sclerosis-associated interstitial lung disease – proposed recommendations for future randomised clinical trials. Clin Exp Rheumatol Suppl 2010;28 Suppl 58:55-62.
10. Khanna D, Hays RD, Maranian P, Siebold JR, Impens A, Mayes MD, et al. Reliability and validity of UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT 2.0) Instrument. Arthritis and Rheumatism 2009;61:1257-1263.
11. Khanna D, Furst DE, Maranian P, Siebold JR, Impens A, Mayes MD, et al. Minimally important differences of the UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. J Rheumatol 2011;38:1920-4.

Table 1. Baseline demographic and clinical characteristics: full analysis set (N=22)

Characteristic	Placebo n = 12	POM 1 mg QD n = 10
Age, mean (SD), years	44.8 (13.8)	49.8 (9.9)
Female, no. (%)	10 (83.3)	9 (90.0)
Race, no. (%)		
White	10 (83.3)	7 (70.0)
Asian	0 (0.0)	2 (20.0)
Hawaiian Islander	1 (8.3)	0 (0.0)
Black	0 (0.0)	1 (10.0)
Missing	1 (8.3)	0 (0.0)
Weight, mean (SD), kg	80.5 (14.2)	70.8 (25.2)
BMI, mean (SD), kg/m^2	30.64(5.4)	26.67 (9.3)
Disease type		
Diffuse	9 (75.0)	8 (80.0)
Limited	3 (25.0)	2 (20.0)
Calcium Channel Blockers	2 (16.7)	4 (40.0)
Systemiccorticosteroids	5 (41.7)	7 (70.0)
Drugs for Acid Related Disorders[§]	4 (33.3)	7 (70.0)

Note: The N reflects the number of randomized patients who received at least one dose of investigational study drug.
[§]esomeprazole, omeprazole, pantaprazole, or sucralfate.
BMI=body mass index; SD=standard deviation.

Table 2. Primary end points Weeks 24 and 52: full analysis set (N=22)

			Placebo (N=12)			Pomalidomide 1 mg QD (N=10)		
Parameter	**Visit**		**Baseline**	**Value at Visit**	**Change from Baseline**	**Baseline**	**Value at Visit**	**Change from Baseline**
Predicted FVC (%)	**Baseline**[a]	n	-	12	-	-	10	-
		Mean (±SD)	-	60.9 (8.6)	-	-	53.7 (7.3)	-
		Min, Max	-	47, 77	-	-	45, 67	-
	Week 24	n[b]	10	10	10	8	8	8
		Mean (±SD)	63.2 (7.3)	61.9 (8.6)	-1.3 (3.3)	53.6 (8.1)	55.9 (13.6)	2.3 (12.6)
		Min, Max	55, 77	52, 78	-7, 4	45, 67	45, 86	-8, 32
	Week 52[a]	n[b]	11	11	11	8	8	8
		Mean (±SD)	60.7 (9.0)	57.9 (10.0)	-2.8 (4.0)	53.2 (8.2)	48 (8.6)	-5.2 (5.3)
		Min, Max	47, 77	41, 77	-8, 5	45, 67	40, 61	-15, 4
mRSS	**Baseline**	n	-	11	-	-	10	-
		Mean (±SD)	-	20.5 (10.0)	-	-	17.1 (9.4)	-
		Min, Max	-	2, 32	-	-	4, 30	-
	Week 24	n[a]	10	10	10	8	8	8
		Mean (±SD)	19.6 (10.1)	16 (9.8)	-3.6 (5.7)	15 (9.0)	13 (10.5)	-2 (3.4)
		Min, Max	2, 32	3, 28	-13, 3	4, 27	2, 29	-6, 3
	Week 52	n[a]	11	11	11	10	10	10
		Mean (±SD)	20.5 (10.0)	16.7 (10.9)	-3.7 (7.0)	17.1 (9.4)	14.4 (10.1)	-2.7 (5.7)
		Min, Max	2, 32	1, 31	-15, 7	4, 30	2, 30	-9, 10
UCLA SCTC GIT 2.0	**Baseline**	n	-	12	-	-	10	-
		Mean (±SD)	-	0.2 (0.18)	-	-	0.5 (0.29)	-
		Min, Max	-	0, 1	-	-	0, 1	-
	Week 24	n[a]	10	10	10	8	8	8
		Mean (±SD)	0.2 (0.19)	0.3 (0.32)	0.1 (0.23)	0.5 (0.28)	0.4 (0.24)	-0.1 (0.2)
		Min, Max	0, 1	0, 1	0, 0	0, 1	0, 1	0, 0
	Week 52	n[a]	12	12	12	10	10	10
		Mean (±SD)	0.2 (0.18)	0.3 (0.2)	0 (0.18)	0.5 (0.29)	0.5 (0.39)	0.1 (0.29)
		Min, Max	0, 1	0, 1	0, 0	0, 1	0, 1	0, 0

[a]FVC Baseline: average of Screening and Baseline. FVC Week 52: average of Week 48 and Week 52.
[b] At a post-baseline time point for Baseline and Change from Baseline column, n = number of patients with a Baseline value and a post-baseline value at the time point. None of the primary end points achieved statistical significance. As a result, *P* values are not provided.
FVC = forced vital capacity; mRSS = modified Rodnan skin score; QD = once daily; SD = standard deviation; UCLA SCTC GIT = University of California, Los Angeles, Scleroderma Clinical Trial Consortium Gastrointestinal Tract score

Table 3. Adverse events through Week 52/study termination

	Placebo-Controlled Weeks 0 to 52*		Open-Label/ study termination§	
Patients, n (%)	Placebo n= 12	POM 1 mg QD n= 10	Placebo* n = 6	POM 1 mg QD n= 2
AE summary				
≥1 AE	12 (100.0)	9 (90.0)	5 (83.3)	2 (100.0)
≥1 serious AE	1 (8.3)	4 (40.0)	0 (0.0)	1 (50.0)
≥1 severe AE	1 (8.3)	4 (40.0)	0 (0.0)	0 (0.0)
AEs leading to drug withdrawal discontinuation	0 (0.0)	4 (40.0)	0 (0.0)	1 (50.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs reported by ≥10% of patients in any treatment group, n (%)				
Constipation	1 (8.3)	3 (30.0)	0 (0.0)	0 (0.0)
Diarrhea	3 (25.0)	1 (10.0)	0 (0.0)	0 (0.0)
Nausea	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Bronchitis	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	3 (25.0)	1 (10.0)	0 (0.0)	0 (0.0)
Influenza	2 (16.7)	0 (0.0)	2 (33.3)	0 (0.0)
Urinary tract infection	2 (16.7)	0 (0.0)	2 (33.3)	0 (0.0)
Ligament sprain	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)
Arthralgia	4 (33.3)	4 (40.0)	0 (0.0)	0 (0.0)
Headache	3 (25.0)	1 (10.0)	0 (0.0)	0 (0.0)
Dyspnea	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Oropharyngeal pain	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Productive cough	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)
Rash	1 (8.3)	2 (20.0)	0 (0.0)	0 (0.0)
Skin ulcer	2 (16.7)	0 (0.0)	2 (33.3)	0 (0.0)
Serious AEs				
Infections and infestations				
Pneumonia	1 (8.3)	1 (10.0)	0 (0.0)	1 (50.0)
Upper respiratory tract infection	0 (0.0)	1 (10.0)		
Sepsis	1 (8.3)	0 (0.0)	1 (16.7)	0 (0.0)
Renal and urinary disorders				
Renal failure	0 (0.0)	1 (10.0)	1 (16.7)	0 (0.0)
Respiratory, thoracic, mediastinal disorders				
Pulmonary embolism	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)

Acute respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)
Chronic respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)
Pulmonary hypertension	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)
AEs Leading to Discontinuation				
C-reactive protein increased	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)
Renal failure	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)
Pulmonary embolism	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)
Toxic skin eruption	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)

AE = adverse event; POM = pomalidomide; QD = once daily

* Placebo-controlled period includes all data through week 52, and for the open-label extension data is for patients initially assigned to placebo who were re-randomized to active treatment appear in the placebo column.