



Treatment of allergic rhinitis using mobile technology with real-world data: The MASK observational pilot study

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Abbreviations: AHA, active and healthy aging; AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; AZE, azelastine; EIP, European Innovation Partnership; EU, European Union; FF, fluticasone furoate; FP, fluticasone propionate; GRADE, grading of recommendations, assessment, development, and evaluations; ICT, information and communications technology; INCS, intranasal corticosteroid; MACVIA, Contre les MALadies Chroniques pour un Vieillessement Actif; MASK, MACVIA-ARIA Sentinel Network; MF, mometasone furoate; MP-AzeFlu, Azelastine-Fluticasone propionate; OAH, oral H₁-antihistamines; OTC, over the counter; RCT, randomized controlled trial; RTSS, rhinoconjunctivitis total symptom score; REST, restricted analysis; TNSS, total nasal symptom score; VAS, visual analog scale.

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Abstract

Background: Large observational implementation studies are needed to triangulate the findings from randomized control trials as they reflect “real-world” everyday practice. In a pilot study, we attempted to provide additional and complementary insights on the real-life treatment of allergic rhinitis (AR) using mobile technology.

Methods: A mobile phone app (*Allergy Diary*, freely available in Google Play and Apple App stores) collects the data of daily visual analog scales (VAS) for (i) overall allergic symptoms, (ii) nasal, ocular, and asthma symptoms, (iii) work, as well as (iv) medication use using a treatment scroll list including all medications (prescribed and over the counter (OTC)) for rhinitis customized for 15 countries.

Results: A total of 2871 users filled in 17 091 days of VAS in 2015 and 2016. Medications were reported for 9634 days. The assessment of days appeared to be more informative than the course of the treatment as, in real life, patients do not necessarily use treatment on a daily basis; rather, they appear to increase treatment use with the loss of symptom control. The *Allergy Diary* allowed differentiation between treatments within or between classes (intranasal corticosteroid use containing medications and oral H1-antihistamines). The control of days differed between no [best control], single, or multiple treatments (worst control).

Conclusions: This study confirms the usefulness of the *Allergy Diary* in accessing and assessing everyday use and practice in AR. This pilot observational study uses a very simple assessment (VAS) on a mobile phone, shows novel findings, and generates new hypotheses.

KEYWORDS

mHealth, mobile technology, observational study, rhinitis, treatment

1 | INTRODUCTION

The treatment of allergic rhinitis (AR) is complex as many drugs are available in oral and/or topical formulations. Many guidelines for AR are evidence-based and have led to a better understanding and management of AR. However, guidelines are mostly based on randomized controlled trials (RCTs), typically undertaken on highly selected populations, often with limited/unclear generalizability to routine care contexts.¹⁻³

Large observational implementation studies are needed to triangulate RCT as they reflect “real world” every day use and practice more closely than RCTs in terms of the heterogeneous patient populations included, and the variety of medical interventions assessed.⁴ In RCTs, each subject is randomly assigned to a treatment or control group, whereas observational studies examine the possible effect of a treatment on subjects where the investigator has no control over the experiment and cannot randomize subject allocation.⁵ However, observational studies provide clinically relevant information in addition to RCTs.

MACVIA-ARIA Sentinel Network (MASK)-rhinitis (MASK for AR), an information and communications technology (ICT) system centered around the patient,⁶⁻⁸ is one of the implementation tools of the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA).^{9,10} A mobile phone app (*Allergy Diary*), launched in 22 countries,¹¹ uses visual analog scales (VAS) to assess rhinitis control and work impairment,¹² as well as a treatment scroll list including all medications customized for each country. The use of mobile health applications to conduct observational clinical studies requires the establishment of feasibility.

This pilot study was undertaken to provide additional and complementary insights into evidence derived from RCTs in the real-life treatment of AR. The *Allergy Diary*¹¹ was used to assess the control of rhinitis by medications.

2 | METHODS

2.1 | Design of the study

This prospective observational study of a mobile application—the *Allergy Diary*—was used to assess self-reported medication use.

The objectives of this study were (i) to report the median VAS global-measured values depending on the treatment received, (ii) to undertake a sensitivity analysis by comparing the results for 1 day of treatment, the full data set, and a restricted data set (ie, 2016 and the first 2 weeks of treatment), (iii) to investigate users receiving single prescribed treatments (MP-Aze-Flu, fluticasone furoate [FF], or MP monotherapy for rhinitis) and those receiving several treatments for rhinitis on the same day (comedication for rhinitis), and (iv) to assess initial severity monitored on the first day of use of the App on the treatment reported by users.

2.2 | Users

All consecutive users from May 21, 2015, to November 8, 2016, were included with no exclusion criteria. Some demographic characteristics (age, sex, country, and language) were recorded. The *Allergy Diary* was used by people who found it on the Internet, Apple App store, Google Play, or any other way. The pages of the App are on the Euforea-ARIA website (www.euforea.eu/about-us/aria.html). A few users were clinic patients who were asked by their physicians to use the app. Users were not requested to complete the diary for a minimum of days. However, due to anonymization of data, no specific information on the route of access to the app could be gathered as previously reported.^{11,13}

2.3 | Setting

Users from 15 countries filled in the *Allergy Diary* (Table 1).

2.4 | Allergy Diary

Geolocalized users assess their daily symptom control using the touch screen functionality on their smart phone to click on 5 consecutive VAS (ie, general, nasal and ocular symptoms, asthma, and work) (Figure S1). Users input their daily medications using a scroll list which contains all country-specific over the counter (OTC) and prescribed medications available (Figure S2). The list has been populated using IMS data.

2.5 | Ethics

The *Allergy Diary* is CE1 registered, but it was not considered by the Ethical Committee of the Cologne Hospital of the Medicines and Healthcare products Regulatory Agency (MHRA—GOV.UK) as a medical device given that it does not provide any recommendations concerning treatment or diagnosis. The terms of use were translated into all languages and customized according to the legislation of each country, allowing the use of the results for research purposes. The example of the UK terms of use has been provided in a previous paper.¹¹

The data were anonymized except for the geolocalized data which are never totally anonymous. This issue was carefully considered in the first paper on the *Allergy Diary*.¹¹

An Independent Review Board approval was not required.

2.6 | Outcomes

In this study, initial characteristics (Table S1),¹¹ 4 VAS measurements (VAS—global measured, VAS-nasal, VAS-ocular, and VAS-work, Table S2) and a calculated VAS-global-calculated score (VAS-nasal + VAS-ocular divided by 2) were considered. The VAS-asthma was not analyzed as there was a change in the question on June 1, 2016. VAS levels range from zero (not at all bothersome) to 100 (very bothersome). Independency of VAS questions was previously assessed using the Bland and Altman regression analysis.^{13,14}

TABLE 1 Country and number of users recording visual analog scale score using the *Allergy Diary* in the full data set

Country	Visual analog scales (VAS) measurements (d)				Total
	VAS measurements	1 (%)	2-7	8-14	
Austria	81 (55.5)	48	4	13	146
Belgium	22 (51.2)	18	1	2	43
Denmark	12 (52.2)	8	1	2	23
Finland	10 (43.5)	8	2	3	23
France	232 (69.0)	84	7	13	336
Germany	74 (50.7)	52	6	14	146
Greece	8 (57.1)	5	0	1	14
Italy	379 (55.4)	211	38	56	684
Lithuania	18 (35.3)	16	5	12	51
Netherlands	60 (54.5)	35	7	8	110
Poland	157 (60.1)	82	10	12	261
Portugal	305 (49.9)	226	28	52	611
Spain	64 (28.3)	59	31	72	226
Sweden	18 (52.9)	12	2	2	34
United Kingdom	86 (60.1)	43	6	8	143
Total	1526 (53.5)	907 (31.8%)	148 (5.2%)	270 (9.5%)	2851

Data from Australia, Brazil, Canada, Mexico, and Switzerland were excluded due to the low number of users (enrollment started in October 2016).

Days reported by users included days with or without treatment.

This study is another *Allergy Diary* study. None of the data used in the first paper¹¹ were used in this study. Data of the second paper were used, but the analysis was totally different as we analyzed medication effects whereas in the former paper the focus was on work productivity.¹³

2.7 | Selection of medications

The International Nonproprietary Names (INNs) classification was used for drug nomenclature.¹⁵ Monotherapy was defined as days when only one single medication for rhinitis was taken. Polymedication (comedication) was defined as days with 2 or more medications for rhinitis. Asthma medications were not considered in polymedication.

Avamys[®] (FF) and Dymista[®] (MP-AzeFlu) were the only prescribed medications. Mometasone furoate (MF) is OTC in the UK (since mid 2015), Sweden (since Feb 2013), and Finland (since Nov 2012), and we excluded users with possible OTC drugs.

2.8 | Biases

There are potential measurement biases when using apps as the information collected is usually restricted. The self-reported nature of the data represents another bias inherent to App usage. A bias might be introduced because app users may be a selected subset, and are therefore not fully representative of all patients with rhinitis. Finally, it is not known whether users fill in their information before or after treatment for a given day.

2.9 | Size of the study

In this exploratory pilot study, all registered users between May 21, 2015, and November 8, 2016, were included to obtain the best possible estimates for the specified time window.

2.10 | Statistical methods

A non-Gaussian distribution was found for the data. Nonparametric tests and medians (and percentiles) were used.

Some users reported VAS scores more than once a day. Before analysis, we proposed that if the same treatment was reported and the daily variation was under 30%, the highest VAS score would be used as previously.¹³ In the full data set, there were 631 days with multiple values, and of these, only 133 (1.4%) had a variation >30%. We decided that this number was not sufficient enough to impact the results and we used the highest value for the day.

2.11 | Analysis of the data

The study was not a longitudinal study because (i) there was an insufficient number of users reporting data over a period of 5 days (335), (ii) there was no clear pattern of treatment in users, (iii) most users did not report a stable and continuous period of treatment, and (iv) many users modified their treatment during the reporting period. Moreover, in the study, users are unselected, and it is not known whether the first day of use was the first day of treatment. Although there may be causal inferences, we used cross-sectional data for days of treatment. We analyzed the full data set and performed the following sensitivity analyses: (i) A restricted analysis

(REST) was performed on up to the first 15 days of treatment in users who initiated their study in 2016, and (ii) the first day of reporting was analyzed as there was a higher level of VAS on day 1 than on the other days and there were more users with a single day than with multiple days.

2.11.1 | Medications used and adherence to treatment

All users were investigated for 2015 and 2016, and the number of days of reporting VAS levels was assessed. We then studied 2016 and examined the adherence to treatment in users who reported 5-7, 8-15 and >16 days. In the latter group, only the first 30 days were investigated. Adherent users were those reporting $\geq 80\%$ consecutive days and $\geq 80\%$ days with the same treatment. Non-adherent users were those reporting $< 80\%$ consecutive days and $\geq 80\%$ days with same treatment. We then checked the number of medications reported during the period of examination.

2.11.2 | Control of the disease

Using the full data set and REST, we studied median VAS levels for medications reported for at least 1000 days and for days without medications. We used the global-measured VAS as a primary endpoint and the other VAS measures (nose, eyes, work) as secondary endpoints.¹² As this was a pilot study, only the primary endpoint was analyzed using the Kruskal-Wallis test with Dunn's post hoc analysis.

2.11.3 | Prescribed medications

We then focussed on the 3 medications always prescribed, that is, those not available OTC (MP-AzeFlu, FF, and MF). For MF, we carefully checked the dates of OTC introduction for the different molecules in the different countries. We first analyzed the frequency of days with monotherapy (FF and MF) or MP-AzeFlu and days with added medications (comedication). We then compared VAS global-measured levels the first day of use, REST, and full data. Data were analyzed using the Kruskal-Wallis test with Dunn's post hoc analysis.

3 | RESULTS

3.1 | Users

A total of 2871 users filled in 17 091 days of VAS (Figure 1). There were 39% females, 44% males, and 17% of unknown. The mean age was 37 ± 17 years. The age of the users (by days) is reported in Figure S3 and shows that the App was used from 12 to 80 years of age with a peak at 30-49 years.

Medications were reported for 9634 days and no medications for 7457 days. 2741 users (1686 with medication) responded "Yes" to Q1 (ie, "Do you have rhinitis?"), and 130 users (52 with

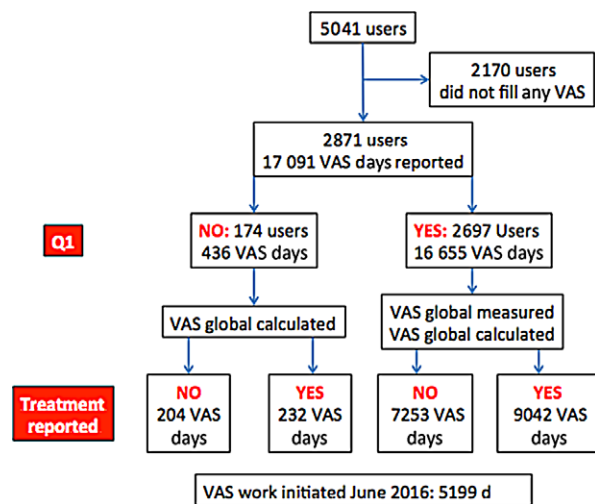


FIGURE 1 Flowchart

medication) responded "No" but ticked nasal symptoms (Q3). VAS-work was only included in the App after June 1, 2016, and fewer days with VAS are available (Table 1).

Among the 17 091 VAS days, all users filled in VAS-nasal and VAS-ocular, but 436 days were not filled in for VAS-global measured ("No" to Q1).

3.2 | Treatments and adherence

The number of reported days per user ranged from one (1539 users) to over 60 (2-7 days: 911 users, 8-15 days: 149 users, >15 days: 266 users). Among the 2016 users, 98 reported 5-7 days, 85 8-14 days, and 181 over 15 days (Table 2). Only 33.9% of users reported a single medication, and 42.1% reporting over 8 days of VAS used 3 treatments. In users reporting 5 or more days of VAS, adherence to treatment ranged from 32.9% to 40.8% (Table 2).

The treatments reported included 504 drugs and 86 INNs or combinations associated with medications. 475 users received an asthma treatment.

3.3 | Overall results

Data obtained were extremely consistent for different VAS measurements (global measured, nose, eyes, and work) or different analyses (full data set and restricted data set across all outcomes) (Table 3). In the full data set, VAS scores were greater on days with treatment (median, 25-75 percentiles for VAS-global measured: 25 (9-50)) than on days without treatment (11 (2-33)) ($P < .0001$). Similar levels of VAS were reported on days without treatment in users who never reported any medication (15 (0-47)) and in those who were sometimes treated (Non-adherent 15 (5-37)). There were minimal differences in recorded VAS scores between MP-AzeFlu (19 (8-45)), FF (22 (4-52)), and MF (25 (11-48)).

The median scores for the 6 medications imputed for over 1000 days showed that days with any of the 3 medications

TABLE 2 Adherence to treatment in users reporting ≥ 5 d of visual analog scales (VAS) in 2016

Treatment reporting (d)	N	Pattern ^a			Number of treatments during the reporting			
		Adherent (%)	Discontinuous (%)	Non-adherent (%)	1 (%)	2 (%)	3 (%)	≥ 4 (%)
5-7	98	40 (40.8)	12 (10.2)	46 (47)	41 (41.8)	33 (33.7)	21 (21.4)	3 (3.1)
8-14	85	28 (32.9)	17 (20)	40 (47.1)	27 (31.7)	20 (23.5)	19 (22.3)	19 (22.3)
15-30 ^b	181	71 (39.2)	18 (10)	92 (50.1)	52 (28.7)	55 (30.4)	37 (19.9)	37 (19.9)

^aAdherent: reporting $\geq 80\%$ consecutive days and $\geq 80\%$ days with treatment. Non-adherent: reporting $< 80\%$ days with treatment. Discontinuous: reporting $< 80\%$ consecutive days and $\geq 80\%$ days with treatment.

^bAssessment of day 1 up to day 30 in users who reported ≥ 15 d of VAS.

containing intranasal corticosteroid (INCS) had a lower VAS-global-measured level than days in which oral H₁-antihistamines (OAH) were reported.

3.4 | Single therapy and comedication

The results were extremely consistent as, for all medications apart from desloratadine, days under monotherapy (or MP-AzeFlu) had significantly lower VAS-global-measured median levels than days with comedication (Table 4).

3.5 | Prescribed medications

Only 3 medications containing INCS were exclusively prescribed. MF was OTC in some countries, but the users were low in number and therefore not included in the analysis. There were major differences between treatments in the percentage of mono- and comedication including OAH used. MP-AzeFlu was used more often alone (64-68%) than FF (32-37%) or MF (38-46%), and these trends were found in day 1 and persisted across the study (Figure 2).

The results for the 3 INCS-containing medications as rhinitis monotherapy, treatment with an oral H₁-antihistamine (OAH), or any other medication for rhinitis (polymedication) are presented in Table 5. For the full data set, MP-AzeFlu had a median VAS score (14 [6-33.5]) similar to FF monotherapy (15 [0-39]) and MF monotherapy (17 [8-32]), but significantly lower than FF + OAH (31 [14-58]) or MF + OAH 34 (16-58). On the other hand, MP-AzeFlu + OAH had a VAS score (33 [13.5-54]) similar to FF or MF + OAH. Similar trends were observed for REST and the results of Day 1. VAS levels were higher for Day 1 than for REST and the full data set for all medications and combinations.

4 | DISCUSSION

The feasibility of using mobile health applications to conduct observational clinical studies requires assessment: (i) The present study confirms the usefulness of the *Allergy Diary* in accessing and assessing everyday use and practice in AR. (ii) This observational study, using a very simple assessment (VAS) on a cell phone, shows novel concepts concerning our knowledge of AR treatment and should be considered as an exploratory hypothesis generating pilot study. (iii)

In real life, the assessment of days appears to be informative. (iv) The *Allergy Diary* allows the differentiation between treatments. (v) The control of days differs between no (best control), single, or multiple treatments (worst control).

4.1 | Strengths and limitations

Smart devices and Internet-based applications are already used in rhinitis,¹⁶⁻²¹ but none have assessed real-life treatment in a large number of users. The strengths of mobile technology include its wide acceptance and easy use, but there is a need to use appropriate questions, and results should be assessed by pilot studies. This pilot study was based on 2871 users who filled in 17 091 days of VAS.

Data obtained were extremely consistent for different VAS measurements (global measured, nose, eyes, and work) or different analyses (full data set, day 1 and REST). In a previous paper, we showed that there were strong to very strong correlations between the overall control of rhinitis and work VAS.¹³

In the present study, the definition of having rhinitis is purely user dependent. As the definition of rhinitis is not clear to the users other conditions, such as chronic rhinosinusitis or nasal septal deviation, could have been considered as AR. Although the App does not allow the assessment of all the analyses proposed to differentiate between these diseases, sneezers and blockers will be differentiated in the next analysis as previously done.¹¹ However, this was not done in the present study because (i) there was an insufficient number of users, and (ii) in this pilot analysis, we wanted to mimic a real-life study. From our experience in GPs, differentiation between allergic and nonallergic rhinitis is difficult and most GPs do not attempt to make any differences between nasal symptoms.^{1,22,23}

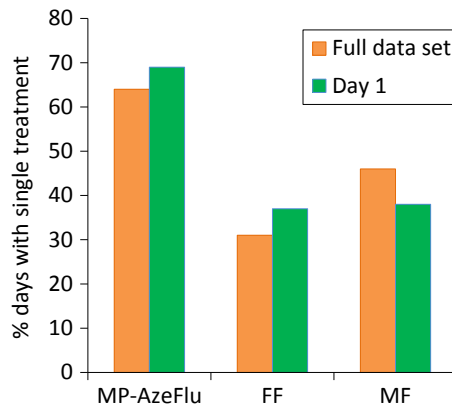
The study as already mentioned has no pretensions of reflecting the general population because (i) only one shot was taken into account, (ii) people using an App are not representative of the general population, and (iii) the users reported few days. However, the sample size is important, and according to the law of large numbers, the characteristics of a random sample approach the statistical characteristics of the population from which the sample is extracted when the sample size increases.

Adherence is difficult to analyze without a real assessment by electronic pill counters or inhalers. These do not exist for nasal

TABLE 4 Daily global-measured visual analog scales (full data set)

	MP AzeFlu		FF		MF		Loratadine		Cetirizine	
	Single	CoM	Single	CoM	Single	CoM	Single	CoM	Single	CoM
N	1039	589	406	846	625	743	610	492	622	671
Minimum	0	0	0	0	0	0	0	0	0	0
Maximum	100	99	100	100	100	100	100	100	100	100
Median	14.0	32.0	15.0	25.5	17.0	34.0	34.0	35.0	22.0	33.0
25%	6.0	13.0	0.0	6.0	8.0	17.0	14.0	15.0	8.0	10.0
75%	33.5	54.0	39.0	55.0	32.0	55.0	53.0	59.0	53.0	61.5
	$P < .001$		$P < .001$		$P < .001$		NS		$P < .001$	

Single, single treatment; Poly, P value by Mann-Whitney U test.

**FIGURE 2** Percentage of days with single treatment

products or are currently being tested. Questionnaires can be used, but it appears that real-life data are more appropriate. However, it should be emphasized that users may not report all medications used.

Longitudinal data capture was very challenging because treatment trajectories are specific for almost each user, and most users have gaps in treatment days when they are well-controlled, hence the focus on a cross-sectional analysis on days of treatment.

4.2 | Interpretation of the results and generalizability

The real-world assessment of the *Allergy Diary* using VAS allows assessment of treatment efficacy by days. This may represent a

TABLE 5 Median global visual analog scale scores measured in days with intranasal corticosteroid-containing medications

	Full data set		Restricted data set [REST]		Day 1 Median [25-75] [day counts]	
	Median [25-75] [day counts]	Users	Median [25-75] [day counts]	Users		
FF	15 [0-39] [377]	107	21 [4-44.25] [222]	92	40 [24-54] [57]	
FF + OAH	25 [5-55] [803]	149	31 [14-58] [514]	134	59 [33-76] [93]	
FF + other comedication	26 [12-34] [43]	19	25 [10.5-34] [35]	14	23 [13.5-23] [3]	
AMP-Aze Flu	14 [6-33.5] [1023]	149	21.5 [9-44] [458]	123	36 [16.25-58.25] [90]	
AMP-Aze Flu + OAH	33 [13.5-54] [459]	71	41 [20.75-59.25] [228]	56	56 [27.5-70] [32]	
AMP-Aze Flu + other comedication	25 [13-54] [119]	31	24 [10.75-42] [46]	14	44 [30.25-83.25] [12]	
MF	17 [8-32] [623]	99	19 [6-38] [270]	89	32 [18-57] [53]	
MF + OAH	34 [16-58] [606]	137	40 [17-62] [386]	124	54.5 [30-78] [76]	
MF + other comedication	31 [21-48] [137]	20	30 [19.5-50] [35]	14	53 [50-58] [9]	
Statistical analysis						
	AzeFlu	AzeFlu + OHA	FF	FF + OHA	MF	MF + OHA
AzeFlu		$P < .05$	NS	$P < .05$	NS	$P < .05$
AzeFlu + OHA	$P < .05$		$P < .05$	$P < .05$	$P < .05$	NS
FF	NS	$P < .05$		$P < .05$	NS	$P < .05$
FF + OHA	$P < .05$	NS	$P < .05$		$P < .05$	$P < .05$
MF	NS	$P < .05$	NS	$P < .05$		$P < .05$
MF + OHA	$P < .05$	NS	$P < .05$	$P < .05$	$P < .05$	

FF, fluticasone furoate; OAH, oral antihistamine; MF, mometasone furoate; MP-AzeFlu, intranasal azelastine; and fluticasone propionate.

Statistical analysis by Kruskal-Wallis test ($P < .0001$) and Dunn' post hoc analysis. $P < .05$: significant for full data set and REST, $P < .05$: significant for full data set only. Users with comedication other than OAH were not included due to their low number.

more objective estimation of AR treatments than patients' comments as (i) it is known that AR is a highly variable disease, and control varies widely between days in relation to allergen exposure, (ii) patients are not always adherent with their treatment, (iii) patients often stop treatment when they feel better (as found by the study but not shown), and (iv) patients increase their treatment when uncontrolled.

VAS scores were greater on treatment days than on days without treatment, suggesting that users reporting no treatment had milder disease than those who were occasionally treated. However, median VAS levels on days without treatment were similar in users who never reported any medication use and in those who were occasionally treated. Days without treatment were better controlled than days with treatment and days with a single treatment were better controlled than days with multiple treatments. These data suggest that, in real life, patients treat themselves when they suffer from symptoms and stop their treatment when they are controlled. This accords with previous data.^{24,25} This study, using objective data, confirmed that adherence is poor. Most patients with rhinitis may have mild and/or intermittent disease that does not need a regular treatment to achieve control. The concept of proactive medication²⁶-the patient starting treatment when experiencing symptoms and continuing for a few days after getting control-may be of great interest and could be tested with the App. In asthma, self-guided treatment was found to be of interest.²⁶⁻²⁸ Such real-life findings may ultimately affect the way in which guidelines are constructed to align them more with human behavior.

This observational study made it possible to differentiate OAH and INCS, confirming known data,²⁹ but may be able to differentiate between OAH when more data are analyzed. It could also differentiate the 3 medications containing INCS, FF, MF, and MP-AzeFlu, and confirm previous studies,³⁰ extending our understanding of how AR treatment is used. RCTs showed that MP-AzeFlu is more effective than single components available in pharmacies³¹ or components using the same formulation.³² However, observational studies comparing prescribed medications containing INCS are not available. In the present study, a clear difference was found between medications. Disease control assessed by VAS was similar in users who reported a single treatment for the 3 medications and was similarly increased in those with comedication. However, a major difference is that around one-third of MP-AzeFlu received the treatment without comedication whereas FF or MF users required comedication in 31%-46%. Although this is a pilot study, over 1000 days of treatment were reported for each medication. A bias may, however, be confounding by indication.

5 | CONCLUSIONS

This observational study shows highly consistent results between different outcomes (VAS levels), days of treatment and medications. It appears possible to use this approach to better tailor treatments to individuals.

CONFLICTS OF INTEREST

J Bousquet reports personal fees and other from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Sanofi-Aventis, Takeda, Teva, Uriach, other from Kyomed, outside the submitted work. S Bosnic-Anticevich reports grants from TEVA Pharmaceuticals, other from TEVA Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, outside the submitted work. P Devillier reports personal fees from MEDA Pharma, personal fees from Stallergenes, personal fees from ALK-Abello, outside the submitted work. L Klimek reports grants and personal fees from ALK-Abelló, personal fees from MEDA, Sweden, grants and personal fees from Novartis, Switzerland, grants and personal fees from Allergopharma, Germany, grants and personal fees from Bionorica, Germany, personal fees from Boehringer Ingelheim, Germany, grants and personal fees from GSK, Great Britain, grants and personal fees from Lofarma, Italy, grants from Biomay, Austria, grants from HAL, Netherlands, grants from LETI, Spain, grants from Roxall, Germany, grants from Bencard, Great Britain, outside the submitted work. P Kuna reports personal fees from Berlin Chemie Menarini, personal fees from FAES, personal fees from Hal, personal fees from ALK, personal fees from Allergopharma, personal fees from Adamed, personal fees from Polpharma, outside the submitted work. P McDowall reports other from IQ4U Consultants, during the conduct of the study. R Mösges reports personal fees from ALK, grants from ASIT biotech, personal fees from allergopharma, personal fees from Allergy Therapeutics, grants and personal fees from Bencard, grants from Leti, grants, personal fees and non-financial support from Lofarma, non-financial support from Roxall, grants and personal fees from Stallergenes, grants from Optima, personal fees from Friulchem, personal fees from Hexal, personal fees from Servier, personal fees from Klosterfrau, non-financial support from Atmos, personal fees from Bayer, non-financial support from Bionorica, personal fees from FAES, personal fees from GSK, personal fees from MSD, personal fees from Johnson&Johnson, personal fees from Meda, personal fees and non-financial support from Novartis, non-financial support from Otonomy, personal fees from Stada, personal fees from UCB, non-financial support from Ferrero, grants from BitopAG, grants from Hulka, personal fees from Nuvo, grants from Ursapharm outside the submitted work. E Murphy reports other from IQ4U CONSULTANTS, during the conduct of the study. N Papadopoulos reports grants from Menarini, personal fees from Novartis, personal fees from Faes Farma, personal fees from BIOMAY, personal fees from HAL, personal fees from Nutricia Research, personal fees from Menarini, personal fees from Novartis, personal fees from MEDA, personal fees from Abbvie, personal fees from Novartis, personal fees from MEDA, personal fees from MSD, personal fees from MEDA, personal fees from Omega Pharma, personal fees from Danone, outside the submitted work. D Price reports other from Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals, other from Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Napp, Novartis, Pfizer, Teva Pharmaceuticals, and Theravance, grants from Aerocrine, AKL Research and Development Ltd, AstraZeneca, Boehringer Ingelheim,

British Lung Foundation, Chiesi, Mylan, Mundipharma, Napp, Novartis, Pfizer, Respiratory Effectiveness Group, Teva Pharmaceuticals, Theravance, UK National Health Service, Zentiva, other from Ammirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Merck, Mundipharma, Novartis, Pfizer, Skyepharma, and Teva Pharmaceuticals, other from Mundipharma and Teva Pharmaceuticals, other from Aerocrine, AstraZeneca, Boehringer Ingelheim, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals, other from Chiesi, Novartis, Teva Pharmaceuticals, and Zentiva, other from Mundipharma and Novartis, non-financial support from Efficacy and Mechanism Evaluation programme, and Health Technology Assessment, outside the submitted work; and stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; and owns 74% of the social enterprise Optimum Patient Care Ltd (Australia, Singapore, and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore). D Ryan reports personal fees from MEDA, personal fees from Stallergenes, outside the submitted work. A Todo-Bom reports grants and personal fees from Novartis, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Mundipharma, grants and personal fees from GSK (GlaxoSmithKline), personal fees from Teva Pharma, personal fees from AstraZeneca, outside the submitted work. O Pfaar reports grants and personal fees from ALK-Abelló, grants and personal fees from Allergopharma, grants and personal fees from Stallergenes Greer, grants and personal fees from HAL Allergy Holding B.V./HAL Allergie GmbH, grants and personal fees from Bencard Allergie GmbH/Allergy Therapeutics, grants and personal fees from Lofarma, grants from Biomay, grants from Nuvo, grants from Circassia, grants and personal fees from Biotech Tools S.A., grants and personal fees from Laboratorios LETI/LETI Pharma, personal fees from Novartis Pharma, personal fees from MEDA Pharma, grants and personal fees from Anergis S.A., personal fees from Mobile Chamber Experts (a GA2LEN Partner), personal fees from Pohl-Boskamp, personal fees from Indoor Biotechnologies, grants from Glaxo Smith Kline, outside the submitted work. The other authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Bousquet J, Arnavielhe S, Bedbrook A, et al. Treatment of allergic rhinitis using mobile technology with real-world data: The MASK observational pilot study. *Allergy*. 2018;73:1763-1774. <https://doi.org/10.1111/all.13406>