



HAL
open science

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

Annabelle Bédard, Xavier Basagana, Josep M Antó, Judith Garcia-Aymerich, Philippe Devillier, Sylvie Arnavielhe, Anna Bedbrook, Gabrielle L Onorato, Wienczyslawa Czarlewski, Ruth Murray, et al.

► To cite this version:

Annabelle Bédard, Xavier Basagana, Josep M Antó, Judith Garcia-Aymerich, Philippe Devillier, et al.. Mobile technology offers novel insights into the control and treatment of allergic rhinitis: The MASK study. *Journal of Allergy and Clinical Immunology*, 2019, 144 (1), pp.135-143.e6. 10.1016/j.jaci.2019.01.053 . hal-02867894

HAL Id: hal-02867894

<https://hal.umontpellier.fr/hal-02867894v1>

Submitted on 25 Oct 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

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

3
4 Annabelle Bédard, MD, (1-3), Xavier Basagaña, PhD, (1-3), Josep M Anto, PhD, (1-3), Judith
5 Garcia-Aymerich, MD, (1-3), Philippe Devillier, MD, (5), Sylvie Arnavielhe, PhD, (6), Anna
6 Bedbrook, BSc, (7), Gabrielle L Onorato, MSc, (7), Wienczyslawa Czarlewski, MD, (8), Ruth
7 Murray, PhD, (9), Rute Almeida, PhD, (10), Joao Fonseca, MD, (10), Elisio Costa, PhD, (11), Joao
8 Malva, MD, (12), Mario Morais-Almeida, MD, (13), Ana Maria Pereira, MD, (14), Ana Todo-
9 Bom, MD, (15), Enrica Menditto, PhD, (16), Cristiana Stellato, MD, (17), Maria Teresa Ventura,
10 MD, (18), Alvaro A Cruz, MD, (19), Rafaël Stelmach, MD, (20), Jane da Silva, MD, (21), Désirée
11 Larenas-Linnemann, MD, (22), José M Fuentes-Pérez, MD (23), Yunuen R Huerta-Villalobos,
12 MD, (23), Regina Emuzyte, MD, (24), Violeta Kvedariene, MD, (25), Arunas Valiulis, MD, (26),
13 Piotr Kuna, MD, (27), Boleslaw Samolinski, MD, (28), Ludger Klimek, MD, (29), Ralph Mösges,
14 MD, (30), Oliver Pfaar, MD, (32), Sara Shamai, MD, (30), Isabelle Annesi-Maesano, MD, (33),
15 Isabelle Bosse, MD, (34), Pascal Demoly, MD, (35), Jean-François Fontaine, MD, (36), Vicky
16 Cardona, MD, (37), Joaquim Mullol, MD, (38), Antonio Valero, MD, (39), Regina E Roller-
17 Wirnsberger, MD, (40), Peter Valentin Tomazic, MD, (41), Niels H Chavannes, MD, (42), Wytske
18 J Fokkens, MD, (43), Sietze Reitsma, MD, (43), Mike Bewick, MD, (44), Dermot Ryan, MD, (45),
19 Aziz Sheikh, MD, (46), Tari Haahtela, MD, (47), Sanna Toppila-Salmi, MD, (47), Erkkka Valovirta,
20 MD, (48), Michael Makris, MD, (49), Nikos G Papadopoulos, MD, (50), Emmanuel P Prokopakis,
21 MD, (51), Fotis Psarros, MD, (52), Cemal Cingi, MD, (53), Bilun Gemicioğlu, MD, (54), Arzu
22 Yorgancioglu, MD, (55), Sinthia Bosnic-Anticevich, PhD, (56), Robyn E O'Hehir, MD, (57), Claus
23 Bachert, MD, (58), Peter W Hellings, MD, (59), Benoit Pugin, PhD (60), Carsten Bindslev-Jensen,
24 MD, (61), Esben Eller, MD, (61), Ingrid Kull, PhD, (62,63), Erik Melén, MD, (63), Magnus
25 Wickman, MD, (64), Gert De Vries, MSc, (65), Michiel van Eerd, MSc, (65), Ioana Agache, MD,
26 (66), Ignacio J Ansotegui, MD, (67), Mark S Dykewicz, MD, (68), Thomas Casale, MD, (69), Dana
27 Wallace, MD, (70), Susan Wasserman, MD, (71), Daniel Laune, PhD, (6), Jean Bousquet, MD, (7,
28 31, 72), and the MASK study group.

- 29
30 1. ISGlobal, Barcelona, Spain.
31 2. Universitat Pompeu Fabra (UPF), Barcelona, Spain.
32 3. CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain.
33 4. Universitat Pompeu Fabra (UPF), Barcelona, Spain.
34 5. UPRES EA220, Pôle des Maladies des Voies Respiratoires, Hôpital Foch, Université Paris-Saclay,
35 Suresnes, France.
36 6. KYomed INNOV, Montpellier, France.
37 7. MACVIA-France, Fondation partenariale FMC VIA-LR, Montpellier, France.
38 8. Medical Consulting Czarlewski, Levallois, France.
39 9. Director, Medical Communications Consultant, MedScript Ltd, Dundalk, Co Louth, Ireland and
40 New Zealand, Honorary Research Fellow, OPC, Cambridge, UK.
41 10. Center for Health Technology and Services Research - CINTESIS, Faculdade de Medicina,
42 Universidade do Porto; and Medida, Lda Porto, Portugal.
43 11. UCIBIO, REQUINTE, Faculty of Pharmacy and Competence Center on Active and Healthy Ageing
44 of University of Porto (Porto4Ageing), Porto, Portugal.
45 12. Institute of Biomedical Imaging and Life Sciences (IBILI), Faculty of Medicine, University of
46 Coimbra, Portugal; Ageing@Coimbra EIP-AHA Reference Site, Portugal.
47 13. Allergy Center, CUF Descobertas Hospital, Lisbon, Portugal
48 14. Allergy Unit, CUF-Porto Hospital and Institute; Center for Research in Health Technologies and
49 information systems CINTESIS, Universidade do Porto, Portugal.
50 15. Imunoalergologia, Centro Hospitalar Universitário de Coimbra and Faculty of Medicine, University
51 of Coimbra, Portugal.

- 52 16. CIRFF, Federico II University, Naples, Italy.
- 53 17. Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno,
- 54 Salerno, Italy.
- 55 18. University of Bari Medical School, Unit of Geriatric Immunoallergology, Bari, Italy.
- 56 19. ProAR – Nucleo de Excelencia em Asma, Federal University of Bahia, Brasil and WHO GARD
- 57 Planning Group, Brazil.
- 58 20. Pulmonary Division, Heart Institute (InCor), Hospital da Clinicas da Faculdade de Medicina da
- 59 Universidade de Sao Paulo, Sao Paulo, Brazil.
- 60 21. Department of Internal Medicine and Allergy Clinic of Professor Polydoro Ernani de São Thiago
- 61 University Hospital, Federal University of Santa Catarina (UFSC), Florianopolis-SC, Brazil.
- 62 22. Center of Excellence in Asthma and Allergy, Hospital Médica Sur, México City, Mexico.
- 63 23. Hospital General Region 1, Dr Carlos Mc Gregor Sanchez Navarro" IMSS. Mexico City, Mexico
- 64 24. Clinic of Children's Diseases, Faculty of Medicine, Vilnius University, Vilnius, Lithuania.
- 65 25. Faculty of Medicine, Vilnius University, Vilnius, Lithuania.
- 66 26. Vilnius University Institute of Clinical Medicine, Clinic of Children's Diseases, and Institute of
- 67 Health Sciences, Department of Public Health, Vilnius, Lithuania; European Academy of Paediatrics
- 68 (EAP/UEMS-SP), Brussels, Belgium.
- 69 27. Division of Internal Medicine, Asthma and Allergy, Barlicki University Hospital, Medical
- 70 University of Lodz, Poland.
- 71 28. Department of Prevention of Environmental Hazards and Allergology, Medical University of
- 72 Warsaw, Poland.
- 73 29. Center for Rhinology and Allergology, Wiesbaden, Department of Otorhinolaryngology, Head and
- 74 Neck Surgery, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University,
- 75 Mannheim, Germany.
- 76 30. Institute of Medical Statistics, and Computational Biology, Medical Faculty, University of Cologne,
- 77 Germany and CRI-Clinical Research International-Ltd, Hamburg, Germany.
- 78 31. University Hospital, Montpellier, France
- 79 32. Department of Otorhinolaryngology, Head and Neck Surgery, Section for Rhinology and Allergy,
- 80 University Hospital Marburg, Philipps-Universität, Marburg, Germany.
- 81 33. Epidemiology of Allergic and Respiratory Diseases, Department Institute Pierre Louis of
- 82 Epidemiology and Public Health, INSERM and UPMC Sorbonne Université, Medical School Saint
- 83 Antoine, Paris, France
- 84 34. Allergist, La Rochelle, France.
- 85 35. Department of Respiratory Diseases, Montpellier University Hospital, France
- 86 36. Allergist, Reims, France.
- 87 37. Allergy Section, Department of Internal Medicine, Hospital Vall 'dHebron & ARADyAL research
- 88 network, Barcelona, Spain.
- 89 38. Rhinology Unit & Smell Clinic, ENT Department, Hospital Clínic; Clinical & Experimental
- 90 Respiratory Immunoallergy, IDIBAPS, CIBERES, University of Barcelona, Spain.
- 91 39. Pneumology and Allergy Department CIBERES and Clinical & Experimental Respiratory
- 92 Immunoallergy, IDIBAPS, University of Barcelona, Spain.
- 93 40. Medical University of Graz, Department of Internal Medicine, Graz, Austria.
- 94 41. Department of ENT, Medical University of Graz, Austria
- 95 42. Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The
- 96 Netherlands
- 97 43. Department of Otorhinolaryngology, Amsterdam University Medical Centres, AMC, Amsterdam,
- 98 the Netherlands.
- 99 44. iQ4U Consultants Ltd, London, UK.
- 100 45. Honorary Clinical Research Fellow, Allergy and Respiratory Research Group, The University of
- 101 Edinburgh, Edinburgh, UK
- 102 46. The Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh,
- 103 Edinburgh, UK.
- 104 47. Skin and Allergy Hospital, Helsinki University Hospital, Helsinki, Finland.
- 105 48. Department of Lung Diseases and Clinical Immunology, University of Turku and Terveystalo
- 106 allergy clinic, Turku, Finland.
- 107 49. Allergy Unit "D Kalogeromitros", 2nd Dpt of Dermatology and Venereology, National &
- 108 Kapodistrian University of Athens, "Attikon" University Hospital, Greece.
- 109 50. Center for Pediatrics and Child Health, Institute of Human Development, Royal Manchester
- 110 Children's Hospital, University of Manchester, Manchester M13 9WL, UK Allergy Department, 2nd

- 111 Pediatric Clinic, Athens General Children's Hospital "P&A Kyriakou," University of Athens, Athens
112 11527, Greece
- 113 51. Department of Otorhinolaryngology University of Crete School of Medicine, Heraklion, Greece.
114 52. Allergy Department, Athens Naval Hospital, Athens, Greece.
115 53. Eskisehir Osmangazi University, Medical Faculty, ENT Department, Eskisehir, Turkey.
116 54. Department of Pulmonary Diseases, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of
117 Medicine, Istanbul, Turkey.
118 55. Department of Pulmonary Diseases, Celal Bayar University, Faculty of Medicine, Manisa, Turkey
119 and GARD Executive Committee.
120 56. Woolcock Institute of Medical Research, University of Sydney and Woolcock Emphysema Centre
121 and Local Health District, Glebe, NSW, Australia.
122 57. Department of Allergy, Immunology and Respiratory Medicine, Alfred Hospital and Central
123 Clinical School, Monash University, Melbourne, Victoria, Australia; Department of Immunology,
124 Monash University, Melbourne, Victoria, Australia.
125 58. Upper Airways Research Laboratory, ENT Dept, Ghent University Hospital, Ghent, Belgium.
126 59. Dept of Otorhinolaryngology, Univ Hospitals Leuven, Belgium, and Academic Medical Center,
127 Univ of Amsterdam, The Netherlands and Euforea, Brussels, Belgium.
128 60. European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA),
129 Brussels, Belgium.
130 61. Department of Dermatology and Allergy Centre, Odense University Hospital, Odense Research
131 Center for Anaphylaxis (ORCA), Odense, Denmark.
132 62. Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, and Sachs' Children
133 and Youth Hospital, Södersjukhuset, Stockholm, Sweden
134 63. Sachs' Children and Youth Hospital, Södersjukhuset, Stockholm and Institute of Environmental
135 Medicine, Karolinska Institutet, Stockholm, Sweden.
136 64. Centre for Clinical Research Sörmland, Uppsala University, Eskilstuna, Sweden.
137 65. Peercode BV, Geldermalsen, The Netherlands.
138 66. Transylvania University Brasov, Brasov, Romania.
139 67. Department of Allergy and Immunology, Hospital Quirón Bizkaia, Erandio, Spain.
140 68. Section of Allergy and Immunology, Saint Louis University School of Medicine, Saint Louis,
141 Missouri, USA.
142 69. Division of Allergy/Immunology, University of South Florida, Tampa, Fla.
143 70. Nova Southeastern University, Fort Lauderdale, Florida, USA.
144 71. Department of Medicine, Clinical Immunology and Allergy, McMaster University, Hamilton,
145 Ontario, Canada.
146 72. INSERM U 1168, VIMA : Ageing and chronic diseases Epidemiological and public health
147 approaches, Villejuif, Université Versailles St-Quentin-en-Yvelines, UMR-S 1168, Montigny le
148 Bretonneux, France and Euforea, Brussels, Belgium

149

150

151

152

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

154

155 **Author for correspondence**

156 Professor Jean Bousquet

157 CHU Arnaud de Villeneuve, 371 Avenue du Doyen Gaston Giraud, 34295 Montpellier Cedex 5,
158 France Tel +33 611 42 88 47, Fax :+33 467 41 67 01 jean.bousquet@orange.f

159

160

161

162 **Conflict of interest**

163

164 Dr. Devillier reports personal fees from Sanofi-Aventis, GlaxoSmithKline, Astra Zeneca, Chiesi,
165 Meda Pharma, Menarini, outside the submitted work.

166 Dr. Almeida reports grants from Project NORTE-01-0145-FEDER-000016 (NanoSTIMA) by
167 North Portugal Regional Operational Programme (NORTE 2020), under the Portugal 2020
168 Partnership Agreement, and through the European Regional Development Fund (ERDF), during
169 the conduct of the study.

170 Dr. Todo-Bom reports grants and personal fees from GSK, Mundipharma Novartis, personal fees
171 from Teva pharma, personal fees from Astrazeneca, grants from Leti, Bial, outside the submitted
172 work.

173 Dr. Cruz reports grants and personal fees from Astrazeneca, grants from GSK, personal fees
174 from Boehringer Ingelheim, CHIESI, NOVARTIS, Eurofarma, MEDA Pharma, Boston Scientific,
175 outside the submitted work.

176 Dr. Larenas Linnemann reports personal fees from Amstrong, Astrazeneca, Boehringer
177 Ingelheim, Chiesi, DBV Technologies, Grunenthal, GSK, MEDA, Menarini, MSD, Novartis,
178 Pfizer, Sanofi, Siegfried, UCB, grants from Sanofi, Astrazeneca, Novartis, UCB, GSK, TEVA,
179 Boehringer Ingelheim, Chiesi, outside the submitted work.

180 Dr. Stelmach reports grants from São Paulo Research Foundation, MSD, grants and personal
181 fees from Novartis, grants, personal fees and non-financial support from AstraZeneca, Chiesi,
182 personal fees and non-financial support from Boehringer Ingelheim, outside the submitted work.

183 Dr. Larenas Linnemann reports personal fees from Amstrong, Astrazeneca, Boehringer
184 Ingelheim, Chiesi, DBV Technologies, Grunenthal, GSK, MEDA, Menarini, MSD, Novartis,
185 Pfizer, Sanofi, Siegfried, UCB, grants from Sanofi, Astrazeneca, Novartis, UCB, GSK, TEVA,
186 Boehringer Ingelheim, Chiesi, outside the submitted work.

187 Dr Kvedariene has received payment for consultancy from GSK and for lectures from
188 StallergensGreer, Berlin-CHemie outside the submitted work.

189 Dr. Kuna reports personal fees from Adamed, Boehringer Ingelheim, AstraZeneca, Chiesi,
190 FAES, Berlin Chemie, Novartis, Polpharma, Allergopharma, outside the submitted work.

191 Dr. Ralph Mösges reports personal fees from ALK, allergopharma, Allergy Therapeutics, Hexal,
192 personal fees from Servier, personal fees from Klosterfrau, Stada, UCB, Friulchem, grants from
193 ASIT biotech, Nuvo, Bayer, FAES, GSK, MSD, Johnson&Johnson, Meda, Optima, Ursapharm,
194 BitopAG, Hulka, grants and personal fees from Bencard, grants from Leti, Stallergenes, grants,
195 personal fees and non-financial support from Lofarma, non-financial support from Roxall, from
196 Atmos, from Bionorica, Otonomy, Ferrero, personal fees and non-financial support from
197 Novartis, outside the submitted work.

198 Dr. Pfaar reports grants and personal fees from ALK-Abelló, Allergopharma, Stallergenes
199 Greer, HAL Allergy Holding B.V./HAL Allergie GmbH, Bencard Allergie GmbH/Allergy
200 Therapeutics, Lofarma, grants from Biomay, Nuvo, Circassia, Glaxo Smith Kline, personal fees
201 from Novartis Pharma, MEDA Pharma, Indoor Biotechnologies, Pohl-Boskamp, outside the
202 submitted work.

203 Dr. Haahtela reports personal fees from Mundipharma, Novartis, and Orion Pharma, outside the
204 submitted work.

205 Dr. Toppila-Salmi reports other from Biomedical Systems Ltd., Roche Ltd., grants from Erkkö
206 Foundation, outside the submitted work.

207 Dr. Papadopoulos reports grants from Gerolymatos, personal fees from Hal Allergy B.V.,
208 Novartis Pharma AG, Menarini, Hal Allergy B.V., Mylan, outside the submitted work.

209 Dr. Bosnic-Anticevich reports personal fees from Teva, Boehringer Ingelheim, Sanofi, GSK,
210 AstraZeneca, outside the submitted work.

211 Bachert reports personal fees from Meda, Stallergenes and ALK (speaker).

212 Dr. Ansotegui reports personal fees from Hikma, Roxall, Astra Zeneca, Menarini, UCB, Faes
213 Farma, Sanofi, Mundipharma, outside the submitted work.

214 J Bousquet reports personal fees and other from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan,
215 Novartis, Sanofi-Aventis, Takeda, Teva, Uriach, outside the submitted work. other from Kyomed.

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 H¹-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

570 References

- 571 1. Price D, Smith P, Hellings P, Papadopoulos N, Fokkens W, Muraro A, et al. Current
572 controversies and challenges in allergic rhinitis management. *Expert Rev Clin Immunol.*
573 2015;1-13.
- 574 2. Travers J, Marsh S, Williams M, Weatherall M, Caldwell B, Shirtcliffe P, et al. External
575 validity of randomised controlled trials in asthma: to whom do the results of the trials
576 apply? *Thorax.* 2017;62(3):219-23.
- 577 3. Brozek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al.
578 Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines - 2016 Revision. *J Allergy*
579 *Clin Immunol.* 2017;140(4):950-8.
- 580 4. Dykewicz MS, Wallace DV, Baroody F, Bernstein J, Craig T, Finegold I, et al. Treatment
581 of seasonal allergic rhinitis: An evidence-based focused 2017 guideline update. *Ann*
582 *Allergy Asthma Immunol.* 2017;119(6):489-511 e41.
- 583 5. Bousquet J, Meltzer EO, Couroux P, Koltun A, Kopietz F, Munzel U, et al. Onset of
584 Action of the Fixed Combination Intranasal Azelastine-Fluticasone Propionate in an
585 Allergen Exposure Chamber. *J Allergy Clin Immunol Pract.* 2018;6(5):1726-32.
- 586 6. Bosnic-Anticevich S, Kritikos V, Carter V, Yan KY, Armour C, Ryan D, et al. Lack of
587 asthma and rhinitis control in general practitioner-managed patients prescribed fixed-dose
588 combination therapy in Australia. *J Asthma.* 2018;55(6):684-94.
- 589 7. Tan R, Cvetkovski B, Kritikos V, Price D, Yan K, Smith P, et al. Identifying the hidden
590 burden of allergic rhinitis (AR) in community pharmacy: a global phenomenon. *Asthma*
591 *Res Pract.* 2017;3:8.
- 592 8. Bourret R, Bousquet J, J M, T C, Bedbrook A, P D, et al. MASK rhinitis, a single tool for
593 integrated care pathways in allergic rhinitis. *World Hosp Health Serv.* 2015;51(3):36-9.
- 594 9. Bousquet J, Schunemann HJ, Fonseca J, Samolinski B, Bachert C, Canonica GW, et al.
595 MACVIA-ARIA Sentinel NetworK for allergic rhinitis (MASK-rhinitis): the new
596 generation guideline implementation. *Allergy.* 2015;70(11):1372-92.
- 597 10. Bousquet J, Hellings PW, Agache I, Bedbrook A, Bachert C, Bergmann KC, et al. ARIA
598 2016: Care pathways implementing emerging technologies for predictive medicine in
599 rhinitis and asthma across the life cycle. *Clin Transl Allergy.* 2016;6:47.
- 600 11. Bousquet J, Anto JM, Annesi-Maesano I, Dedeu T, Dupas E, Pepin JL, et al. POLLAR:
601 Impact of air POLLution on Asthma and Rhinitis; a European Institute of Innovation and
602 Technology Health (EIT Health) project. *Clin Transl Allergy.* 2018;8:36.
- 603 12. Bousquet J, Arnavielhe S, Bedbrook A, Bewick M, Laune D, Mathieu-Dupas E, et al.
604 MASK 2017: ARIA digitally-enabled, integrated, person-centred care for rhinitis and
605 asthma multimorbidity using real-world-evidence. *Clin Transl Allergy.* 2018;8:45.
- 606 13. Bousquet J, Arnavielhe S, Bedbrook A, Alexis-Alexandre G, Eerd Mv, Murray R, et al.
607 Treatment of allergic rhinitis using mobile technology with real world data: The MASK
608 observational pilot study. *Allergy.* 2018:sous presse.
- 609 14. Bousquet J, Bewick M, Arnavielhe S, Mathieu-Dupas E, Murray R, Bedbrook A, et al.
610 Work productivity in rhinitis using cell phones: The MASK pilot study. *Allergy.*
611 2017;72(10):1475-84.
- 612 15. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices. 1993L0042 —
613 EN — 11.10.2007 — 005.001 — 1. [https://eur-](https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:EN:PDF)
614 [lexeuropa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:EN:PDF.](https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:EN:PDF)
615 1993.
- 616 16. Samreth D, Arnavielhe S, Ingenrieth F, Bedbrook A, Onorato GL, Murray R, et al.
617 Geolocation with respect to personal privacy for the Allergy Diary app - a MASK study.
618 *World Allergy Organ J.* 2018;11(1):15.
- 619 17. Kopp-Kubel S. International Nonproprietary Names (INN) for pharmaceutical substances.
620 *Bull World Health Organ.* 1995;73(3):275-9.
- 621 18. Bousquet J, Schunemann HJ, Hellings PW, Arnavielhe S, Bachert C, Bedbrook A, et al.
622 MACVIA clinical decision algorithm in adolescents and adults with allergic rhinitis. *J*
623 *Allergy Clin Immunol.* 2016;138(2):367-74 e2.

- 624 19. Bousquet J, Hellings PW, Agache I, Amat F, Annesi-Maesano I, Ansotegui IJ, et al. ARIA
625 Phase 4 (2018): Change management in allergic rhinitis and asthma multimorbidity using
626 mobile technology. *J Allergy Clin Immunol*. 2018;pii: S0091-6749(18)31359-9. doi:
627 10.1016/j.jaci.2018.08.049.
- 628 20. Caimmi D, Baiz N, Tanno LK, Demoly P, Arnavielhe S, Murray R, et al. Validation of the
629 MASK-rhinitis visual analogue scale on smartphone screens to assess allergic rhinitis
630 control. *Clin Exp Allergy*. 2017;47(12):1526-33.
- 631 21. Bousquet J, Caimmi DP, Bedbrook A, Bewick M, Hellings PW, Devillier P, et al. Pilot
632 study of mobile phone technology in allergic rhinitis in European countries: the MASK-
633 rhinitis study. *Allergy*. 2017;72(6):857-65.
- 634 22. Bousquet J, Arnavielhe S, Bedbrook A, Fonseca J, Morais Almeida M, Todo Bom A, et al.
635 The Allergic Rhinitis and its Impact on Asthma (ARIA) score of allergic rhinitis using
636 mobile technology correlates with quality of life: The MASK study. *Allergy*.
637 2018;73(2):505-10.
- 638 23. Bousquet J, Devillier P, Anto JM, Bewick M, Haahtela T, Arnavielhe S, et al. Daily
639 allergic multimorbidity in rhinitis using mobile technology: a novel concept of the MASK
640 study. *Allergy*. 2018;73(9):1763-74.
- 641 24. Bousquet J, VandenPlas O, Bewick M, Arnavielhe S, Bedbrook A, Murray R, et al. The
642 Work Productivity and Activity Impairment Allergic Specific (WPAI-AS) Questionnaire
643 Using Mobile Technology: The MASK Study. *J Investig Allergol Clin Immunol*.
644 2018;28(1):42-4.
- 645 25. Bonini M. Electronic health (e-Health): emerging role in asthma. *Curr Opin Pulm Med*.
646 2017;23(1):21-6.
- 647 26. Pizzulli A, Perna S, Florack J, Pizzulli A, Giordani P, Tripodi S, et al. The impact of
648 telemonitoring on adherence to nasal corticosteroid treatment in children with seasonal
649 allergic rhinoconjunctivitis. *Clin Exp Allergy*. 2014;44(10):1246-54.
- 650 27. Klimek L, Bergmann KC, Biedermann T, Bousquet J, Hellings P, Jung K, et al. Visual
651 analogue scales (VAS): Measuring instruments for the documentation of symptoms and
652 therapy monitoring in cases of allergic rhinitis in everyday health care: Position Paper of
653 the German Society of Allergology (AeDA) and the German Society of Allergy and
654 Clinical Immunology (DGAKI), ENT Section, in collaboration with the working group on
655 Clinical Immunology, Allergology and Environmental Medicine of the German Society of
656 Otorhinolaryngology, Head and Neck Surgery (DGHNOKHC). *Allergo J Int*.
657 2017;26(1):16-24.
- 658 28. Ohta K, Jean Bousquet P, Akiyama K, Adachi M, Ichinose M, Ebisawa M, et al. Visual
659 analog scale as a predictor of GINA-defined asthma control. The SACRA study in Japan. *J*
660 *Asthma*. 2013;50(5):514-21.
- 661 29. Kremer B, Klimek L, Gulicher D, Degen M, Mosges R. Sequential therapy with azelastine
662 in seasonal allergic rhinitis. *Deutsche Rhinitis Studiengruppe (German Rhinitis Study*
663 *Group)*. *Arzneimittelforschung*. 1999;49(11):912-9.
- 664 30. Salo T, Peura S, Salimaki J, Maasilta P, Haahtela T, Kauppi P. Need for medication and
665 stuffy nose predict the severity of allergic rhinitis. *Asia Pac Allergy*. 2016;6(2):133-5.
- 666 31. Lahdensuo A, Haahtela T, Herrala J, Kava T, Kiviranta K, Kuusisto P, et al. Randomised
667 comparison of cost effectiveness of guided self management and traditional treatment of
668 asthma in Finland. *BMJ*. 1998;316(7138):1138-9.
- 669 32. Lahdensuo A, Haahtela T, Herrala J, Kava T, Kiviranta K, Kuusisto P, et al. Randomised
670 comparison of guided self management and traditional treatment of asthma over one year.
671 *Bmj*. 1996;312(7033):748-52.
- 672 33. McDonald VM, Gibson PG. Asthma self-management education. *Chron Respir Dis*.
673 2006;3(1):29-37.
- 674 34. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al.
675 Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy*
676 *Clin Immunol*. 2010;126(3):466-76.

- 677 35. Meltzer EO, Wallace D, Dykewicz M, Shneyer L. Minimal Clinically Important Difference
678 (MCID) in Allergic Rhinitis: Agency for Healthcare Research and Quality or Anchor-
679 Based Thresholds? *J Allergy Clin Immunol Pract.* 2016;4(4):682-8 e6.
- 680 36. Bachert C, Bousquet J, Hellings P. Rapid onset of action and reduced nasal hyperreactivity:
681 new targets in allergic rhinitis management. *Clin Transl Allergy.* 2018;8:25.
- 682 37. Hampel FC, Ratner PH, Van Bavel J, Amar NJ, Daftary P, Wheeler W, et al. Double-blind,
683 placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery
684 device. *Ann Allergy Asthma Immunol.* 2010;105(2):168-73.
- 685 38. Carr W, Bernstein J, Lieberman P, Meltzer E, Bachert C, Price D, et al. A novel intranasal
686 therapy of azelastine with fluticasone for the treatment of allergic rhinitis. *J Allergy Clin*
687 *Immunol.* 2012;129(5):1282-9 e10.
- 688 39. Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, et al. Real-World
689 Evidence - What Is It and What Can It Tell Us? *N Engl J Med.* 2016;375(23):2293-7.

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
Total	4082 (44.7%)	2827 (31.0%)	717 (7.9%)	1496 (16.4%)	9122

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
No treatment	4991	34 [10-60]	52706 [6236]	8 [0-26]	8.45
Bilastine*	128	48 [19-69.5]	1563 [261]	16 [6-37]	6.00
Cetirizine*	350	52 [28-70]	2169 [545]	22 [9-50]	4.00
Desloratadine*	300	50 [26-71]	2085 [504]	21 [8-46]	4.14
Ebastine*	115	50 [26-72]	980 [201]	23 [9-48]	4.88
Fexofenadine*	112	55 [32.5-71.5]	1128 [183]	14 [8-35]	6.17
Levocetirizine*	149	43 [16-67]	1512 [260]	14 [5-28]	5.81
Loratadine*	175	49 [28-72]	1680 [344]	21 [10-39]	4.88
Rupatadine*	66	49 [23-63]	1138 [146]	18 [5-36]	7.69
FF	176	35 [19.5-58.5]	2182 [336]	5 [0-27]	6.49
+ OAH	129	51 [22-66]	1317 [247]	21 [4-45]	5.33
+ OAH + other	38	64 [49-77]	307 [80]	48 [24-63]	3.84
+ other (no OAH)	84	53.5 [28-72]	968 [168]	23 [9-47]	5.76
+ other INCS	7	50 [4-90]	113 [16]	61 [26-95]	7.06
AzeFlu	155	37 [16-60]	2722 [303]	13 [3-29]	8.98
+ OAH	49	58 [40-73]	994 [113]	17 [7-40]	8.72
+ OAH + other	12	54 [26-80]	174 [33]	31 [9-60]	5.27
+ other (no OAH)	37	40 [21-65]	871 [98]	22 [11-42]	8.89
+ other INCS	7	50 [33-77]	193 [21]	36 [12-73]	8.39
MF	192	36.5 [16.5-59.5]	3420 [409]	15 [5-28]	7.92
+ OAH	144	48 [23-68]	2181 [284]	17 [8-37]	7.68
+ OAH + other	64	61.5 [33.5-75]	914 [114]	26 [14-49]	8.02
+ other (no OAH)	83	53 [26-68]	1158 [167]	26 [9-45]	6.93
+ other INCS	7	33 [0-77]	113 [21]	20 [6-79]	5.38
FP	33	44 [30-65]	156 [55]	23.5 [3.5-52]	2.83
+ OAH	34	56 [40-67]	305 [64]	19 [10-46]	4.77
+ OAH + other	14	52.5 [45-80]	60 [21]	54 [24.5-82.5]	2.89
+ other (no OAH)	13	41 [31-59]	121 [22]	22 [18-41]	5.50
+ other INCS	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: 25th percentile; p75: 75th percentile

702

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

	Day 1		1st non-consecutive day		Other non-consecutive day		P value*
	N	VAS global, median [p25-p75]	N	VAS global, median [p25-p75]	N	VAS global, median [p25-p75]	Day 1 vs 1st non-consecutive day
All days	4132	34 [12-60]	4132	25 [7-51]	24680	12 [2-32]	<0.001
No treatment	2214	26 [7-51]	2154	18 [4-44]	13651	8 [0-24]	<0.001
AzeFlu	162	44 [19-69]	187	26 [9-55]	1566	17 [6-35]	<0.001
Other INCS treatment	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: 25th percentile; p75: 75th 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

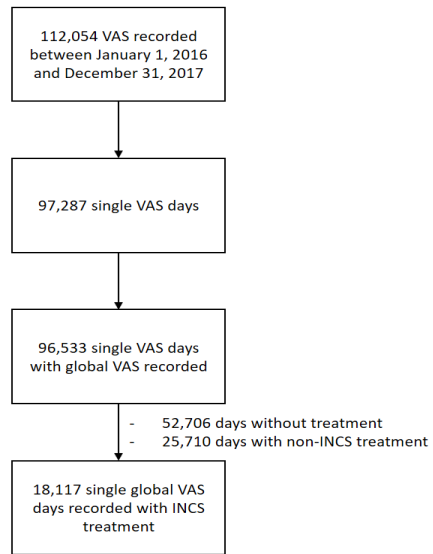
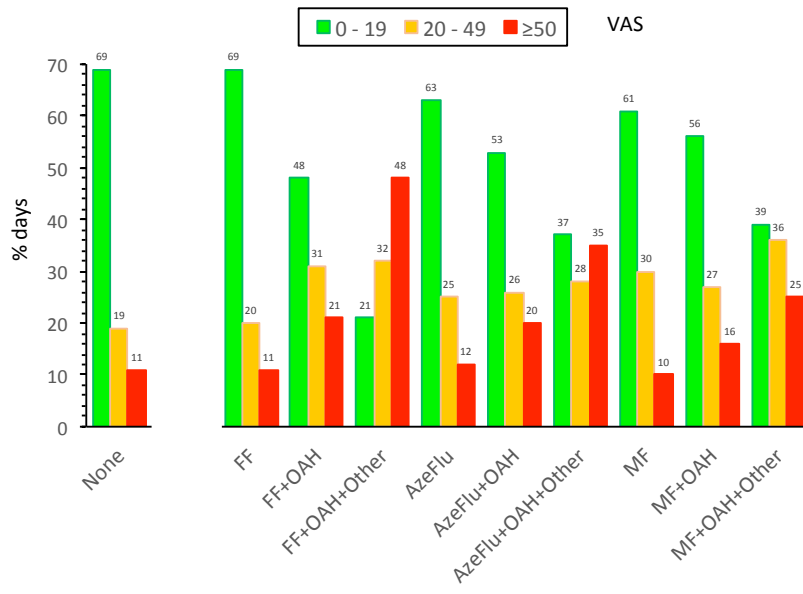
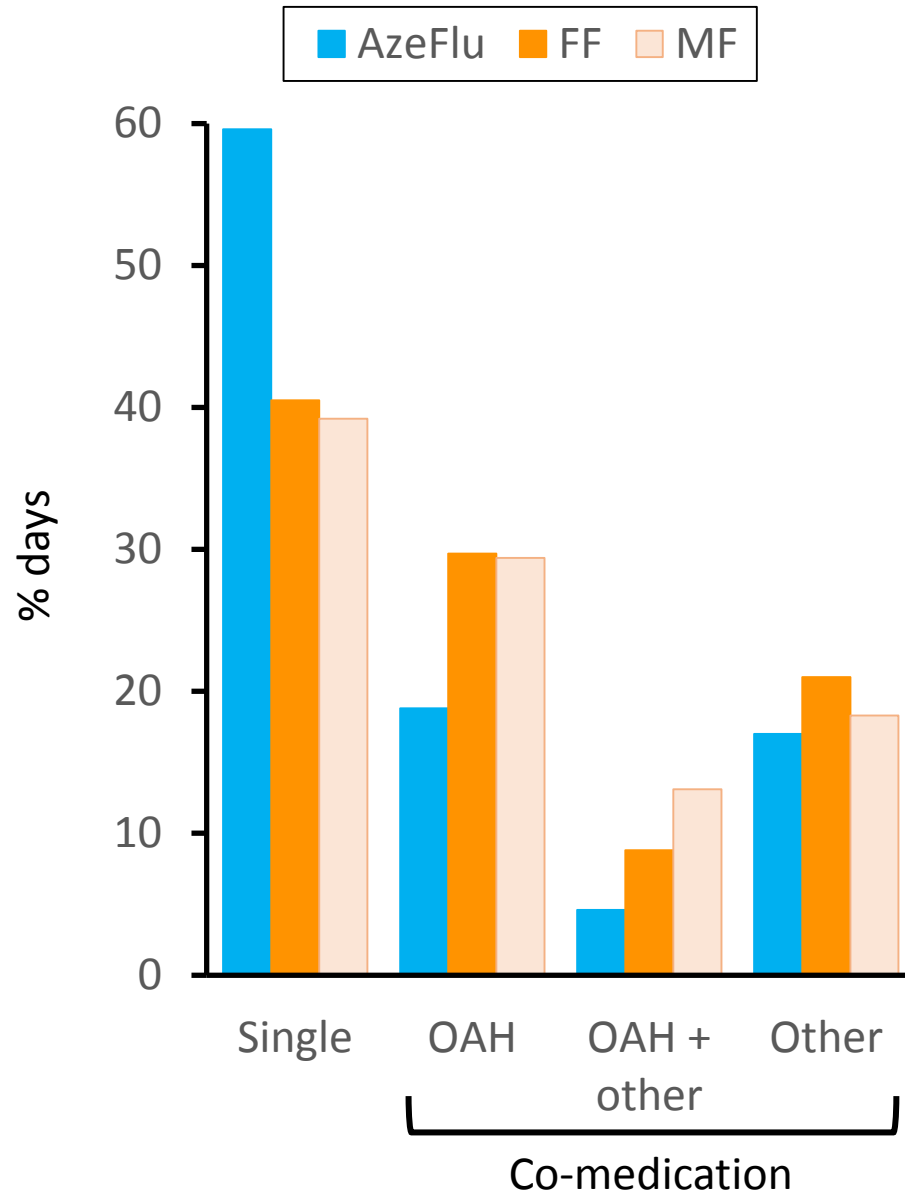


Fig 2



Day 1



All days

