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## Mobile technology offers novel insights into the control and treatment of allergic rhinitis: The MASK study

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# 1 Mobile technology offers novel insights on control and treatment of 2 allergic rhinitis. The MASK study

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149

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152

153 **Short title: Treatment of allergic rhinitis using an App**

154

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160

161

## 162 **Conflict of interest**

163

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216 Dr. Wallace reports other from Mylan Pharmaceutical Company, outside the submitted work;  
217 and I am co-chair of the AAAAI/ACAAI Joint Task Force on Practice Parameters. I helped to  
218 develop the Rhinitis GRADE document published 12/2017.

219

220 The rest of the authors declare that they have no relevant conflicts of interest

221

222

223 **Abstract**

224 **Background:** Mobile health may be used to generate innovative insights into optimizing  
225 treatment to improve allergic rhinitis control.

226 **Objectives:** A cross-sectional real world observational study was undertaken in 22 countries to  
227 complement a pilot study and bring novel information on medication use, disease control and  
228 work productivity in everyday life of patients with allergic rhinitis.

229 **Methods:** A mobile phone app (*Allergy Diary*, freely available Google Play and Apple stores)  
230 was used to collect data of daily visual analogue scales (VAS) for (i) overall allergic symptoms,  
231 (ii) nasal, ocular and asthma symptoms, (iii) work, as well as (iv) medication use using a  
232 treatment scroll list including all allergy medications (prescribed and over-the-counter (OTC))  
233 customized for 22 countries. The four most common intra-nasal medications containing intra-  
234 nasal corticosteroids and eight oral H1-antihistamines were studied.

235 **Results:** 9,122 users filled in 112,054 days of VAS in 2016 and 2017. The assessment of days  
236 was informative. The control of days with rhinitis differed between no [best control], single  
237 [good control for intranasal corticosteroid-treated days] or multiple treatments [worst control].  
238 Users with the worst control increased the range of treatments being used. The same trend was  
239 found for asthma, eye symptoms and work productivity. Differences between oral H1-  
240 antihistamines were found.

241 **Conclusions:** This study confirms the usefulness of the *Allergy Diary* in accessing and  
242 assessing patient behavior in allergic rhinitis. This observational study using a very simple  
243 assessment tool (VAS) on a mobile phone had the potential to answer questions previously  
244 thought infeasible.

245

246 **Capsule summary**

247 Most rhinitis patients use on-demand treatment when they are not controlled. Control was worse  
248 with increasing medications. Real life data may not be aligned with guidelines.

249 **Clinical implications**

250 A behavioural disconnection was found in the study since patients are not adherent to treatment  
251 and treat themselves on-demand when they are not controlled whereas the vast majority of  
252 physicians prescribe long-term treatment to achieve control. Shared-decision making is  
253 essential.

254

255 **Key words**

256 Allergic rhinitis, anti-histamines, asthma, conjunctivitis, corticosteroids, mobile health, MASK,  
257 treatment

258

259 **Abbreviations**

260 AR: Allergic rhinitis  
261 AzeFlu : Intranasal azelastine-fluticasone propionate  
262 CET : Cetirizine  
263 DL: Desloratadine  
264 FEXO: Fexofenadine  
265 FF: Fluticasone Furoate  
266 FP: Fluticasone Propionate  
267 INCS: Intranasal corticosteroid  
268 INN: International Nonproprietary Names  
269 LEVOCET: Levocetirizine  
270 Lora: Loratadine  
271 MASK-rhinitis (Mobile Airways Sentinel Network for allergic rhinitis)  
272 Mometasone Furoate (MF)  
273 OAH: Oral H<sup>1</sup>-anti-histamine  
274 RCT: Randomized controlled trial  
275 visual analogue scales (VAS)

276

277

## 278 Introduction

279 The treatment of allergic rhinitis (AR) is complex as many drugs are available in oral and/or  
280 topical formulations. Many guidelines for AR are evidence-based and have led to a better  
281 management of AR. However, guidelines are mostly based on randomized controlled trials  
282 (RCTs), typically undertaken on highly selected populations, often with limited/unclear  
283 generalizability to routine care contexts (1, 2). They propose to increase treatment to achieve  
284 disease control (i.e. sleep, social and school/work impairment) that is the ultimate aim of the  
285 treatment. Intra-nasal corticosteroids represent the most effective AR treatment for most  
286 patients, but their effect is relatively slow, taking several hours (3) and many patients prefer oral  
287 medications. A formulation of fluticasone propionate (FP) and azelastine (AzeFlu) is more  
288 effective than INCS alone (4) and has the advantage of acting within minutes (5). Patients are  
289 poorly adherent to treatment and often self-medicate (6, 7). They want more effective and fast  
290 acting treatments. Observational real-life studies are therefore needed to complement RCTs in  
291 order to better understand the efficacy of INCS-containing medications since they do not select  
292 patients and report their behavior.

293 MASK-rhinitis (Mobile Airways Sentinel NetworK for allergic rhinitis), an information and  
294 communications technology (ICT) system centered around the patient (8-12) operational in 23  
295 countries, uses a treatment scroll list including all medications customized for each country and  
296 a visual analogue scales (VAS) to assess rhinitis control. A pilot study in over 2,900 users  
297 allowed differentiation between treatments (13). Patients did not necessarily use treatment on a  
298 daily basis in a regular way but appeared to increase treatment use when their symptom's  
299 control worsens. However, the pilot study needs to be confirmed with a larger number of users  
300 and more medications tested.

301 The present cross-sectional observational study was undertaken in 9,122 users in 22 countries  
302 (data collection was just started in Argentina) to confirm the pilot study (13) using the same  
303 methods and to bring novel information on medication use, and associated disease control, work  
304 productivity (14) and allergic multimorbidity (13). The study was focused firstly on the four  
305 most commonly used intra-nasal medications containing intra-nasal corticosteroids: Fluticasone  
306 Furoate (FF), Fluticasone Propionate (FP), Mometasone Furoate (MF) and AZeFlu. We did not  
307 perform the same analysis with oral H1-antihistamines as they are often associated with INCS  
308 and many patients would have been analysed twice. In the second analysis, we examined some  
309 widely used oral H1-antihistamines: Bilastine, Cetirizine (CET), Desloratadine (DL), Ebastine,  
310 Fexofenadine (FEXO), Levocetirizine (LEVOCET), Loratadine (Lora) and Rupatadine. In the  
311 first analysis, we compared days with single treatment with days with multiple treatments. In  
312 the second analysis, we just used days with a single treatment.



## 313 **Methods**

### 314 **Users**

315 All consecutive users from January 1, 2016 to December 31, 2017 were included with no  
316 exclusion criteria according to methods previously described (13, 14).

### 317 **Setting**

318 Users from 22 countries filled in the *Allergy Diary* (Table 1). Data collection was just started in  
319 Argentina and not included

### 320 **Ethics**

321 The Allergy Diary is CE1. CE marking is a [certification mark](#) that indicates conformity with  
322 health, safety, and environmental protection standards for products made in the EU and meets  
323 the essential requirements of all relevant European Medical Device Directives (15). CE1  
324 includes sterile and non-sterile products and assess whether the device has a measuring  
325 function.

326 The data were anonymized including data related to geolocalization  
327 using k-anonymity (16).

328 An independent Review Board approval was not required since the study is  
329 observational and users agreed to have their data analysed (terms of  
330 use).

### 331 **Allergy Diary**

332 Geolocalized users assess their daily symptom control using the touchscreen functionality on  
333 their smart phone to click on five consecutive VAS scores (i.e. general, nasal and ocular  
334 symptoms, asthma and work). Users input their daily medications using a scroll list which  
335 contains all country-specific OTC and prescribed medications available for each country (Figure  
336 1 online). The list has been populated using IMS data.

337 Days reported by users included days with or without treatment.

338 The present study is another *Allergy Diary* study. Some of the raw data used in the first paper  
339 (up to November 2016) (13) were used in this study, but analyses differed.

## 340 **Selection of medications**

341 The International Nonproprietary Names (INN) classification was used for drug nomenclature  
342 (17). Monotherapy was defined as days when only one single medication for rhinitis was  
343 reported. AzeFlu contains two drugs but, as it is a fixed combination it was considered as  
344 monotherapy. Co-medication was defined as days with two or more medications for rhinitis.  
345 Asthma medications were not considered in co-medication.

## 346 **Size of the study**

347 In this study, all registered users were included to obtain the best possible estimates for the  
348 specified time window. From the pilot study, numbers tested largely exceed those needed to  
349 find significant differences in the full set analysis (13). However, we did not consider  
350 medications with a sample size under 1,000 days of reporting.

## 351 **Statistical methods**

352 A non-Gaussian distribution was found for the data. Non-parametric tests and medians (and  
353 percentiles) were used. Correction for multiple testing was made when appropriate.

354 Some users reported VAS scores more than once a day. In the pilot study, we found that the  
355 highest reported value should be used and we followed this study (13). We however tested in an  
356 exploratory analysis VAS levels in duplicates and multiplicates.

## 357 **Analysis of the data**

358 We conducted, as previously published (13), separate analyses using the full-set of data and data  
359 on just the first day of reporting.

360 In the first analysis, only users who reported no treatment or treatment by the intra-nasal FF, FP,  
361 MF and AZeFlu were studied (Figure 2 online). Those receiving other INCS were excluded. For  
362 co-medication, we initially selected second generation oral H1-antihistamines (OAH): CET,  
363 DL, Ebastine, FEXO, LEVOCET, LORA and Rupatadine (Group + OAH). There are many  
364 other OAH, but we did not consider them since their pharmacologic properties vary widely and  
365 they were not often used. We considered two other groups in INCS users for co-medication:  
366 users who reported OAH and another medication (Group OAH + other) and users who reported  
367 another medication (+ Other). Users who reported other medications but no INCS were not  
368 analyzed. As a primary end point, using the full data set, we studied median VAS global  
369 measured (“Overall how much are your allergic symptoms bothering you today?”) levels for

370 days with FF, FP, MF and AZeFlu and for days without medications. The primary and  
371 secondary end points were analyzed using the Kruskal-Wallis test and Wilcoxon and Mann-  
372 Whitney test with Dunn-Bonferroni's post hoc analysis to correct for multiple testing.  
373 Moreover, we analysed the data using three cutoffs: VAS <20/100 (controlled days), VAS 20-  
374 49 (days with moderate control), VAS  $\geq$ 50 (days with poor control) according to a consensus  
375 (18) and available data of the pilot study (13, 14). The same analyses were conducted for the  
376 first day of VAS report. Secondary end-points included VAS eye, asthma and work.

377 In the second analysis, we compared days with monotherapy for the most common OAH: CET,  
378 DL, Ebastine, FEXO, LEVOCET, LORA and Rupatadine monotherapy. We did not consider  
379 other OAH with a sample size under 1,000 days (or close to this number). We only compared  
380 VAS global measured. The mean number of days of reporting was considered for each  
381 treatment.

382 We then performed exploratory analyses to investigate whether there are temporal patterns in  
383 the reporting of VAS in the app users. We assessed the VAS levels on: (i) days with more than  
384 1 VAS reported, (ii) the first day of reporting and first day of new reporting in users with non-  
385 consecutive data, (iii) days without treatment followed by a day with treatment and (iv) days  
386 with treatment followed by a day without treatment.

## 387 **Results**

### 388 **Demographic characteristics**

389 The study included 9,122 users. Roughly 5% of users did not report their age and were ascribed  
390 to "zero". Users ranged in age from zero to 92 years (mean, SD: 32.4  $\pm$  15.2 years). There were  
391 54.7% women and 45.3% men. The age repartition is given in Figure 3 online.

392 A total of 112,054 days was recorded. Duplicates or multiples for the same day were found  
393 in 14,767 days. Global VAS was not recorded in 754 (0.8 %) days with App data reported.  
394 There were 52,706 (54.6%) days without treatment and 18,117 days with the targeted INCS  
395 (Figure 1).

### 396 **Analysis of VAS global measured**

397 On visual inspection, no clear trajectory of VAS could be easily identified, as users reported  
398 erratically their VAS and treatment data. Figure 4 online reports trajectories for French users as  
399 an example.

400 In the figure each user is identified by a member identifier number (vertical axis) and each  
401 user's trajectory is represented horizontally by dots - each dot representing a day of VAS  
402 recording).

403 Results are reported in Table 2, Figures 2 and 3.

#### 404 **Analysis of VAS global measured on days without treatment and days with INCS** 405 **treatment**

406 The first day of reporting, VAS levels were reported by 4,991 users without treatment, 1,395 users  
407 with OAH and 1,281 users with INCS treatment (Table 2). The percentage of users with single  
408 treatment ranged from 34.0% (FP), 39.2% (MF), 40.5% (FF) and 59.6% (AzeFlu). Days with INCS  
409 alone had similar median VAS levels (35 to 44).

410 For the full data set of 96,533 days, VAS levels were reported by 6,236 users without treatment, 3,664  
411 users with OAH and 2,575 users with INCS treatment (Table 2). Monotherapy was reported 45 to 55%  
412 of the days (FF or MF versus AzeFlu – Figure 2). For monotherapy, median VAS levels ranged from 5  
413 (FF) to 23.5 (FP). For day 1 and the full data set, the same trend was found in INCS treated users:  
414 lowest median levels were found for monotherapy, increased levels with co-medication by OAH and  
415 highest levels for co-medication with OAH + other treatments (Figure 3). Variable levels of VAS were  
416 observed for co-medication with other treatments. The numbers of days of co-medication with another  
417 INCS are too low to make any comparison (Table 2).

#### 418 **Analysis of VAS global measured on days with OAH treatment alone**

419 The first day of reporting, days with no treatment or those with INCS in monotherapy had similar  
420 median VAS levels (34 to 44). On the other hand, there were some variations for OAH in  
421 monotherapy. LEVOCET days had a median VAS level intermediate between untreated or INCS-  
422 treated days and the other OAH. For the full data set of 96,533 days, median VAS levels of days with  
423 INCS were lower than those of days with OAH but Bilastine, FEXO, LEVOCET and Rupatadine had  
424 levels similar to those of INCS (Table 2).

425 Apart from days with FP treatment (low numbers), the mean numbers of days of reporting medications  
426 per user ranged from 4.00 (CET) to 8.98 (AzeFlu).

#### 427 **Analyses of VAS for eye, asthma and work**

428 Analyses of VAS eye, asthma and work are reported in Figures 5A, B and C online supplement.  
429 Trends for the three secondary end points are similar to those of VAS global measured, i.e. low  
430 median levels similar to untreated days for the single treatment, increased levels with co-  
431 medication by OAH and highest levels for co-medication with OAH + other medication, and the

432 highest percentage of users with single treatment observed for AzeFlu. Fewer users reported  
433 VAS work, but the trends were similar.

## 434 **Exploratory analyses investigating potential temporal patterns in the reporting of** 435 **VAS**

### 436 **Assessment of duplicates or multiplicates for day 1**

437 Days with 2 or more VAS levels reported at least 1 hour apart within the same day were  
438 selected. The dataset included 1,576 days for VAS global measured. A significantly higher VAS  
439 was found at second reporting compared to the first. When the data were stratified by the type of  
440 treatment recorded at first entry (no treatment, AzeFlu FF, MF and FP), these findings were  
441 only significant for days with no treatment. No difference was found for days with (any)  
442 treatment (Table 1 online).

### 443 **VAS levels depending on consecutive and non-consecutive data**

444 There were 4,132 users with at least two non-consecutive calendar days of VAS reported  
445 (n=89,473 days in total). The global VAS levels measured on day 1 were found to be  
446 significantly higher when compared to the global VAS levels measured on the first day of new  
447 reporting (i.e. or first non-consecutive calendar day reported), regardless of the presence/type of  
448 treatment (Table 3).

449 The distribution of global VAS on the 391 consecutive couple of calendar days consisting of a  
450 day without treatment followed by a day with treatment showed a non-significant increased  
451 level in treated days (median [p25-75] =23 [11-49] to 28 [14-50], (p=0.07, Wilcoxon W test).

452 The distribution of global VAS on the 350 consecutive couple of calendar days consisting of a  
453 day with treatment followed by a day without treatment showed a significant decreased level in  
454 untreated days (median [p25-75] =23 [13-45] to 20 [9-38], (p=0.01 Wilcoxon W test).

## 455 **Discussion**

456 A pilot study using a very simple assessment (VAS) on a cell phone in 2,871 users who filled in  
457 17,091 days suggested that an App may give novel information concerning the treatment of AR  
458 (13). However, the sample size was possibly too small to draw definite conclusions. This study  
459 in a larger sample (9,111 users in 22 countries, 97,287 days) confirms the findings of the pilot  
460 study showing that, in real life, the assessment of days can inform on patient's treatment and  
461 bring novel insight on the behaviour of AR patients towards treatment and novel concepts for  
462 change management of AR (19). The control of days differs between no treatment (best

463 control), single treatment or co-medication (worst control). This study showed for the first time  
464 that the same trends were observed for global symptoms, ocular symptoms, asthma and work  
465 productivity. This study suggests contrary behaviour between physicians and patients since the  
466 range of treatments was increased in those with poor control whereas, according to guidelines,  
467 physicians are recommended to increase the treatment to achieve control. This major gap in AR  
468 treatment may explain the overall low level of satisfaction of severe AR patients reported in  
469 many studies.

## 470 **Strengths and limitations**

471 The current study has many strengths including larger numbers, multiple countries, range of  
472 treatments studied and patient/person-generated data.

473 As for all studies using participatory data, potential biases include (i) the likelihood of sampling  
474 bias likely present, difficult to assess generalizability of the study, (ii) outcome misclassification that  
475 cannot be assessed and, by definition due to ethical problems, there very little information on patient  
476 (or day) characteristics. App users are not representative of all patients with rhinitis. The issue of  
477 potential selection bias was limited by the fact that we considered days and not patients in the  
478 analyses.

479 As in other studies (13, 20), we used days in a cross-sectional analysis because there is no clear  
480 pattern of treatment and a longitudinal study was not feasible since users mostly use the App  
481 intermittently. Although this observation may differ from RCTs, our study is a real-life  
482 approach.

483 For this study, other biases should be considered. The diagnosis of AR was not supported by a  
484 physician but was a response to the question: “Do you have allergic rhinitis? Yes/No”. There  
485 may therefore be some users with non-allergic rhinitis who may have responded “Yes” to the  
486 question. There are potential measurement biases when using apps including collection of  
487 information, education of the patient, availability and ability to use a smartphone (13). Users  
488 self-identified themselves as having AR without confirmation of the diagnosis. Precise patient  
489 characterization is impossible using an App, but every observational study using the *Allergy*  
490 *Diary* was able to identify days with poor control or criteria of severity (20-24). Adherence to  
491 treatment is impossible to prove as users do not report data all days and users may not report all  
492 medications used. Nonetheless, mobile technology is becoming an important tool to better  
493 understand and manage AR and brings novel information that were not available with other  
494 methods (20-26).

495 Asthma was assessed using a single VAS largely validated in rhinitis (27). In asthma, VAS was  
496 shown to be an effective measure of control (28). In the present study, we did not investigate  
497 specific symptoms or perform any pulmonary function test. Thus, it is possible that some users  
498 may have misunderstood the question or overestimated the disease. However, the results are  
499 extremely consistent.

500 We only considered days and not patients' trajectories because these are highly variable,  
501 patients using auto-medication depending on AR control as previously shown (13).

502 Longitudinal capture is very challenging with this App but this appears to be the case for all  
503 Apps. Patient's engagement with digital health in real world scenarios is usually lower than in  
504 RCTs. Although this is a limitation in relation to causal inference, it suggests that a new  
505 methodological approach is needed. It appears that treatment trajectories are specific for almost  
506 each user and most users have gaps in their treatment when they are well controlled.

#### 507 **Interpretation of the results and generalizability**

508 This real world assessment of the *Allergy Diary* using VAS allows assessment of treatment  
509 efficacy by days, which represents real-life estimation of AR control and likely reflects real-life  
510 better than patients' assessments at regular intervals since (i) it is known that AR is a highly  
511 variable disease, and control varies widely between days in relation to allergen and  
512 environmental exposure, (ii) patients are rarely adherent to their treatment, (iii) patients often  
513 stop treatment when they feel better and (iv) patients increase their treatment when  
514 uncontrolled.

515 VAS scores were greater on days with treatment than on days without treatment. This study  
516 confirms the study of the pilot one (13) in which, median VAS levels on days without treatment  
517 were similar in users who never reported any medication use and in those who were  
518 occasionally treated. Moreover, in a small sample, it was found that consecutive days under  
519 treatment are less well controlled than days without treatment. In INCS-treated users, days with  
520 a single treatment were better controlled than days with multiple treatments. An important  
521 message from this paper is that, overall, in real life, patients treat themselves when they suffer  
522 from symptoms and stop their treatment when they are controlled. This accords with previous  
523 data (29, 30). This study, using objective data, confirmed that adherence is poor. Most AR  
524 patients may have mild and/or intermittent disease that does not need a regular treatment to  
525 achieve control. The concept of pro-active medication and patient participation (31) - the patient  
526 starting treatment when experiencing symptoms and continuing for a few days after getting  
527 control - may be of great interest and could be tested with the App. In asthma, self-guided

528 treatment was found to be of interest (31-33). Such real-life findings may ultimately affect the  
529 way in which guidelines are constructed to align them more with human behaviour. We have  
530 already initiated a program entitled Change management in rhinitis and asthma (19) in which  
531 we propose to develop next-generation care pathways and test the recommendations of GRADE  
532 guidelines in AR (3, 4) according to real-world evidence using data of MASK. A first meeting  
533 was held at the Pasteur Institute, Paris (December 3, 2018) to provide guidance for their  
534 development.

535 This observational study made it possible to differentiate OAH and INCS, confirming known  
536 data, (34) and was able to differentiate between OAH. LEVOCET was found to be the most  
537 effective OAH confirming clinical experience. On the other hand, CETI appeared not to have  
538 been as effective. However, there were a large number of generics for CETI and this could be  
539 studied when more users will be available. This study could also differentiate the three  
540 medications containing INCS: FF, MF and MP-AZeFlu and confirm previous studies (35)(36)  
541 extending our understanding of how AR treatment is used. RCTs showed that MP-AzeFlu is  
542 more effective than single components available in pharmacies (37) or components using the  
543 same formulation (38).

544 The same trends for INCS-containing medications were observed for VAS global measured,  
545 eye, asthma and work. However, the percentages of well-controlled, controlled and poorly-  
546 controlled days differed indicating the independence of data already observed. Moreover, data  
547 on work are extremely important to facilitate an economic evaluation of treatments.

548  
549 An important result is that VAS on day 1 was higher than any other consecutive/non-  
550 consecutive day. This indicates that patients start using the App when symptoms are  
551 uncontrolled. This is one specificity of analysing app data and should be considered in studies  
552 that assess the control of allergic diseases in relation to risk factors such as air pollutants and  
553 allergen exposure.

554

## 555 **Conclusions**

556 Real world data (RWD) and real-world evidence (RWE) are playing an increasing role in health  
557 care decisions supporting clinical trial designs and observational studies to generate innovative  
558 and new treatment approaches. These data hold potential to answer questions previously thought  
559 infeasible (39) such as the true patient's attitude towards treatment. This observational study  
560 shows highly consistent results between different outcomes (VAS levels) and brings novel  
561 concepts for the management of allergic diseases. When the patient experiences increased  
562 symptom, indicating a loss of control, he/she increases the number of medications used that day.



563 A total behavioural disconnection was found since most patients treat themselves on-demand  
564 when they are not controlled whereas the vast majority of physicians prescribe long-term  
565 treatment to achieve control. Shared decision making may offer a more rewarding approach AR  
566 management. The results of this paper will be of importance for the implementation of the  
567 MASK Good Practice recently recognized by DG Santé.  
568  
569

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691

692 **Table 1. Country and number of users recording Visual Analogue Scale score using the**  
 693 ***Allergy Diary* in the full data set**

694

| Country        | VAS measurements (days) |                     |                   |                     | Total       |
|----------------|-------------------------|---------------------|-------------------|---------------------|-------------|
|                | 1                       | 2 to 7              | 8 to 14           | >14                 |             |
| Austria        | 226 (56.6%)             | 121                 | 16                | 36                  | 399         |
| Australia      | 49 (49.0%)              | 30                  | 10                | 11                  | 100         |
| Belgium        | 48 (49.5%)              | 35                  | 5                 | 9                   | 97          |
| Brazil         | 572 (55.9%)             | 323                 | 67                | 62                  | 1024        |
| Canada         | 6 (35.3%)               | 7                   | 3                 | 1                   | 17          |
| Czech Republic | 1 (20.0%)               | 0                   | 1                 | 3                   | 5           |
| Denmark        | 37 (45.1%)              | 29                  | 4                 | 12                  | 82          |
| Finland        | 117 (44.8%)             | 93                  | 25                | 26                  | 261         |
| France         | 319 (61.3%)             | 147                 | 19                | 35                  | 520         |
| Germany        | 208 (39.8%)             | 141                 | 35                | 139                 | 523         |
| Greece         | 47 (23.7%)              | 43                  | 24                | 84                  | 198         |
| Italy          | 554 (44.6%)             | 389                 | 87                | 213                 | 1243        |
| Lithuania      | 59 (17.7%)              | 89                  | 52                | 134                 | 334         |
| Mexico         | 101 (13.0%)             | 207                 | 128               | 343                 | 779         |
| Netherland     | 167 (53.9%)             | 94                  | 23                | 26                  | 310         |
| Poland         | 286 (54.9%)             | 159                 | 28                | 48                  | 521         |
| Portugal       | 647 (49.2%)             | 505                 | 64                | 100                 | 1316        |
| Spain          | 129 (30.5%)             | 124                 | 53                | 117                 | 423         |
| Sweden         | 33 (39.3%)              | 34                  | 6                 | 11                  | 84          |
| Switzerland    | 247 (64.0%)             | 111                 | 11                | 17                  | 386         |
| Turkey         | 81 (52.6%)              | 42                  | 10                | 21                  | 154         |
| UK             | 148 (42.8%)             | 104                 | 46                | 48                  | 346         |
| <b>Total</b>   | <b>4082 (44.7%)</b>     | <b>2827 (31.0%)</b> | <b>717 (7.9%)</b> | <b>1496 (16.4%)</b> | <b>9122</b> |

695

696

697 Table 2: Results of VAS global measured

|                         | Day 1  |                  | Full set (96,533 days) |                  |                              |
|-------------------------|--------|------------------|------------------------|------------------|------------------------------|
|                         | N days | Median [p25-p75] | N days [users]         | Median [p25-p75] | Mean number of days per user |
| <b>No treatment</b>     | 4991   | 34 [10-60]       | 52706 [6236]           | 8 [0-26]         | 8.45                         |
| <b>Bilastine*</b>       | 128    | 48 [19-69.5]     | 1563 [261]             | 16 [6-37]        | 6.00                         |
| <b>Cetirizine*</b>      | 350    | 52 [28-70]       | 2169 [545]             | 22 [9-50]        | 4.00                         |
| <b>Desloratadine*</b>   | 300    | 50 [26-71]       | 2085 [504]             | 21 [8-46]        | 4.14                         |
| <b>Ebastine*</b>        | 115    | 50 [26-72]       | 980 [201]              | 23 [9-48]        | 4.88                         |
| <b>Fexofenadine*</b>    | 112    | 55 [32.5-71.5]   | 1128 [183]             | 14 [8-35]        | 6.17                         |
| <b>Levocetirizine*</b>  | 149    | 43 [16-67]       | 1512 [260]             | 14 [5-28]        | 5.81                         |
| <b>Loratadine*</b>      | 175    | 49 [28-72]       | 1680 [344]             | 21 [10-39]       | 4.88                         |
| <b>Rupatadine*</b>      | 66     | 49 [23-63]       | 1138 [146]             | 18 [5-36]        | 7.69                         |
| <b>FF</b>               | 176    | 35 [19.5-58.5]   | 2182 [336]             | 5 [0-27]         | 6.49                         |
| <b>+ OAH</b>            | 129    | 51 [22-66]       | 1317 [247]             | 21 [4-45]        | 5.33                         |
| <b>+ OAH + other</b>    | 38     | 64 [49-77]       | 307 [80]               | 48 [24-63]       | 3.84                         |
| <b>+ other (no OAH)</b> | 84     | 53.5 [28-72]     | 968 [168]              | 23 [9-47]        | 5.76                         |
| <b>+ other INCS</b>     | 7      | 50 [4-90]        | 113 [16]               | 61 [26-95]       | 7.06                         |
| <b>AzeFlu</b>           | 155    | 37 [16-60]       | 2722 [303]             | 13 [3-29]        | 8.98                         |
| <b>+ OAH</b>            | 49     | 58 [40-73]       | 994 [113]              | 17 [7-40]        | 8.72                         |
| <b>+ OAH + other</b>    | 12     | 54 [26-80]       | 174 [33]               | 31 [9-60]        | 5.27                         |
| <b>+ other (no OAH)</b> | 37     | 40 [21-65]       | 871 [98]               | 22 [11-42]       | 8.89                         |
| <b>+ other INCS</b>     | 7      | 50 [33-77]       | 193 [21]               | 36 [12-73]       | 8.39                         |
| <b>MF</b>               | 192    | 36.5 [16.5-59.5] | 3420 [409]             | 15 [5-28]        | 7.92                         |
| <b>+ OAH</b>            | 144    | 48 [23-68]       | 2181 [284]             | 17 [8-37]        | 7.68                         |
| <b>+ OAH + other</b>    | 64     | 61.5 [33.5-75]   | 914 [114]              | 26 [14-49]       | 8.02                         |
| <b>+ other (no OAH)</b> | 83     | 53 [26-68]       | 1158 [167]             | 26 [9-45]        | 6.93                         |
| <b>+ other INCS</b>     | 7      | 33 [0-77]        | 113 [21]               | 20 [6-79]        | 5.38                         |
| <b>FP</b>               | 33     | 44 [30-65]       | 156 [55]               | 23.5 [3.5-52]    | 2.83                         |
| <b>+ OAH</b>            | 34     | 56 [40-67]       | 305 [64]               | 19 [10-46]       | 4.77                         |
| <b>+ OAH + other</b>    | 14     | 52.5 [45-80]     | 60 [21]                | 54 [24.5-82.5]   | 2.89                         |
| <b>+ other (no OAH)</b> | 13     | 41 [31-59]       | 121 [22]               | 22 [18-41]       | 5.50                         |
| <b>+ other INCS</b>     | 3      | 4 [0-65]         | 127 [11]               | 22 [8-48]        | 11.55                        |

698 \*: monotherapy

699 FF: Fluticasone Furoate, FP: Fluticasone Propionate, MF: Mometasone Furoate, AZeFlu:  
700 Azelastine-Fluticasone Propionate

701 p25: 25<sup>th</sup> percentile; p75: 75<sup>th</sup> percentile

702

703 **Table 3. Day 1 versus non-consecutive days**

|                             | <b>Day 1</b> |                                     | <b>1<sup>st</sup> non-consecutive day</b> |                                     | <b>Other non-consecutive day</b> |                                     | <b>P value*</b>                                    |
|-----------------------------|--------------|-------------------------------------|---|-------------------------------------|----------------------------------|-------------------------------------|--|
|                             | <b>N</b>     | <b>VAS global, median [p25-p75]</b> | <b>N</b>                                  | <b>VAS global, median [p25-p75]</b> | <b>N</b>                         | <b>VAS global, median [p25-p75]</b> | <b>Day 1 vs 1<sup>st</sup> non-consecutive day</b> |
| <b>All days</b>             | 4132         | 34 [12-60]                          | 4132                                      | 25 [7-51]                           | 24680                            | 12 [2-32]                           | <0.001   |
| <b>No treatment</b>         | 2214         | 26 [7-51]                           | 2154                                      | 18 [4-44]                           | 13651                            | 8 [0-24]                            | <0.001   |
| <b>AzeFlu</b>               | 162          | 44 [19-69]                          | 187                                       | 26 [9-55]                           | 1566                             | 17 [6-35]                           | <0.001   |
| <b>Other INCS treatment</b> | 555          | 43 [22-64]                          | 601                                       | 30 [11-55]                          | 3403                             | 17 [6-38]                           | <0.001   |

704 \*Statistical analysis by Wilcoxon and Mann-Whitney test

705 p25: 25<sup>th</sup> percentile; p75: 75<sup>th</sup> percentile

706

707 **Figure 1. Flow-chart of the study population**

708 **Figure 2: Percentage of days in each category of INCS treatment (first day and full data set)**

709 **Figure 3: Percentage of days in each category of treatment for VAS global measured (full**  
710 **dataset)**

711

712



Fig 1

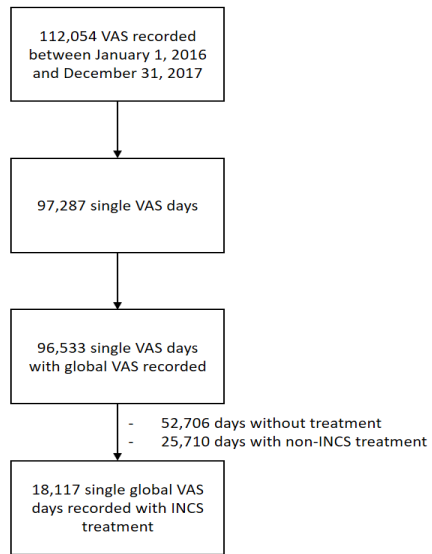
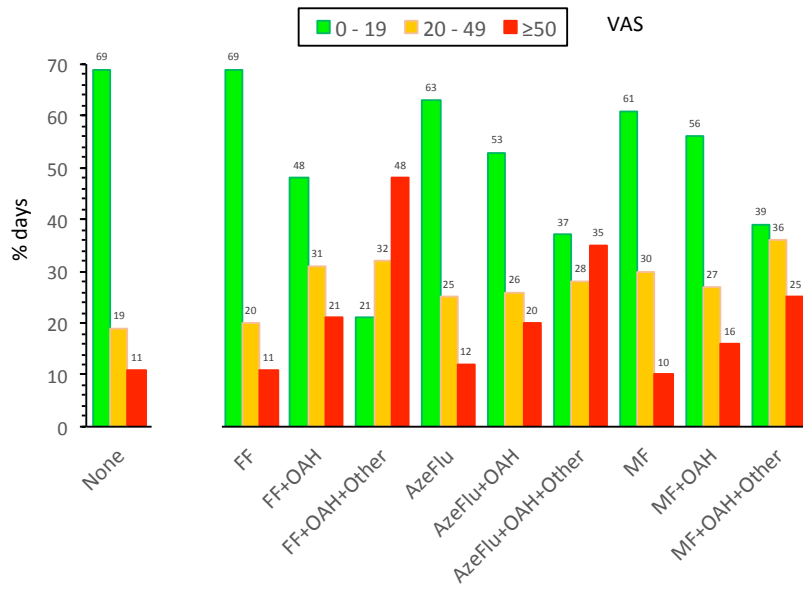
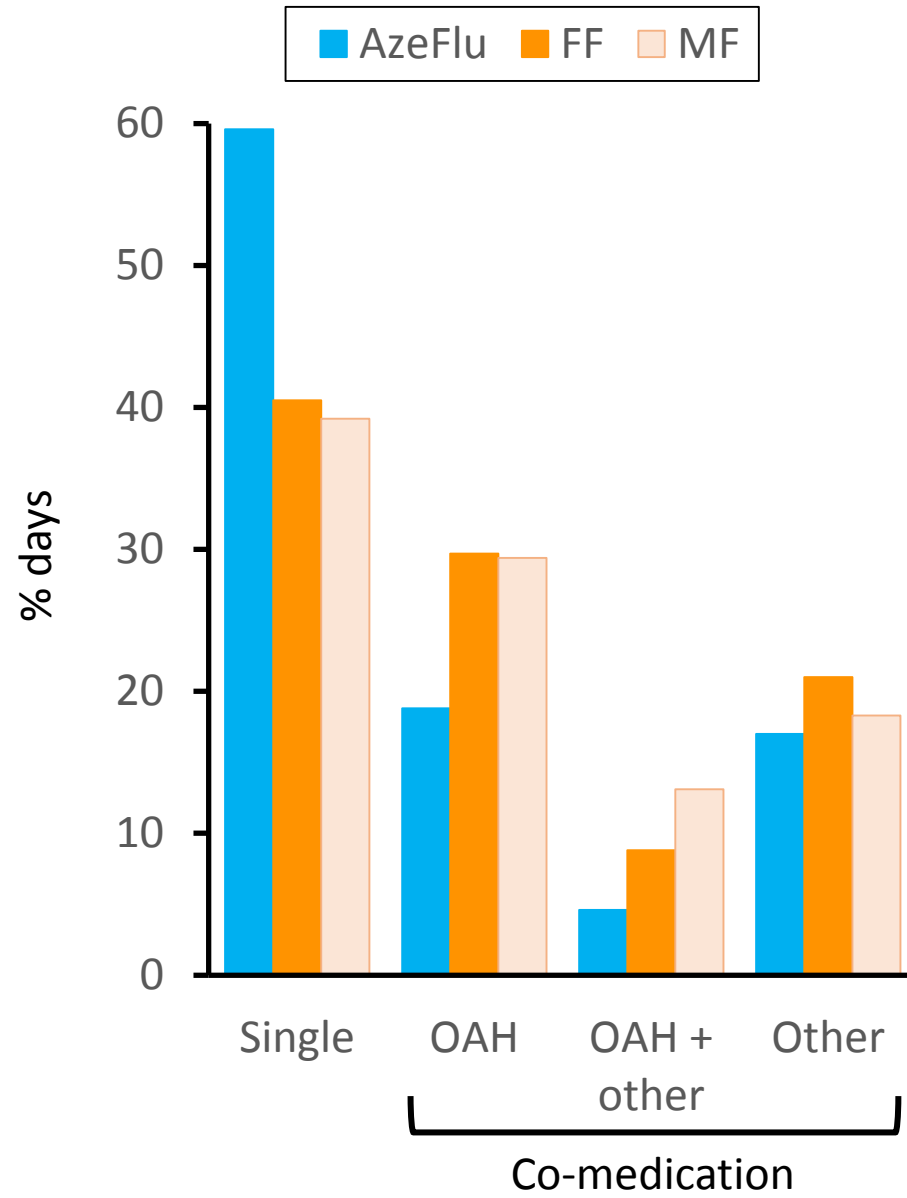


Fig 2



# Day 1



# All days

