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Use of systemic therapies in adults with atopic dermatitis: 12-month results from the European prospective observational study in patients eligible for systemic therapy for atopic dermatitis (EUROSTAD)

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ABSTRACT

Background: The European Prospective Observational Study in Patients Eligible for Systemic Therapy for Atopic Dermatitis (EUROSTAD) is an ongoing observational study aiming to describe characteristics of patients with atopic dermatitis (AD) treated with systemic therapy over time and the management of their disease in a real-world setting.

Methods: Data from patients enrolled in EUROSTAD between March 2017 and April 2019 were analyzed for systemic therapy use and treatment change over 12 months.

Results: 288 patients reported taking systemic medications; 42.7% received cyclosporine, 35.3% dupilumab, 28.1% methotrexate, 25.4% oral corticosteroids, 6.8% azathioprine, 6.1% injectable corticosteroids, and 3.4% mycophenolate. The median duration of treatment was 1.1 months for oral systemic corticosteroids, 3.2 months for injectable corticosteroids, 4.8 months for cyclosporine, 7.3 months for methotrexate, and 14.9 months for dupilumab. The most frequent reasons for stopping treatment included lack of efficacy, patient decision, adverse events, and disease well controlled.

Conclusion: The 12-month interim EUROSTAD study analysis highlights the current trends and outcomes of systemic treatments for moderate-to-severe AD. Among all systemic treatments for AD, dupilumab was the least likely to be discontinued, whereas cyclosporine and corticosteroids, whilst effective, were primarily limited to episodic flare management consistent with treatment guidelines.

Introduction

Atopic dermatitis (AD), a predominantly type 2 inflammatory skin disease characterized by pruritus (itch) and eczematous lesions, is often associated with other type 2 (atopic/allergic) comorbidities such as asthma, certain chronic sino-nasal conditions, and allergic conjunctivitis (1,2). AD affects approximately 2%–7% of adults worldwide, with the highest rates observed in Europe and the USA (3–5). In moderate-to-severe AD, lesions can be extensive with intense pruritus. Sleep and mental health disturbances can occur, which might impact the quality of life (QoL) (6–8). Due to the chronic and relapsing nature of moderate-to-severe AD, patients often require long-term, systemic treatments (9–11). Insight into real-world treatments and disease burdens are needed to help inform clinical and health policy decisions.

The European Prospective Observational Study in Patients Eligible for Systemic Therapy for Atopic Dermatitis (EUROSTAD) is an ongoing observational study aiming to inform physician treatment choices by describing characteristics over time of patients with AD treated with systemic therapy and the management of their disease in a real-world setting (12).

The objective of this paper is to describe the patient characteristics, outcomes, and the median duration of use of different systemic therapies (drug survival) in real-world conditions in adult AD patients from an interim 1-year analysis of the EUROSTAD observational study.

Methods

EUROSTAD was a prospective observational study of patients with moderate-to-severe AD receiving systemic treatment in various European countries. The study design and baseline characteristics have been previously published (12,13). Briefly, EUROSTAD was designed to characterize the real-world demographics and medical history of patients receiving systemic therapies, their disease activity, symptoms, and QoL, and lastly,

real-world effectiveness and safety of systemic AD therapy. The study aimed to enroll 500 patients at 51 sites in ten European countries.

Eligible patients were aged ≥ 18 years and were eligible for systemic treatment and had started or switched to a new systemic treatment on Day 1 or in the 30 days before enrollment. Patients were intended to continue for 60 months in total, with follow-up visits every 3–4 months; however, the study was terminated early due to the impact of COVID-19. This analysis includes interim data at 12 months, collected between March 2017 and April 2019 with a database lock of April 4, 2019.

Study outcomes

Patients enrolled in EUROSTAD were analyzed for both clinical and patient-reported outcomes. The treating clinician assessed the disease status using the Investigator's Global Assessment (IGA) scale (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe) (14) and Eczema Area and Severity Index (EASI; range 0 − 72) (15). Patient-reported data included Peak Pruritus Numeric Rating Scale (NRS; range 1–10) (16), Dermatology Life Quality Index (DLQI; range 0–30) (17); Patient-Oriented Eczema Measure (POEM; range 0–28) (18); Hospital Anxiety and Depression Scale (HADS; 0–7 = normal; 8–10 = borderline abnormal, 11–21 = abnormal) (19); sleep quality Visual Analog Scale (VAS; 0–100 mm [0 to <40 mm indicating none or mild impairment, 40 to <70 mm moderate, 70 to <90 mm severe, and ≥90 mm very severe impairment]); and the 5-dimension EuroQoL 3-level questionnaire (EQ-5D-3L) VAS (range 0–100) (20). For each of these metrics, higher scores represent greater severity. IGA 0 or 1, or 2-point improvement was also recorded.

Systemic therapy and treatment change (including the reasons for starting, stopping, or changing systemic treatment), as well as the most common reason for treatment discontinuation during the follow-up period, were also recorded. All patient data was pseudo-anonymized.

Statistical analyses

The enrollment and safety populations included patients who completed the enrollment visit (Visit 1). Demographic, clinical characteristics, and outcomes data were summarized using descriptive statistics and measures of central tendency. No imputation of missing data was performed. All statistical analyses were performed using SAS version 9.2 or higher (SAS Institute, Cary, NC, USA). Kaplan–Meier curve analysis was used to illustrate the median duration of treatment for each systemic therapy until the day of discontinuation of therapy. If the discontinuation day was not reached (for example, due to the data cutoff for the interim analysis), the patient was censored at the date of the last available information. If multiple treatment durations were present, the longest treatment cycle was used in the illustration.

EUROSTAD is being conducted in accordance with the principles defined by the 18th World Medical Association General Assembly Declaration of Helsinki and all subsequent amendments. The EUROSTAD protocol was reviewed and approved by institutional review boards before patient recruitment. All patients provided written informed consent before any EUROSTAD procedures began.

Results

Patient disposition

In total, 308 patients were included in EUROSTAD, with baseline demographics and disease characteristics as shown in Table 1. A breakdown by country of enrollment is shown in Figure 1. Patients had a mean age of 37 years, with a mean duration of AD of ~25 years. Disease burden at baseline was relatively high, with a mean EASI of 16.2 and IGA score of 3.1. QoL metrics at baseline showed a moderate impact on sleep, anxiety, and depression. At database lock, follow-up 3-month data were available for 290 patients, 6-month data for 269 patients, 9-month data for 235 patients, 12-month data for 192 patients, and more-than-12 months' data for 95 patients.

Systemic treatments

At baseline, most patients (286 [92.9%]) reported taking systemic medication, of whom 39.2% received cyclosporine, 23.1% methotrexate, 19.6% dupilumab,14.0% oral corticosteroids, 5.6% azathioprine, 3.8% injectable corticosteroids, and 2.8% mycophenolate (Table 2). During the 12-month treatment follow-up, 288 patients used systemic medications, of whom 42.7% received cyclosporine, 35.3% dupilumab, 28.1% methotrexate, 25.4% oral corticosteroids, 6.8% azathioprine, 6.1% injectable corticosteroids, and 3.4% mycophenolate (Table 2).

Treatment sequence and overlap analysis

Common treatment sequences of patients included, but were not limited to, cyclosporine -> dupilumab; oral corticosteroids -> injectable corticosteroids -> dupilumab; and methotrexate and oral corticosteroids -> methotrexate -> dupilumab. Patients may have received more than one systemic treatment concurrently, and data are shown for combinations of methotrexate, cyclosporine, and dupilumab (Table 2). Treatment sequences visualized per patient by initiating or switching medication are

Table 1. Baseline demographics and disease characteristics.

	$n = 308$
Age, years	37.2 (13.8)
Male sex, n (%)	175 (56.8)
Weight, kg	73.3 (17.7)
Height, cm	171.9 (9.3)
Duration of AD, years	25.4 (15.6)
EASI, mean (SD), N1	16.2 (10.9), 281
IGA score, mean (SD), N1	3.1 (0.8), 266
0 – Clear, n (%)	2 (0.8)
1 – Almost clear, n (%)	8 (3.0)
2 – Mild disease, n (%)	29 (10.9)
3 – Moderate disease, n (%)	143 (53.8)
4 – Severe disease, n (%)	84 (31.6)
Peak Pruritus NRS score, mean (SD), N1	5.5 (2.5), 290
DLQI, mean (SD), N1	11.8 (6.9), 272
POEM, mean (SD), N1	17.0 (7.2), 279
HADS-anxiety, mean (SD), N1	8.3 (3.7), 271
HADS-depression, mean (SD), N1	8.6 (4.7), 271
EQ-5D-3L VAS score, mean (SD), N1	65.9 (21.4), 270
Sleep VAS score, mean (SD), N1	49.8 (31.6), 272

Values are means (SD) unless otherwise specified.
AD: atopic dermatitis; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; EQ-5D-3L: 5-dimension EuroQoL 3-level scale; HADS: Hospital Anxiety and Depression Scale; IGA: Investigator's Global Assessment; N1: number of patients with available data; NRS: Numerical Rating Scale; POEM: Patient-Oriented Eczema Measure; SD: standard deviation; VAS: visual analog scale.
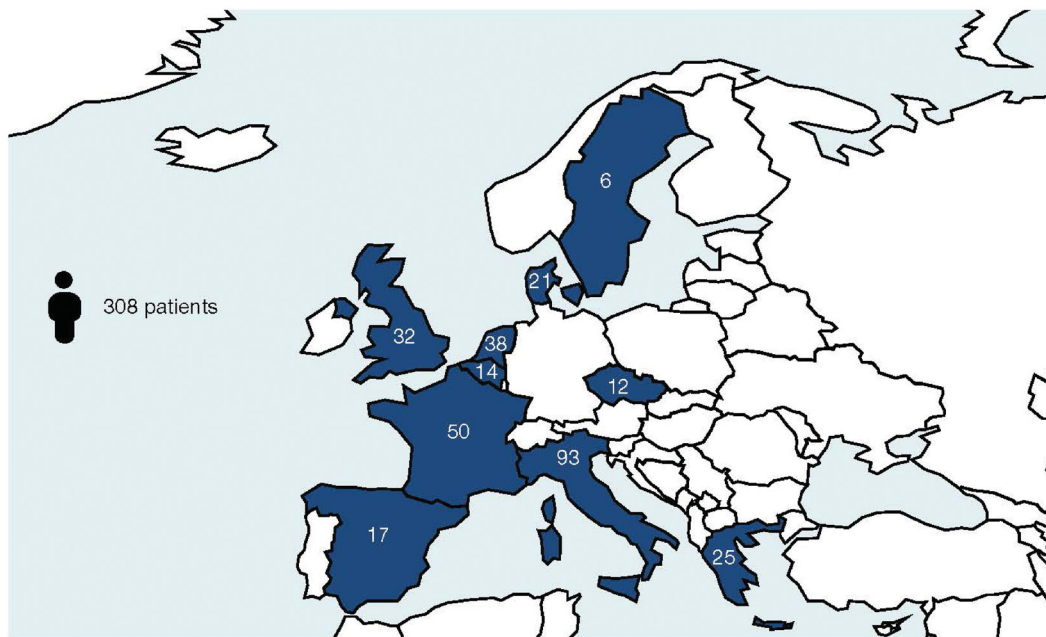
Figure 1. Patient enrollment in EUROSTAD by country.

Table 2. Systemic treatment at enrollment and during 12-month follow-up.

n (%)	Enrollment N = 286	Use during 12-month follow-up N = 288
Cyclosporine	112 (39.2)	126 (42.7)
Dupilumab	56 (19.6)	104 (35.3)
Methotrexate	66 (23.1)	83 (28.1)
Systemic steroids		
Oral corticosteroid	40 (14.0)	75 (25.4)
Injectable corticosteroid	11 (3.8)	18 (6.1)
Azathioprine	16 (5.6)	20 (6.8)
Mycophenolate	8 (2.8)	10 (3.4)
Hydroxyquinoline	1 (0.3)	1 (0.3)
Other systemic drugs	5 (1.7)	7 (2.4)
Drug combinations during study	N = 286	
Cyclosporine/dupilumab	14 (4.8)	
Cyclosporine/methotrexate	5 (1.8)	
Dupilumab/methotrexate	12 (4.7)	
Cyclosporine/dupilumab/methotrexate	3 (1.04)	

Percentages of each systemic treatment are calculated over the number of patients reporting any systemic treatments. Multiple start reasons of treatment are allowed per each medication.

shown in Supplementary Figure S1. The percentage of patients who had 2 or more sequential overlapping systemic treatments (overlap of fewer than 4 weeks) in this study was 20.7%. Overlap of 2 or more systemic treatments of 4 weeks or more occurred in 7.1% of patients.

Drug survival analysis

The median duration of treatment was 1.1 months for oral systemic corticosteroids, 3.2 months for injectable corticosteroids, 4.8 months for cyclosporine, 7.3 months for methotrexate, and 14.9 months for dupilumab. Kaplan–Meier plots of drug survival showed dupilumab treatment persistence was highest and declined slowly over 12 months (Figure 2). The most frequent reasons for initiating systemic treatment are shown in Table 3, with the exacerbation of disease being the most common

reason for starting. Of note, methotrexate was recorded as being used for treatment induction in 33.7% of patients receiving it. Reasons for stopping treatment are also shown in Table 3 for each therapy, the most common reasons across all drugs were as follows: disease well-controlled, lack of efficacy, adverse events, and patient decision. Among the patients who discontinued cyclosporine, less than half (40.2%) did so because of good disease control. In patients who discontinued systemic corticosteroids, good disease control was reported as the reason for discontinuation in 72.3% of them.

Disease severity

Table 4 shows the overall change in EASI and IGA score over the study, with both metrics trending toward better disease severity over time.

Discussion

This 12-month interim analysis from the EUROSTAD study highlights the current real-world medical trends and outcomes in the treatment of moderate-to-severe AD. Patients enrolled in EUROSTAD had moderate-to-severe disease, with a mean baseline EASI of 16.2, and >85% of patients having an IGA score of 3 or 4. The burden of AD experienced in the enrolled patients is consistent with other real-world studies from around the world (21–24). A previous study of 1467 patients at multiple centers in Europe and Canada reported that moderate and severe AD disease (as classified by the IGA) was accompanied by a substantial and significantly high burden across multiple domains, including sleep, anxiety, depression, pain, and overall QoL measured by HADS, DLQI, and components of Scoring of Atopic Dermatitis (SCORAD) and POEM (21). Data from analysis of the Optum research database, including 801 AD patients in the USA receiving systemic therapies, showed that 81.3% of patients experienced AD flares over 12 months, despite being on systemic treatment (25).
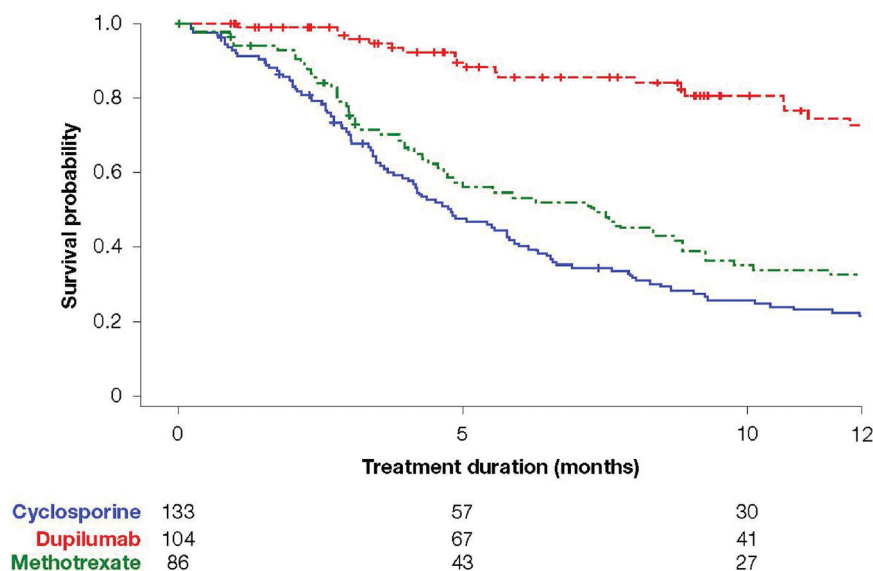
Figure 2. Treatment duration: Kaplan–Meier analysis of time to treatment discontinuation. Values underneath the graphs show patients with available measurements at each visit. Month 0 is the therapy start time. The X-axis represents the time (month) since the start of therapy.

Table 3. Most common reasons for initiating or discontinuing systemic therapy.

	Cyclosporine	Dupilumab	Methotrexate	Oral corticosteroid	Injectable corticosteroid
Initiation reason, n (%)	n = 126	n = 104	n = 83	n = 75	n = 18
Exacerbation	80 (63.5)	66 (63.5)	29 (35.0)	59 (79.73)	13 (72.2)
Maintenance	21 (16.7)	13 (12.5)	31 (37.5)	18 (24.32)	3 (16.7)
Use on an as-needed basis	0	1 (1.0)	0	2 (2.7)	2 (11.1)
Used for induction	29 (23.0)	27 (26.0)	28 (33.7)	0	2 (11.1)
Unable to taper TCS	7 (5.6)	0	3 (3.6)	0	0
Missing	0	0	0	1	0
Reasons for stopping, n (%)	**n = 97 (77.0)**	**n = 23 (22.1)**	**n = 53 (63.9)**	**n = 65 (86.7)**	**n = 17 (94.4)**
Lack of efficacy	31	6	19	11	3
Low compliance	2	1	0	0	0
Adverse events	16	7	14	3	1
Patient decision	12	3	8	0	2
Disease well controlled	39	4	11	50	10
Labelling in the country limits the use to a certain period of time	2	0	0	4	0
Issue with reimbursement	1	1	0	0	0
Contraindication with another concomitant therapy	3	0	2	1	0
Other	6	2	3	3	1
Number of therapy changes, mean (SD)	1.2 (1.07)	0.8 (0.72)	1.2 (1.17)	2.2 (1.95)	2.0 (1.41)
Number of changes due to lack of efficacy of prior treatment, mean (SD)	0.2 (0.43)	0.1 (0.23)	0.3 (0.57)	0.1 (0.36)	0.3 (0.75)

Table shows number of patients discontinuing from treatment by reason. A patient could have multiple instances of discontinuation from the same or different drugs. They could also select multiple reasons for discontinuation from a drug.
SD: standard deviation; TCS: topical corticosteroid.

Table 4. Change in EASI and IGA score over time from the start of EUROSTAD.

Disease activity	Baseline	Month 3	Month 6	Month 9	Month 12
EASI global score					
Number of patients	273	204	163	131	114
Mean (SD)	16.1 (10.7)	9.0 (9.4)	8.2 (8.8)	9.1 (9.5)	8.3 (9.1)
IGA, n (%)					
Number of patients	259	192	160	130	114
0 – Clear	2 (0.8)	5 (2.6)	11 (6.9)	9 (6.9)	14 (12.3)
1 – Almost clear	8 (3.1)	49 (25.5)	39 (24.4)	35 (26.9)	24 (21.1)
2 – Mild erythema/infiltration	29 (11.2)	56 (29.2)	45 (28.1)	36 (27.7)	38 (33.3)
3 – Moderate erythema/infiltration	140 (54.1)	58 (30.2)	49 (30.6)	37 (28.5)	29 (25.4)
4 – Severe erythema/infiltration	80 (30.9)	24 (12.5)	16 (10.0)	13 (10.0)	9 (7.9)

Patients who completed follow-up visits within a (±) 1-month window are included in the summaries.
EASI: Eczema Area and Severity Index; IGA: Investigator's Global Assessment.

Another facet of disease burden can be measured in terms of the lost time and productivity of AD patients, and an earlier study by Zuberbier et al. discussed the high costs of untreated allergic conditions, including dermatitis, with indirect costs of up to €2405/year (2014) (26). Similarly, the patient burden of inadequately controlled AD is a significant limitation for patients

and has been published previously for the EUROSTAD patient cohort, with time lost from work or activities of 4.1 and 16.8 days/year, respectively (12).

In this study the highest drug persistence was with dupilumab: 14.9 months. Of note, analysis of the reasons for starting and stopping treatment with cyclosporine and corticosteroids is consistent with their use for acute flare management, as a rescue and not as a maintenance treatment, in line with treatment guidelines (11). For example, with cyclosporine, 64% started therapy due to exacerbation, and 40% discontinued due to disease under control; with injectable corticosteroids, 72% started due to AD exacerbation, and 59% discontinued due to disease well controlled. Methotrexate was recorded in this study to be used for treatment induction which seems at odds with its relatively slow onset of action to improve AD from 2 weeks to 3 months onwards (11).

With respect to treatment persistence, a retrospective cohort study of 1963 adult patients in the USA who received dupilumab treatment showed the persistence at 6 and 12 months was 91.9% (95% CI: 90.7%–93.2%) and 77.3% (75.0%–79.7%), respectively (27). Similarly, in the BioDay registry, which included 402 adult patients receiving dupilumab across multiple centers in the Netherlands, the overall drug survival rates for dupilumab were 91% and 88% after 1 and 2 years, respectively (28). This is in contrast to the drug persistence seen with other systemic treatments − 4.8 months for cyclosporine and 7.3 months for methotrexate observed in the present study, and of 7.9 and 7.3 months for cyclosporine and methotrexate, respectively, in the BioDay study (28). Studies prior to the introduction of biologics also showed poor drug persistence of immunosuppressants as a class, of less than 32% over 12 months (29). In another small retrospective study of 56 patients in France, drug survival was 12 months with methotrexate compared with two months with cyclosporine (30). Taken together, the real-world persistence of dupilumab appears to offer stable treatment for AD patients.

Limitations of the current study include that this is an observational study with limited patient numbers and that the patient population is relatively young, with a high disease burden, including patients receiving systemic treatments, which is not representative of all AD patients. However, we feel that real-world data collected in a practice setting, rather than a clinical trial, adds an additional source of data to inform physician treatment choices more reflective of everyday practice. EUROSTAD will continue to follow this patient cohort over time, allowing for more insight into ongoing treatment choices and disease course of patients with relatively severe AD in a real-world setting.

Conclusions

In conclusion, this 12-month interim EUROSTAD study analysis highlights the current trends and duration of use in systemic treatments for moderate-to-severe AD. Among all systemic treatments for AD, dupilumab was the least likely to be discontinued, while cyclosporine and corticosteroids were primarily limited to episodic flare management, consistent with current treatment guidelines.

Author contribution

MdBW, MA contributed to study concept and design, analysis, and interpretation, provided critical feedback on the manuscript, approved the final manuscript for submission, and were accountable for the accuracy and integrity of the manuscript. SJ conducted statistical analyses on the data. All authors interpreted the data, provided critical feedback on the manuscript, approved the final manuscript for submission, and were accountable for the accuracy and integrity of the manuscript.

Disclosure statement

MdBW is a consultant, advisory board member, and/or speaker for AbbVie, Almirall, Aslan Pharmaceuticals, Eli Lilly, Galderma, Janssen, LEO Pharma, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, and UCB. AEP is an advisory board member, speaker or investigator for AbbVie, Almirall, Bristol Myers Squibb, Eli Lilly, La Roche-Posay, LEO Pharma, Novartis, Pfizer, Sanofi, and UCB. SMF is a speaker and consultant for Drex Pharma, Menarini, Novartis, Pierre Fabre Laboratories, Sanofi Genzyme, and SVR; Principal Investigator for Eli Lilly, Novartis, Regeneron Pharmaceuticals, Inc., and Sanofi Genzyme. AP is an advisory board member, investigator for, and received grants from Eli Lilly; advisory board member, and/or investigator, and/or speaker for, and/or has received grants from AbbVie; and advisory board member for and received grants from Almirall, Eli Lilly, La Roche-Posay, LEO Pharma, Menarini, Novartis, Pierre Fabre, Roche, Sanofi Genzyme, Pfizer, and UCB. AS is a Principal Investigator for Regeneron Pharmaceuticals, Inc. and Sanofi Genzyme. MLS is an advisory board member and consultant for Sanofi Genzyme; investigator for AbbVie, Novartis, and Sanofi Genzyme; and consultant for Regeneron Pharmaceuticals, Inc. MT is an investigator, speaker, and consultant for Regeneron Pharmaceuticals, Inc. and/or Sanofi Genzyme; investigator, speaker and consultant for AbbVie; investigator and consultant for Lilly; consultant for Medac. MA is an employee and shareholder for Regeneron Pharmaceuticals, Inc. SJ and MD are employees of Sanofi Genzyme and may hold stock and/or stock options in the company.

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