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Secukinumab demonstrates sustained efficacy in clearing skin and improving patient-reported outcomes in patients with moderate-to-severe psoriasis through 2 years of treatment: Results from the CLEAR study

To the Editor: Secukinumab is a fully human monoclonal antibody that selectively neutralizes interleukin 17A, a key cytokine involved in the development of psoriasis.[1] Secukinumab has shown long-lasting efficacy and safety in the complete spectrum of psoriatic disease, including disease localized to nails, scalp, palms and soles, and joints (peripheral and axial arthritis).[1-3] Given the chronic and relapsing nature of psoriasis, long-term data might help to fully characterize the efficacy and safety profile of secukinumab as well as its impact on quality of life.

The CLEAR study (NCT02074982) was a phase 3b, head-to-head, randomized, double-blind study on the efficacy and safety of secukinumab compared with ustekinumab over 52 weeks of treatment in adult patients with moderate-to-severe psoriasis. Results from the 16-week and 52-week time points showed higher and sustained superior efficacy of secukinumab versus ustekinumab; secukinumab use also provided a greater improvement in patient-reported outcomes (PROs), and its safety profile was comparable with ustekinumab.[4,5] Patients from the secukinumab arm who completed 52 weeks of treatment and consented to continue in the open-label extension phase received secukinumab 300 mg at week 52, followed by dosing every 4 weeks to week 100. Methods for the CLEAR study have been described in detail elsewhere.[4,5] Here, we present the efficacy, safety, and PROs from a total of 2 years of secukinumab treatment.

Of 337 patients randomized to receive secukinumab 300 mg, 312 completed the 52-week study, and 303 patients entered the extension phase. In total, 277 patients completed the 2-year extension study. Irrespective of the analysis (observed, multiple imputation, modified nonresponder imputation), Psoriasis Area and Severity Index 75, 90, and 100, and Investigator's Global Assessment 2011 modified version 0/1 response rates with secukinumab treatment at week 16 were sustained up to year 2 (Table I). A similar trend was seen for the Dermatology Life Quality Index 0/1 response. Further, the mean scores for patient assessment of psoriasis-related pain, itching, and scaling severity remained low up to year 2 of secukinumab treatment (Table I). Secukinumab treatment resulted in a mean percentage of change of −85.6% for pain, −77.6% for itching, and −81.9% for scaling from baseline to year 2. Furthermore, a high proportion of patients achieved complete relief (score 0) of psoriasis-related pain, itching, and scaling at week 16, and the response was sustained up to year 2 (Table I).

Among adverse events of interest, *Candida* infections were reported in 24 (7.2%) patients (all events were nonserious and did not lead to study discontinuation) and malignant or unspecified tumors were reported in 5 (1.5%) patients. Neutropenia was reported in 1 patient during the first year of treatment (mild severity, not associated with any infection or opportunistic infections). Overall, there was no increase in the rate of adverse events, and no new or unexpected signals were identified (Table II).

In conclusion, the 2-year results from the CLEAR study confirm the sustained efficacy and improved PROs provided by secukinumab in patients with

Table I. Efficacy and patient-reported outcomes through year 2 of secukinumab 300-mg treatment

	Week 16			Year 1			Year 2		
Efficacy	**As observed**	**MI**	**mNRI**	**As observed**	**MI**	**mNRI**	**As observed**	**MI**	**mNRI**
PASI 75	94.5 (310/328)	94.2 (315/334)	93.1 (311/334)	93.7 (282/301)	92.4 (308/334)	91.6 (306/334)	89.6 (138/154)	83.1 (278/334)	83.8 (280/334)
PASI 90	80.5 (264/328)	80.1 (268/334)	79.0 (264/334)	78.4 (236/301)	76.3 (255/334)	74.9 (250/334)	74.7 (115/154)	62.6 (209/334)	66.8 (223/334)
PASI 100	45.1 (148/328)	45.0 (150/334)	44.3 (148/334)	48.2 (145/301)	45.8 (153/334)	44.9 (150/334)	47.4 (73/154)	36.9 (123/334)	38.6 (129/334)
IGA mod 2011 0/1	84.5 (277/328)	84.3 (282/334)	83.2 (278/334)	81.7 (246/301)	80.2 (268/334)	78.1 (261/334)	68.8 (106/154)	66.5 (222/334)	66.5 (222/334)

	Week 16		Year 1		Year 2	
PROs	**As observed**	**LOCF**	**As observed**	**LOCF**	**As observed**	**LOCF**
DLQI 0/1	72.2 (236/327)	71.9 (238/331)	71.9 (210/292)	71.6 (237/331)	66.0 (105/159)	65.9 (218/331)
Pain, mean score (m)	0.8 (327)	0.8 (333)	0.8 (292)	0.8 (333)	0.7 (159)	0.9 (333)
Itching, mean score (m)	1.2 (327)	1.2 (333)	1.2 (292)	1.3 (333)	1.3 (159)	1.5 (333)
Scaling, mean score (m)	0.8 (327)	0.8 (333)	1.0 (292)	1.0 (333)	1.1 (159)	1.3 (333)

	As observed		
Complete relief*	**Week 16**	**Year 1**	**Year 2**
Pain	69.4 (177/255)	67.1 (151/225)	70.9 (90/127)
Itching	49.7 (157/316)	48.9 (138/282)	47.4 (72/152)
Scaling	61.2 (197/322)	53.3 (153/287)	54.8 (86/157)

Values are % (n/m), except where indicated. Efficacy variables and PROs were primarily assessed by using observed values (no imputation of missing values). In addition, the MI and mNRI methods were used as sensitivity analyses for efficacy variables, and the LOCF method was used for PROs. Missing values were imputed in MI analysis by using the missing at random assumption. In mNRI analyses, the missing values were imputed as nonresponse regardless of the reason for missing data, except if the patient had been a responder for 2 consecutive visits before the study completion or discontinuation or if the patient had been a responder at visits both before and after the missed visit. In LOCF analyses, the last available measurement for each patient was carried forward to all later visits. *DLQI*, Dermatology Life Quality Index; *IGA mod 2011*, Investigator Global Assessment 2011 modified version; *LOCF*, last observation carried forward; *m*, number of patients evaluable; *MI*, multiple imputation; *mNRI*, modified nonresponder imputation; *n*, number of patients with response; *PASI*, Psoriasis Area Severity Index; *PROs*, patient-reported outcomes.

*Complete relief of psoriasis-related pain, itching, and scaling was defined as absence of symptoms (item score of 0) in patients with baseline score for symptom >0.

Table II. Adverse events during 2-year study period

Adverse event	Secukinumab 300 mg		
	Overall, N = 335, n (%)	Up to year 1, N = 335, n (%)	From >1 year to end of study, N = 307, n (%)
Any adverse event	299 (89.3)	286 (85.4)	198 (64.5)
Serious adverse event	41 (12.2)	32 (9.6)	13 (4.2)
Death	0 (0)	0 (0)	0 (0)
Adverse events leading to study treatment discontinuation	18 (5.4)	11 (3.3)	8 (2.6)
Primary system organ class			
Infections and infestations	231 (69.0)	197 (58.8)	137 (44.6)
Most common (≥5%)*			
Nasopharyngitis	96 (28.7)	77 (23.0)	39 (12.7)
Headache	50 (14.9)	40 (11.9)	18 (5.9)
Upper respiratory tract infection	42 (12.5)	31 (9.3)	23 (7.5)
Arthralgia	36 (10.7)	26 (7.8)	13 (4.2)
Influenza	33 (9.9)	22 (6.6)	12 (3.9)
Oropharyngeal pain	32 (9.6)	28 (8.4)	4 (1.3)
Back pain	29 (8.7)	21 (6.3)	11 (3.6)
Pruritus	25 (7.5)	20 (6.0)	6 (2.0)
Diarrhea	23 (6.9)	23 (6.9)	4 (1.3)
Psoriasis	22 (6.6)	12 (3.6)	11 (3.6)
Cough	21 (6.3)	13 (3.9)	10 (3.3)
Bronchitis	20 (6.0)	13 (3.9)	9 (2.9)
Fatigue	20 (6.0)	18 (5.4)	2 (0.7)
Eczema	19 (5.7)	15 (4.5)	5 (1.6)
Conjunctivitis	18 (5.4)	16 (4.8)	4 (1.3)
Select adverse events of interest			
Candida infections†	24 (7.2)	19 (5.7)	8 (2.6)
Oral candidiasis	15 (4.5)	12 (3.6)	5 (1.6)
Vulvovaginal candidiasis	4 (1.2)	3 (0.9)	1 (0.3)
Genital candidiasis	2 (0.6)	1 (0.3)	1 (0.3)
Esophageal candidiasis	2 (0.6)	2 (0.6)	0 (0)
Balanitis candida	1 (0.3)	0 (0)	1 (0.3)
Candida infection	1 (0.3)	1 (0.3)	0 (0)
Oropharyngeal candidiasis	1 (0.3)	1 (0.3)	0 (0)
Skin candida	1 (0.3)	1 (0.3)	0 (0)
Malignant or unspecified tumors‡	5 (1.5)	4 (1.2)	1 (0.3)
Malignant melanoma in situ	2 (0.6)	2 (0.6)	0 (0)
Basal cell carcinoma	1 (0.3)	0 (0)	1 (0.3)
Keratoacanthoma	1 (0.3)	1 (0.3)	0 (0)
Lung adenocarcinoma	1 (0.3)	1 (0.3)	0 (0)

Events listed under Candida infections and Malignant or unspecified tumors are preferred terms. One year is defined as 365 days.
*Preferred term.
†High-level term.
‡Standard MedDRA query.

moderate-to-severe plaque psoriasis, while maintaining a favorable safety profile.

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Conflicts of interest: Dr Thaci has served as a consultant, advisor, and speaker and has received honoraria from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dignity, Dr Reddy, Galapagos, GSK, Janssen, Leo, Lilly, Morphosis, MSD, Novartis, Pfizer, Regeneron, Sanofi, and UCB. Dr Thaci's institute has received research grants from Celgene and Novartis. Dr Puig has served as a consultant and speaker and has received fees and honoraria from AbbVie, Almirall, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Celgene, Gebro, Janssen, Leo-Pharma, Lilly, Merck-Serono, MSD, Novartis, Pfizer, Regeneron, Roche, and Sandoz. Dr Puig's institution has received research funding in relationship with the treatment of psoriasis from AbbVie, Amgen, Janssen, Lilly, Novartis, and Pfizer. Dr Reich has served as advisor or paid speaker and participated in clinical trials sponsored by AbbVie, Affibody, Almirall, Amgen, Biogen Idec, Boehringer Ingelheim, Celgene, Covagen, Forward Pharma, Fresenius Medical Care, GlaxoSmithKline, Janssen-Cilag, Kyowa Kirin, Leo, Lilly, Medac, Merck Sharp & Dohme Corp, Miltenyi, Novartis, Ocean Pharma, Pfizer, Samsung Bioepis, Sanofi, Takeda, UCB Pharma, Valeant, and Xenoport. Dr Reich has received honoraria for his role as advisor and speaker. For participating in clinical trials, Dr Reich's research site has received patient fees, and Prof Reich has received fees if acting as coordinating investigator. Dr Tsai has served as an investigator or advisor and speaker and has received fees and honoraria from Janssen-Cilag, AbbVie, Pfizer, Leo Pharmaceuticals, Novartis, Celgene, Galderma, Eli-Lilly, Boehringer Ingelheim, GSK, MSD, Allegra, and Tanabe. Dr Tsai's institute has received fees for his role as an investigator. Dr Tyring has served as a principal investigator and his institution has received grant and research funding from Novartis. Dr Kingo has received fees for serving as an investigator in studies sponsored by Celgene, Merck, Mitsubishi Tanabe Pharma, Novartis, Regeneron Pharmaceuticals, and Sandoz. Dr Ziv has served as principal investigator and has received fees from Novartis. Dr Pinter has served as a scientific advisor or clinical study investigator for AbbVie, Allmirall-Hermal, Amgen, Biogen Idec, Boehringer-Ingelheim, Celgene, GSK, Eli-Lilly, Galderma, Hexal, Janssen, Leo Pharma, Medac, Merck Serono, Mitsubishi, MSD, Novartis, Pfizer, Tigercat Pharma, Regeneron, Roche, Sandoz Biopharmaceuticals, Schering-Plough, and UCB pharma. Dr Pinter has served as a paid speaker for AbbVie, Celgene, Eli-Lilly, Janssen, Leo Pharma, Medac, Novartis, and Sanofi Genzyme. Dr Vender has served as an advisory board member, investigator, and on the speakers bureau and has received honoraria from Novartis, AbbVie, Janssen, Lilly, UCB, Amgen, Celgene, Pfizer, and Bauch Health. Ms Lacombe, Ms Xia, and Ms Gilloteau are employees of Novartis. Dr Guana and Ms Bhosekar were employees of Novartis during the conduct of the study and development of the manuscript. Dr Blauvelt has served as a scientific adviser or clinical study investigator for AbbVie, Aclaris, Akros, Allergan, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dermavant, Dermira Inc, Eli Lilly and Company, Galderma, Genentech/Roche, GlaxoSmithKline, Janssen, Leo, Meiji, Merck Sharp & Dohme, Novartis, Pfizer, Purdue Pharma, Regeneron, Revance, Sandoz, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, UCB Pharma, Valeant, and Vidac and as a paid speaker for Eli Lilly and Company, Janssen, Regeneron, and Sanofi Genzyme.

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Association of particulate matter air pollution and itch: A digital epidemiology approach

To the Editor: Ambient air pollution secondary to industrialization is a growing health concern with the potential to cause exposure-related skin toxicity.[1] Among skin conditions, itch may be especially susceptible to environmental modulation, given that free nerve endings of sensory neurons are located in the epidermis.[2] Although several air pollutants are postulated to affect health, one well-studied marker of air quality is atmospheric particulate matter no larger than 2.5 μm ($PM_{2.5}$). Fine particulate matter of this size has important health effects, given its ability to penetrate the body systemically and serve as a carrier of pathogens and toxins.[1] We thus hypothesized that increasing levels of $PM_{2.5}$ are associated with increased population-level search interest in itch as a proxy for itch sensation.

Google Trends is an open-access database aggregating search queries across various regions that has been used for health care research, with successful validation against external data sets.[3] Search volume index (SVI) is a normalized value ranging from 0 to 100 that indicates the quantity of queries for a searched topic relative to all other queries within the given time frame. SVI data were evaluated within the United States in 2014 for the term *itch*, and for purposes of comparison, SVI data for the term *acne* were evaluated. We obtained data on annual state averages for $PM_{2.5}$ for 2014 from the US Centers for Disease Control and Prevention's National Environmental Public Health Tracking Network. Multivariate linear regression was conducted to examine the association between SVI for skin-related complaints and $PM_{2.5}$ adjusted for climate, population density, and percentage of population located in urban areas.

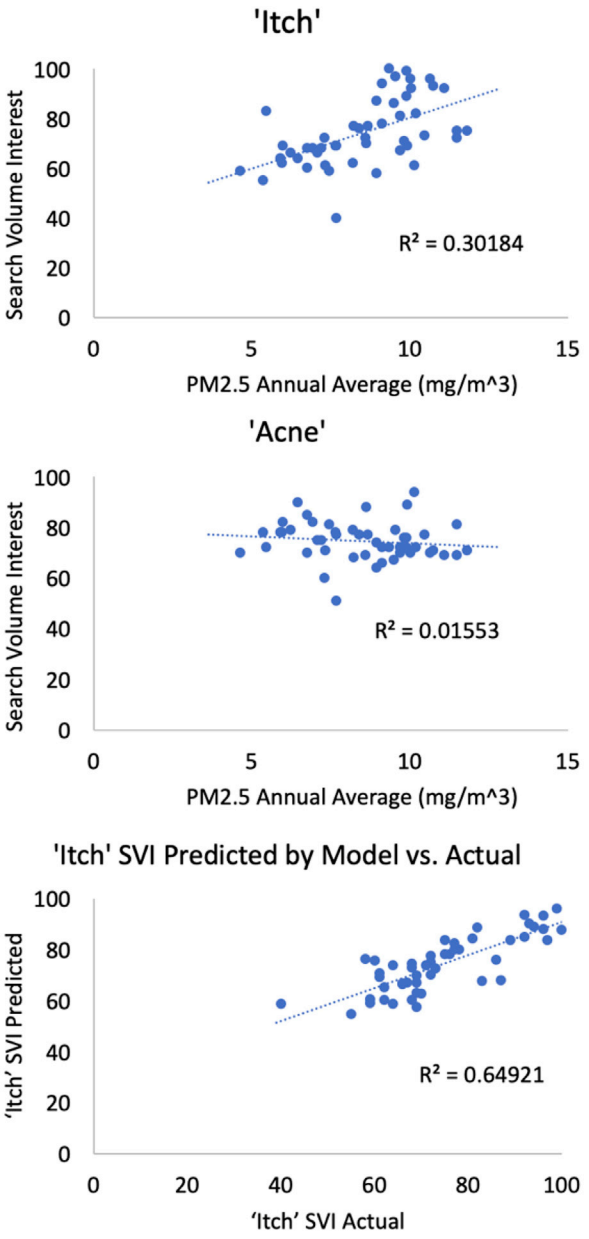

Fig 1. Air pollution and Google search volume index (SVI) for 49 States in the United States in 2014. *$PM_{2.5}$*. Particulate matter no larger than 2.5 μm.