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Effect of Specific Immunoglobulin E Response and Comorbidities on Effectiveness of MP-AzeFlu in a Real-Life Study

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Keywords
Allergic rhinitis · Allergic rhinitis phenotype · Comorbidities · Immunoglobulin E response · Visual analog scale

Abstract
Introduction: Phenotyping allergic rhinitis (AR) by immunoglobulin E (IgE) sensitivity and comorbidities may help characterize AR and provide a framework for treatment decisions. ***Methods:*** This prospective, noninterventional study evaluated the effectiveness of MP-AzeFlu (azelastine hydrochloride plus fluticasone propionate intranasal spray formulation) across AR phenotypes. Patients with moderate-to-severe seasonal or perennial AR for whom MP-AzeFlu was prescribed were enrolled. AR subpopulations (ARPs) were assigned based on the classification of IgE response and comorbidities. AR symptoms over the previous 24 h were documented using an AR visual analog scale (AR-VAS), with ratings from "not at all bothersome" (0 mm) to "extremely bothersome" (100 mm), at the inclusion visit and on days 1, 3, 7, and the last day of the study (approximately day 14). AR quality-of-life measures were recorded using a VAS. ***Results:*** A total of 1,103 patients with AR were included. Mean baseline AR-VAS scores ranged from 70.3 to 75.1 mm (severe) across ARPs. In the overall population, 86.6% of patients responded to treatment (AR-VAS score <50 mm on ≥1 days). In the ARPs, response rates ranged from 79.3 to 89.6%. Mean reduction in AR-VAS scores ranged from 47.9 to 40.9 mm, a decrease from severe to mild across all ARPs. Quality-of-life VAS scores were similarly reduced in the total population and ARPs. ***Discussion/Conclusion:*** MP-AzeFlu treatment reduced VAS severity and quality-of-life scores from baseline in the total population and ARPs, supporting MP-AzeFlu as an effective treatment for all patients with moderate-to-severe AR, regardless of AR phenotype or comorbidities.

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Introduction

Allergic rhinitis (AR) is a common atopic disorder that frequently co-occurs with other conditions [1]. Common atopic comorbidities include asthma, conjunctivitis, atopic dermatitis, food allergy, urticaria, and anaphylaxis [1–3]. Furthermore, other disorders are related to AR, presenting as multimorbid rhinosinusitis, middle ear problems (e.g., otitis media), and throat and laryngeal problems [1].

The presence of allergic comorbidities is often linked with the persistence or severity of allergic diseases, including AR. When the presence of comorbidities is considered in conjunction with specific immunoglobulin E (IgE) sensitization characteristics, phenotypic patterns emerge [4, 5]. Therefore, the presence of comorbidities and IgE polysensitization have been utilized to develop a new phenotypic classification system for allergic diseases. According to the MeDALL study by Bousquet and colleagues, the 3 primary phenotypes are IgE response to a single environmental allergen with no family history (low IgE responders), polyclonal IgE response to environmental allergens with family history (high IgE responders), and nonallergic polyclonal IgE response without family history (late-onset and local polyclonal IgE disease) [6]. Patients who do not fit within 1 of these 3 classifications are considered to have an intermediate phenotype. Phenotyping AR using specific IgE sensitization and family history of disease may help characterize allergic diseases, provide a clinical framework to inform treatment decisions, and improve the design of clinical trials [6].

Treatments for AR include oral H_1 antihistamines, intranasal corticosteroid (INCS) sprays, or intranasal H_1 antihistamine (INAH) sprays [7]. For some patients with moderate-to-severe persistent AR, INCS-INAH combination therapies may be required. In the Allergic Rhinitis and its Impact on Asthma (ARIA) 2016 guideline update, treatment with an INCS-INAH combination formulation is a first-line recommendation for patients with AR [8].

Azelastine hydrochloride has been formulated with fluticasone propionate in a single spray (MP-AzeFlu) for the treatment of AR. MP-AzeFlu is a safe, effective, and rapid-acting option for treating AR symptoms, including nasal congestion [9], loss of smell [10], and nasal hyperreactivity [11]. MP-AzeFlu has demonstrated a superior effect compared with other intranasal drugs in monotherapy at both the symptom and anti-inflammatory levels [12, 13]. In this analysis of a real-life study, the objective was to evaluate the effectiveness of MP-AzeFlu (azelastine hydrochloride/fluticasone propionate nasal spray) across AR phenotypes.

Materials and Methods

Study Design

This multinational, multicenter, prospective, noninterventional, real-life study was conducted in Austria, Germany, Czech Republic, Hungary, The Netherlands, and Ireland. Ethics approval was obtained according to the national laws and guidelines for each country. The study was conducted from February 21, 2018, to April 30, 2019. General practitioners, allergists, otorhinolaryngologists, pneumonologists, dermatologists, and pediatricians participated in the study.

The study period was approximately 2 weeks long and consisted of an inclusion visit (day 0) and a control visit on or around day 14 (last day), allowing for some flexibility depending on usual clinical practice. Patients received 5 patient cards at the inclusion visit to record symptom scores and other outcomes using an AR visual analog scale (AR-VAS, 0–100 mm). Physicians collected patient cards at the control visit or by mail.

All patients enrolled in the study received MP-AzeFlu (Dymista®, Mylan Pharmaceuticals), which was prescribed by physicians independently and before the decision to include a patient in the study, for 14 consecutive days. Prior to administration, physicians confirmed that patients understood the instructions for use. MP-AzeFlu was dosed as 1 spray in each nostril twice daily (total daily dose, 548 μg azelastine hydrochloride, and 200 μg fluticasone propionate), as recommended in the prescribing information [14].

Participants

Patients had moderate-to-severe (defined by meeting at least 1 of the following 4 criteria: impaired sleep, impaired daily activities, impaired work productivity/school performance, or troublesome symptoms) seasonal AR or perennial AR according to ARIA criteria [15]. For all participants, MP-AzeFlu was prescribed for the first time at study initiation.

Inclusion criteria were first-time prescription of MP-AzeFlu according to the summary of product characteristics, age 12 years or older, moderate-to-severe seasonal AR or perennial AR, acute symptoms of AR (AR-VAS ≥50 mm, suggestive of uncontrolled AR) [16] on the day of inclusion, written informed consent by patient and (if applicable) by caregiver for patients younger than 18 years, and ability to understand the instructions for the use of MP-AzeFlu according to the summary of product characteristics and patient leaflet. Exclusion criteria were known allergic reaction to MP-AzeFlu or any of its ingredients, pregnancy or planned pregnancy, breastfeeding, inability to provide informed consent, or missing consent.

Study Measures

On day 0, the physician documented patient data, including demographics, medical history of AR, number and types of allergens, allergies and other comorbidities, specific IgE response results according to prior serum IgE testing or skin prick testing, and family history of allergies. The numbers and types of allergens were defined by either the results of specific IgE testing or answers to a question about known allergic sensitization. If both specific IgE test results and survey question response data were available, the higher number of allergens was chosen for the classification. For example, a patient with 4 allergens identified by specific IgE testing and 5 allergens selected in the survey was considered to have 5 allergens for the purposes of the study. Prior specific IgE testing results were available for 372 of the 1,103 patients in the study.

Table 1. Allergic rhinitis subpopulations

ARPs	Criteria	MeDALL description [6]
ARP1	Specific IgE response restricted to 1 environmental allergen, without family history	Low IgE responders, both in number of components and level of specific IgE
ARP2	Polyclonal IgE response to >5 environmental allergens, with family history	High IgE responders, both in number of components and level of IgE; usually symptomatic, with an early-life onset and a high rate of comorbidities over time
ARP3	Nonallergic polyclonal IgE (patients with IgE test, but no increased total IgE value), without family history	Usually late-onset disease and local polyclonal IgE (e.g., local IgE production in the upper airway mucosa but skin prick tests and serum IgE testing are negative)
ARP4	Intermediate phenotypes	Polyclonal IgE response without family history or IgE response restricted to few allergens (e.g., 2–5 allergens)
ARP5	Comorbidities, including asthma, food allergy, eczema/atopic dermatitis, or severe allergic reaction	Not applicable

ARP, allergic rhinitis subpopulation; IgE, immunoglobulin E.

Patient data were used to assign AR subpopulations (ARPs) for all patients. The ARPs are described in Table 1. ARP1, ARP2, ARP3, and ARP4 were defined based on the classification of IgE-mediated diseases as described by Bousquet and colleagues [6]. ARP1 through ARP4 were mutually exclusive groups, but patients in ARP1 through ARP4 could also be assigned to ARP5 on the basis of the presence of comorbidities.

AR symptoms over the past 24 h were documented using a printed, single-line VAS with ratings from "not at all bothersome" (0 mm) to "extremely bothersome" (100 mm). How bothersome a patient found his or her symptoms over the past 24 h was recorded during the inclusion visit (day 0), and on days 1, 3, 7, and the last study day (on or around day 14). The primary outcome was treatment response, which was considered an AR-VAS score of <50 mm (suggestive of AR control) [16] at least once during the study.

Secondary objectives included AR quality-of-life VAS measures, using some of the criteria for ARIA severity classification: troublesomeness of sleep quality; daily home, work, or school activities; daily social activities; and daily outdoor activities. These measures were recorded on days 0 and 7, as well as on the last day of the study.

Statistical Methods

Subpopulation analyses were performed for patients with different ARPs, countries, age ranges, and sexes. Statistical analyses were performed using the statistical software package SAS (SAS Institute Inc., Cary, NC, USA) version 9.4 or higher.

Results

Study Population

Of the 1,154 patients enrolled in the study, 51 were excluded because their data had not been confirmed by the physician, leaving 1,103 patients for the final analysis (full analysis set). Within the past year, the majority of patients (82.9%) had used ≥1 treatments for symptomatic AR, and 62% used ≥2 allergy medications. Patients comprising the full analysis set had a mean (standard deviation) age of 40.0 (16.6) years, and 56.6% were female. Mean baseline VAS for overall AR symptoms ranged from 70.3 to 75.1 mm (severe) across the different ARPs. Baseline demographics, including baseline VAS scores, are outlined in Table 2. Previous symptomatic AR treatments during the past year are reported in Table 3.

Effectiveness of MP-AzeFlu by ARP

Response to treatment was defined as a reduction in AR symptoms to <50 mm on the VAS, the cutoff that differentiates controlled AR from uncontrolled AR [16], in ≥1 measurements. The response rate in the full analysis set was 86.6%. In the ARPs, the response rates ranged from 79.3 to 89.6%. By day 1, the median (interquartile range) change in VAS was 10 mm (25.3 mm); by day 3, the median (interquartile range) change was 22 mm (40.1 mm). By the last day, the median change was 49 mm (62.3 mm).

From day 1 through the last day of the study, mean AR-VAS scores decreased across all subpopulations ($p < 0.0001$; shown in Fig. 1). Mean reduction in VAS score from baseline to the last day ranged from 47.9 mm (ARP2) to 40.9 mm (ARP3). Furthermore, the rates of reduction of AR-VAS scores were comparable across countries, age ranges, and sexes.

Table 2. Baseline patient demographics

Baseline characteristics	Full analysis set (N = 1,103)	ARP1 (IgE response to 1 environmental allergy without family history) (n = 115)	ARP2 (polyclonal IgE response to >5 allergens with family history) (n = 89)	ARP3 (nonallergic polyclonal IgE without family history) (n = 53)	ARP4 (intermediate phenotypes) (n = 667)	ARP5 (patients with comorbidity) (n = 421)
Sex, *n* (%)						
Male	474 (43.0)	53 (46.1)	40 (44.9)	17 (32.1)	289 (43.4)	171 (40.6)
Female	624 (56.6)	62 (53.9)	49 (55.1)	36 (67.9)	373 (55.9)	248 (58.9)
Missing	5 (0.5)	0	0	0	5 (0.75)	2 (0.48)
Age, *n* (%)						
12–17 years	82 (7.4)	7 (6.1)	7 (7.9)	3 (5.7)	55 (8.3)	35 (8.3)
18–65 years	937 (85.0)	94 (81.7)	78 (87.6)	48 (90.6)	573 (85.9)	353 (83.9)
>65 years	84 (7.6)	14 (12.2)	4 (4.5)	2 (3.8)	39 (5.9)	33 (7.8)
Allergic sensitization by number of allergens, *n* (%)						
1	178 (16.1)	115 (100)	0	20 (37.7)	9 (1.35)	43 (10.2)
2–5	570 (51.7)	0	7 (7.9)	25 (47.2)	563 (84.4)	230 (54.6)
>5	176 (16.0)	0	82 (92.1)	6 (11.3)	94 (14.1)	111 (26.4)
Unknown	179 (16.2)	0	0	2 (3.8)	1 (0.2)	37 (8.8)
Type of AR, *n* (%)						
PAR	120 (10.9)	61 (53.0)	1 (1.1)	11 (20.8)	30 (4.5)	30 (7.1)
SAR	435 (39.4)	51 (44.4)	17 (19.1)	23 (43.4)	274 (41.1)	137 (32.5)
PAR + SAR	444 (40.3)	0	71 (79.8)	17 (32.1)	359 (53.8)	237 (56.3)
Missing	104 (9.4)	3 (2.6)	0	2 (3.8)	4 (0.6)	17 (4.0)
Allergic comorbidities, *n* (%)						
Asthma	267 (24.2)	19 (16.5)	43 (48.3)	17 (32.1)	179 (26.8)	267 (63.4)
Dermatitis/eczema	127 (11.5)	9 (7.8)	28 (31.5)	4 (7.6)	76 (11.4)	127 (30.2)
Food allergy/allergies	109 (9.9)	3 (2.6)	17 (19.1)	5 (9.4)	73 (10.9)	109 (25.9)
Severe allergic reactions	30 (2.7)	0	3 (3.4)	1 (1.9)	22 (3.3)	30 (7.1)
None	593 (53.8)	75 (65.2)	25 (28.1)	27 (50.1)	350 (52.5)	0
None	164 (14.9)					
Baseline VAS score for overall AR symptoms (0–100 mm), mm						
Mean	73.2	71.4	75.1	70.3	73.1	74.4
SD	13.4	13.4	13.7	13.1	13.5	13.4

AR, allergic rhinitis; ARP, allergic rhinitis subpopulation; IgE, immunoglobulin E; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis; SD, standard deviation; VAS, visual analog scale.

Changes in Quality-of-Life Measures

Quality of life was evaluated using VAS scores, as shown in Figure 2. Changes in troublesomeness of sleep quality from day 0 to the last day ranged from 33.3 mm (ARP2) to 39.6 mm (ARP3). Changes in troublesomeness of daily activities at work or school from day 0 to the last day ranged from 35.0 mm (ARP1) to 38.6 mm (ARP2). Improvements in troublesomeness of daily social activities from day 0 to the last day ranged from 32.3 mm (ARP4) to 38.3 mm (ARP3). Finally, troublesomeness of daily outdoor activities from day 0 to the last day improved by a range of 35.5 mm (ARP1) to 46.4 mm (ARP2).

Moderate, statistically significant correlations were seen between overall symptom improvement and improvement in sleep quality and daily activities (Pearson correlation coefficient = 0.40–0.46; $p < 0.0001$). By contrast, the correlations among the different activities were stronger (Pearson correlation coefficient = 0.44–0.82; $p < 0.0001$).

Table 3. Previous symptomatic AR treatments since last year

	Full analysis set (N = 1,103), *n* (%)
Oral, nonsedating H_1 antihistamine	506 (45.9)
INCS	471 (42.7)
Intranasal decongestant	191 (17.3)
INAH	177 (16.0)
Oral first-generation H_1 antihistamine	162 (14.7)
Ocular H_1 antihistamine	133 (12.1)
Oral or nebulized corticosteroid	99 (9.0)
Intranasal mast cell stabilizer	62 (5.6)
Oral leukotriene antagonist	50 (4.5)
Ocular mast cell stabilizer	42 (3.8)
Oral decongestant	26 (2.4)
Other	54 (4.9)
Unknown	24 (2.2)

AR, allergic rhinitis; INCS, intranasal corticosteroid; INAH, intranasal H_1 antihistamine.

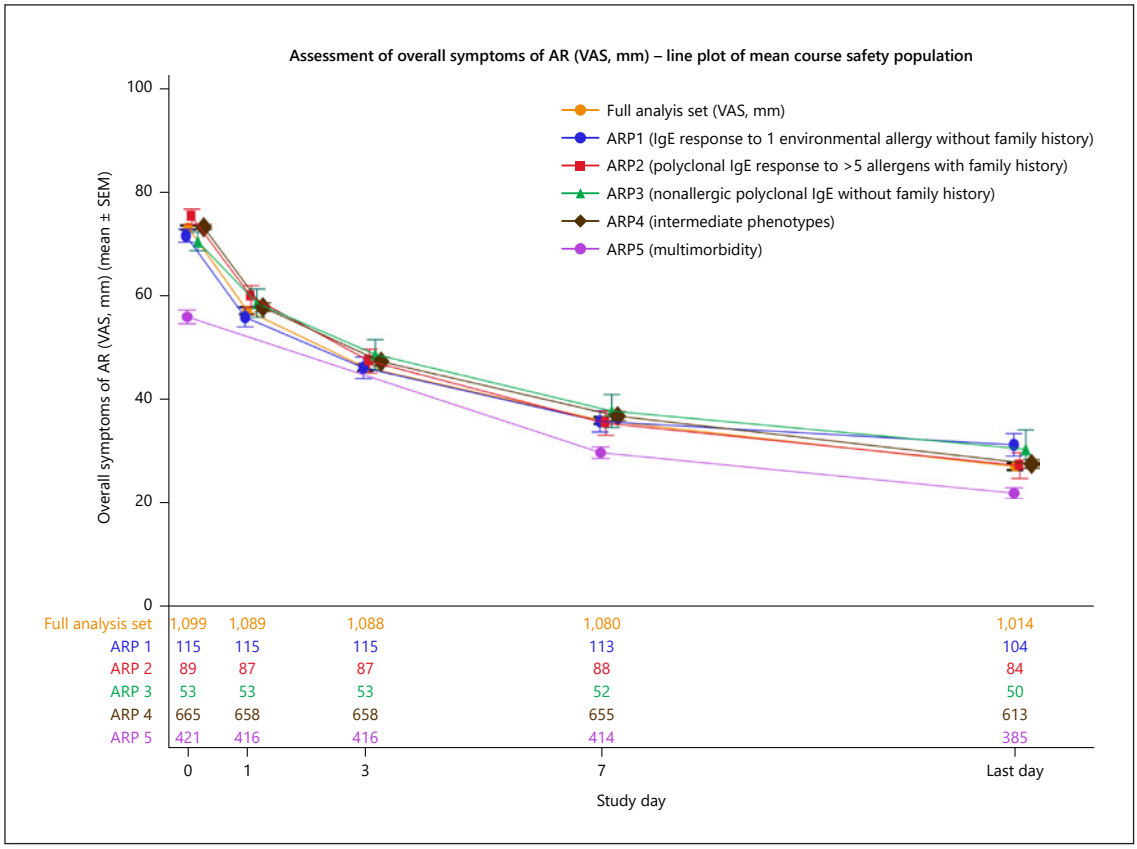


Fig. 1. Time course of mean VAS score (mm) for overall AR symptoms from day 0 to the last study day. AR, allergic rhinitis; ARP, allergic rhinitis subpopulation; IgE, immunoglobulin E; SEM, standard error of the mean; VAS, visual analog scale.

Discussion

In this prospective, noninterventional, real-life study, MP-AzeFlu was associated with significantly reduced AR symptom severity according to AR-VAS scores. In past studies, VAS scores have shown concordance with AR severity according to ARIA criteria [17, 18]. In a study by Del Cuvillo and colleagues, VAS scores were used to classify AR symptom severity as mild (<40 mm), moderate (40–70 mm), or severe (>70 mm) [19]. The baseline VAS scores in our study suggest that despite high baseline use of allergy medication in the past year, AR symptoms were severe, potentially resulting in low quality of life.

In previous studies, VAS scores have also been used to evaluate the clinical relevance of changes in AR symptoms following treatment. Suggested cutoffs of clinical relevance for changes in VAS scores range from 10 to 23 mm [17, 18, 20]. After 1 day of treatment with MP-AzeFlu, the mean VAS score improved by more than 10 mm in the full analysis set, suggesting rapid onset of action, with a clinically relevant improvement in scores. Furthermore, by day 3, a clinically important change of ≥23 mm was reported in nearly 50% of all patients (median change, 22 mm); on the last day, >75% of patients had a clinically relevant improvement (upper quartile, 30 mm). The VAS scores for quality-of-life measures collected in this study provide additional support for the benefit of MP-AzeFlu treatment in the overall patient population, as well as in the subpopulations that were analyzed.

Use of MP-AzeFlu significantly reduced mean AR-VAS scores from approximately 73–27 mm, reflecting a change from severe to mild AR symptom severity in the full analysis set and across all ARPs. Furthermore, these changes in scores reflect improvement in AR symptom control. All enrolled patients had uncontrolled AR at the time of enrollment (AR-VAS ≥50 mm) [16]. By the end of the study, the vast majority of patients (86.6%) fulfilled response criteria, and thus control criteria, for ≥1 time points.

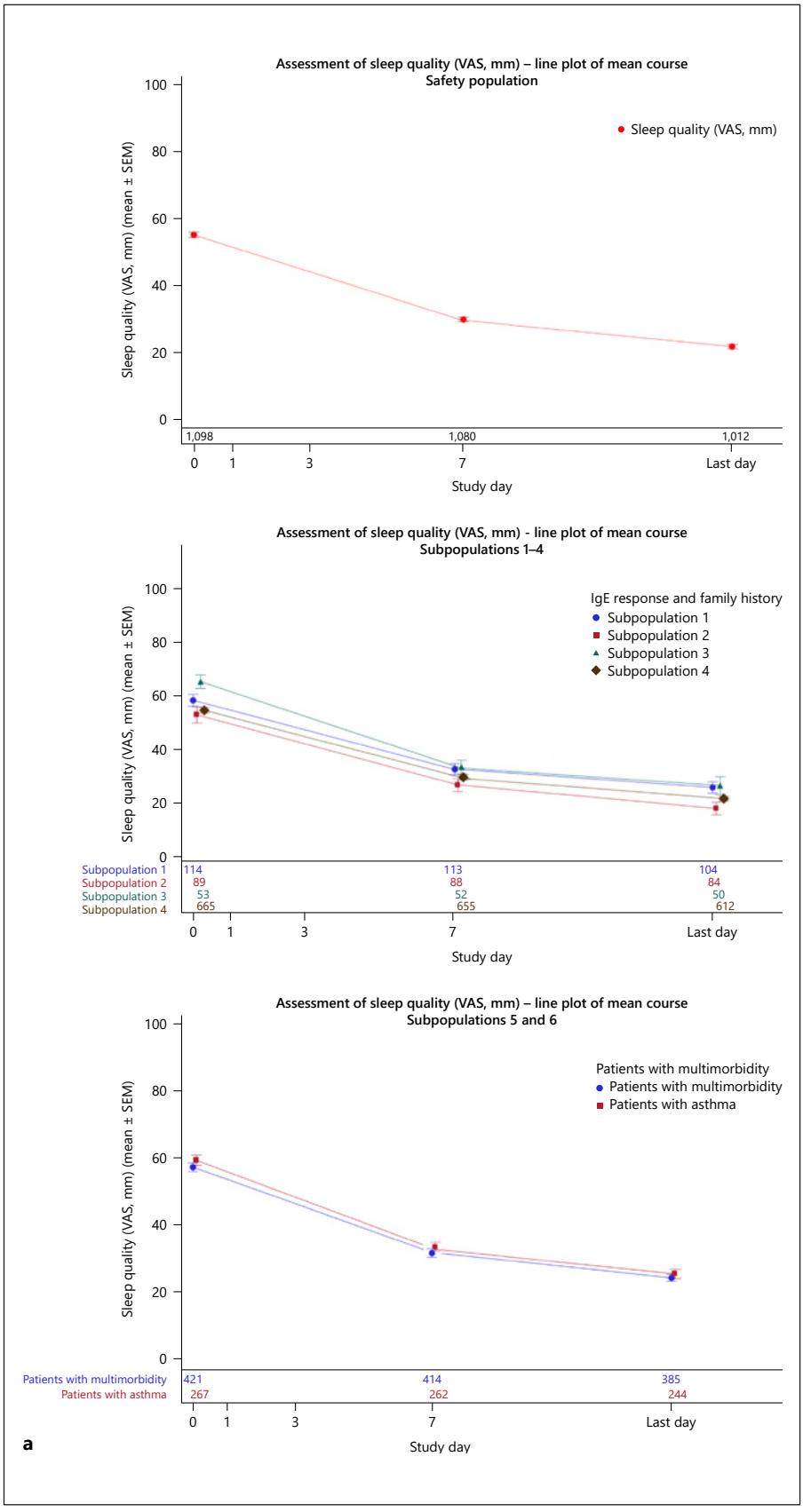
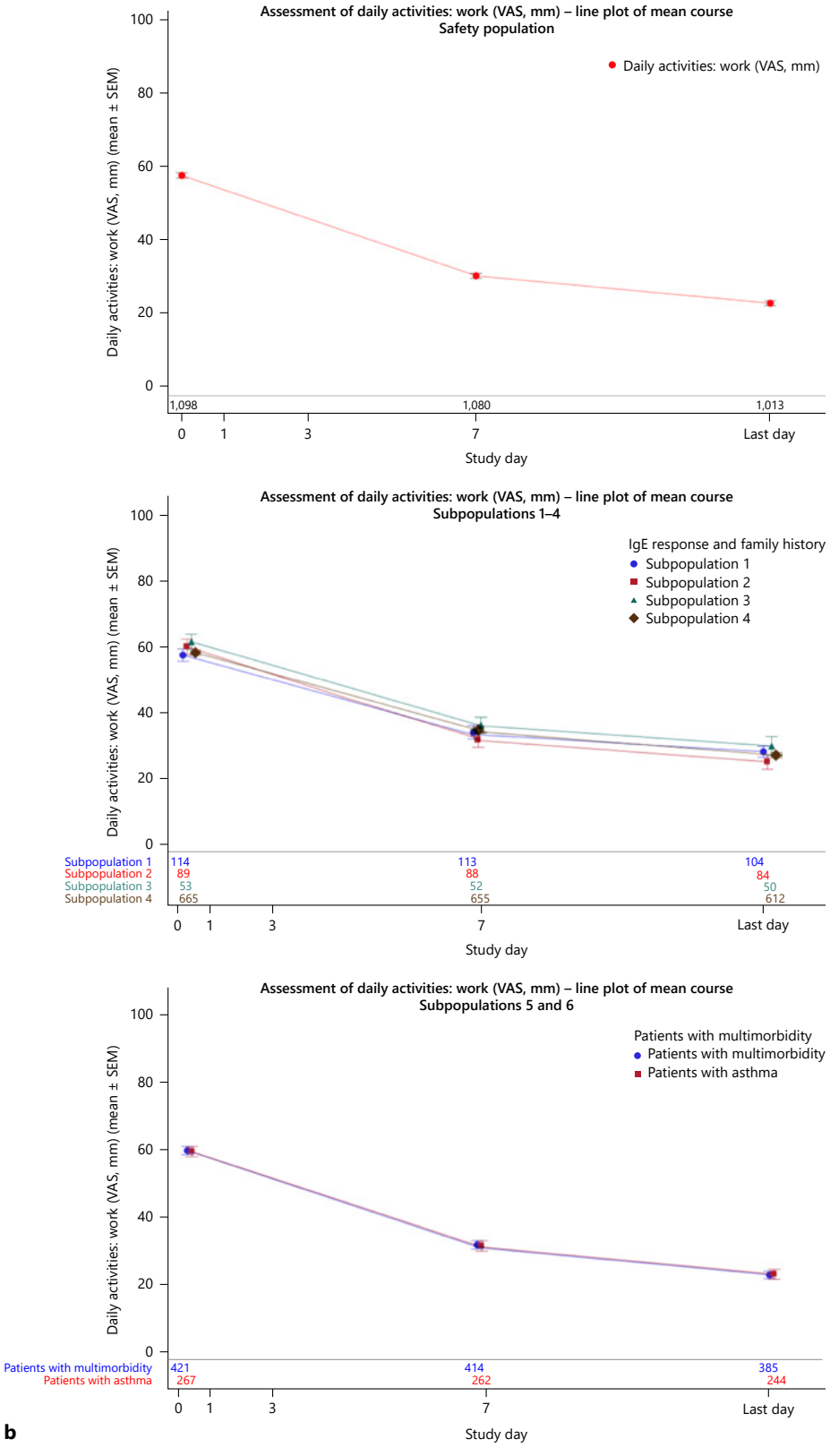


Fig. 2. Change in VAS score from day 0 to last day of the study (approximately day 14) in the general study population and ARPs for sleep quality (**a**), daily activities at work or school (**b**), daily social activities (**c**), and daily outdoor activities (**d**). ARP, allergic rhinitis subpopulation; IgE, immunoglobulin E; SEM, standard error of the mean; VAS, visual analog scale.



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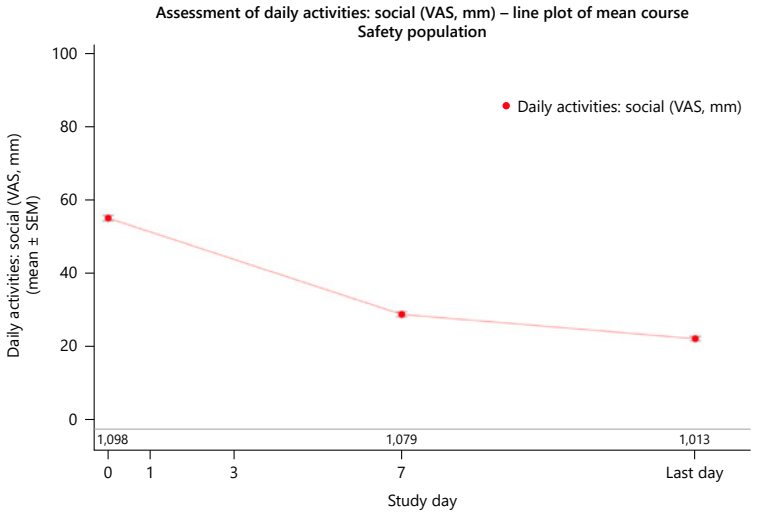

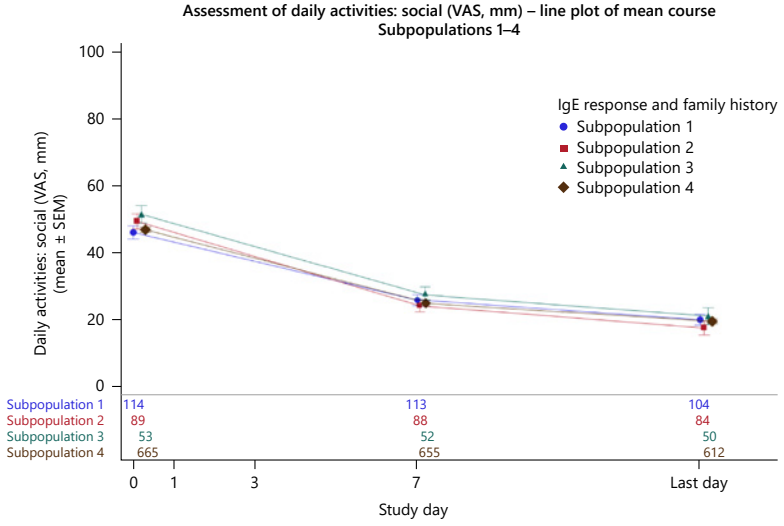

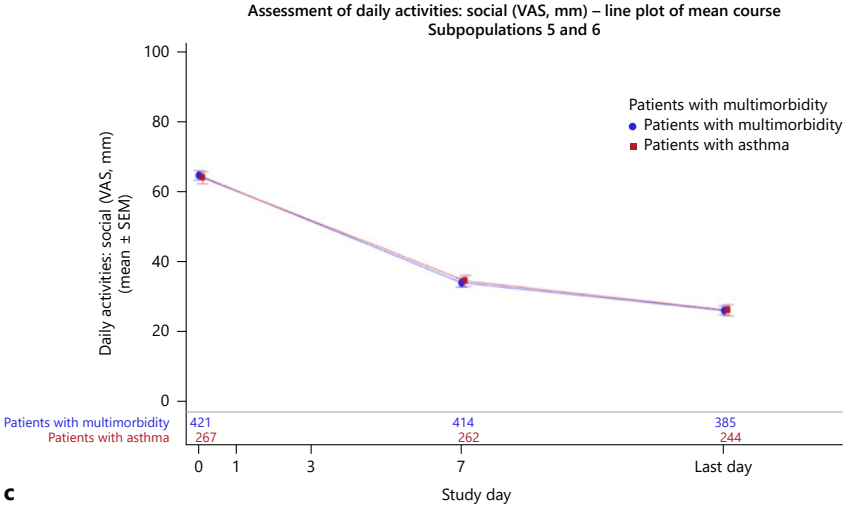

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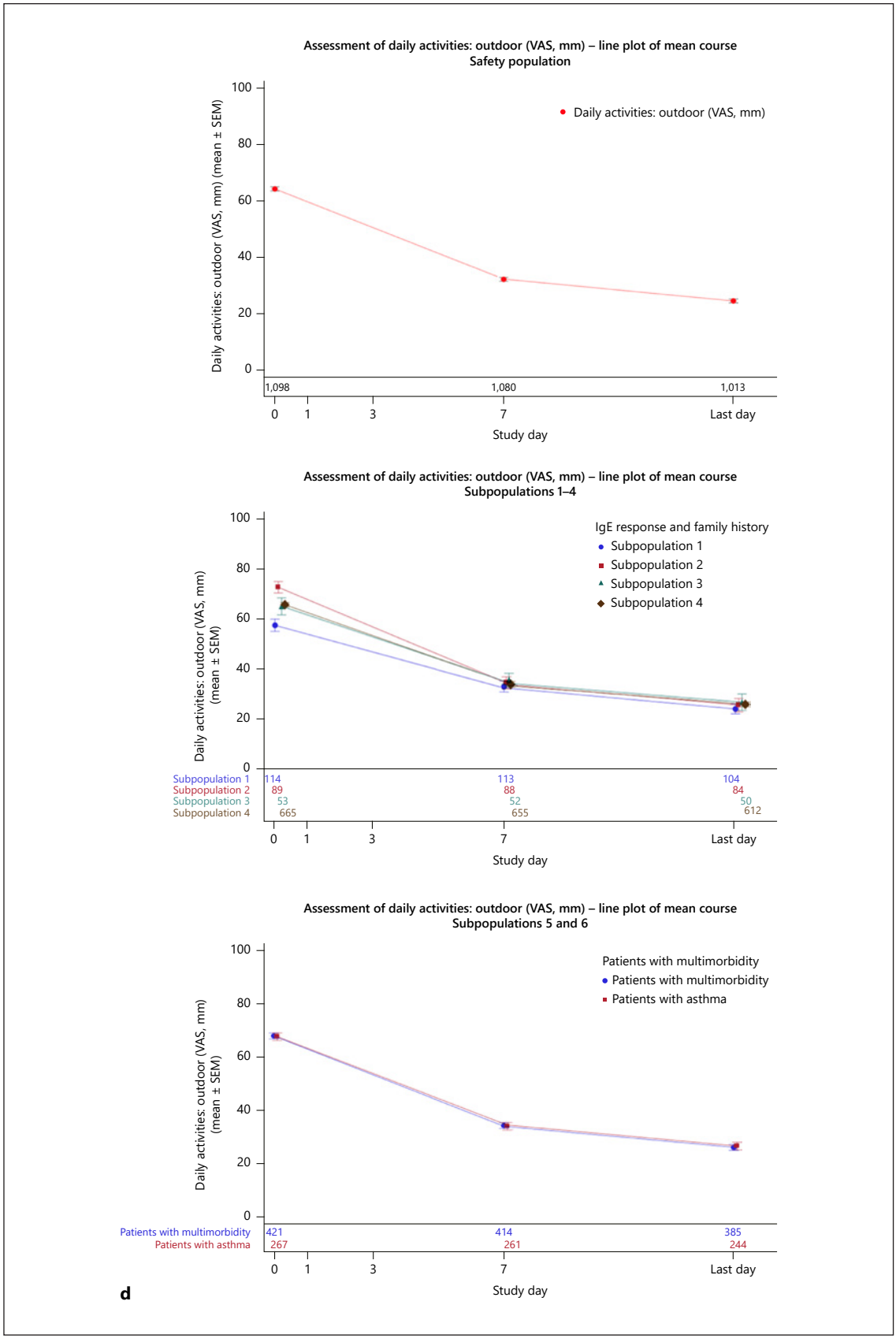
Assessment of daily activities: outdoor (VAS, mm) – line plot of mean course
Safety population
Daily activities: outdoor (VAS, mm)
Daily activities: outdoor (VAS, mm) (mean ± SEM)
100
80
60
40
20
0
1,098
1,080
1,013
0
1
3
7
Last day
Study day
Assessment of daily activities: outdoor (VAS, mm) – line plot of mean course
Subpopulations 1–4
IgE response and family history
Subpopulation 1
Subpopulation 2
Subpopulation 3
Subpopulation 4
Daily activities: outdoor (VAS, mm)
(mean ± SEM)
Subpopulation 1 114 113 104
Subpopulation 2 89 88 84
Subpopulation 3 53 52 50
Subpopulation 4 665 655 612
Study day
Assessment of daily activities: outdoor (VAS, mm) – line plot of mean course
Subpopulations 5 and 6
Patients with multimorbidity
Patients with multimorbidity
Patients with asthma
Daily activities: outdoor (VAS, mm)
(mean ± SEM)
Patients with multimorbidity 421 414 385
Patients with asthma 267 261 244
Study day
d
2
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One of the goals of characterizing AR phenotypes was to provide a clinical framework for management decisions [6]. Asthma is an example of a disease state with endotype- and phenotype-driven treatment paradigms [21]. Since the proposal of AR phenotypes based on IgE sensitization and comorbidities, no studies have evaluated AR treatment safety and efficacy based on the disease phenotype classification system described by Bousquet and colleagues [6]. In the present study, we have characterized treatment response to MP-AzeFlu based on AR phenotypes. Our results suggest that MP-AzeFlu is effective across the studied subpopulations, regardless of IgE sensitization, family history, or the presence of comorbidity, with no noted differences in effectiveness among subpopulations.

Study limitations include the observational nature of the study and the relatively small size of the different subpopulations, particularly ARP3. However, participants were enrolled from several countries, providing evaluable datasets with no notable differences among countries.

Conclusion

MP-AzeFlu was associated with substantially reduced AR symptom severity and increased control from baseline to days 1, 3, and 7, as well as the last day, in the general study population and in all ARPs. Overall, more than three-quarters of patients achieved clinically significant reductions in AR-VAS during the study. These results support MP-AzeFlu as an effective treatment for patients with moderate-to-severe AR, regardless of phenotype.

Acknowledgements

We would like to thank the subjects who participated in the trial.

Statement of Ethics

Ethics approval was obtained according to the national laws and guidelines for each country. This investigation represented a noninterventional study as defined by European regulations, that is, the rules imposed for this observational plan did not interfere with the physician's common therapy. The study was carried out in accordance with the national laws and guidelines current at that time for conducting noninterventional studies.

Conflict of Interest Statement

L.K. worked as a paid consultant for Allergopharma, MEDA/Mylan, HAL Allergie, ALK Abello, and LET! Pharma and has received financial grants from Allergopharma, ALK Abello, Allergy Therapeutics, Stallergenes, Quintiles, HAL Allergie, LET! Pharma, Sanofi, AstraZeneca, GSK, ASIT Biotech, and Lofarma. D.P. has board membership with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Napp, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, and Teva Pharmaceuticals; consultancy agreements with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Napp, Novartis, Pfizer, Teva Pharmaceuticals, and Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational & Pragmatic Research Institute Pte Ltd.) from AKL Research and Development Ltd., AstraZeneca, Boehringer Ingelheim, British Lung Foundation, Chiesi, Circassia, Mylan, Mundipharma, Napp, Novartis, Pfizer, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Teva Pharmaceuticals, Theravance, UK National Health Service, and Zentiva (Sanofi Generics); payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Merck, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi Genzyme, and Teva Pharmaceuticals; payment for manuscript preparation from Mundipharma and Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma and Novartis; payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Circassia, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; funding for patient enrollment or completion of research from Chiesi, Novartis, Teva Pharmaceuticals, and Zentiva (Sanofi Generics); stock/stock options from AKL Research and Development Ltd., which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 74% of Observational & Pragmatic Research Institute Pte. Ltd. (Singapore); and is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation Programme and Health Technology Assessment. G.G. was a paid consultant and speaker for AstraZeneca, Chiesi, BMS, MSD, Berlin Chemi, Boehringer Ingelheim, Roche, Novartis, Pfizer, Orion, including Ipsen, and Mylan as speaker. M.E. is an employee of MEDA Pharma GmbH & Co. KG (a Mylan Company). A.K. is a Mylan, Inc. employee and shareholder. AK has also been employed at Novartis and Lundbeck pharmaceutical companies. F.K. is an employee of MEDA Pharma GmbH & Co. KG (a Mylan Company). D.T.N. is an employee of MEDA Pharma GmbH & Co. KG (a Mylan Company). R.V.W. has nothing to disclose. W.P. has been a paid speaker for and worked as a paid consultant for AstraZeneca, Boehringer lngelheim, Chiesi, GSK, Novartis, and TEVA. H.K. worked as a paid consultant for AstraZeneca, Boehringer lngelheim, Chiesi, GSK, and Novartis. G.S. has received financial grants from GSK for mepolizumab study and has worked as a paid consultant and speaker for Meda/Mylan and ALK-Abello. J.M. has conducted research/received research grant support from MYLAN-MEDA Pharma, URIACH Group, GSK, MSD, FAES, UCB; received consultancy fees from MYLAN-MEDA Pharma, URIACH Group, Allakos, ALK-Abelló, Genentech – Roche, Novartis, Regeneron, Sanofi Genzyme, GSK, MSD, Harlington Pharmaceuticals, and UCB; and has worked as paid instructor for Novartis and as speaker for MYLAN-MEDA Pharma, URIACH Group, and Genentech – Roche.

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Author Contributions

L.K., D.P., G.G., M.E., A.K., F.K., D.T.N., R.v.W., W.P., H.K., G.S., and J.M. have made substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work: drafting the work or revising it critically for important intellectual content; provided final approval of the version to be published; and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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