

Title

Omalizumab outcomes for up to 6 years in pediatric patients with severe persistent allergic asthma

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Abstract

Background: Various studies have assessed omalizumab outcomes in the clinical practice setting but follow-up and/or number of patients included were limited. We aim to describe the long-term outcomes of pediatric patients with severe persistent allergic asthma receiving omalizumab in the largest real-life cohort reported to date.

Methods: ANCHORS was a multicenter, observational, retrospective cohort study conducted in 25 Pediatric Allergy and Pulmonology units in Spain. We collected data of patients <18 years and initiating omalizumab between 2006-2018, from the year prior to omalizumab initiation to discontinuation or last available follow-up. The primary outcome was the evolution of the annual number of moderate-to-severe exacerbations compared to the baseline period.

Results: Of the 484 patients included, 101 (20.9%) reached six years of treatment. The mean±standard deviation number of exacerbations decreased during the first year of treatment (7.9 ± 6.6 to 1.1 ± 2.0 , $p<0.001$) and remained likewise for up to six years. The other clinical parameters assessed also improved significantly during the first year and stabilized or continued to improve thereafter. The percentage of patients experiencing adverse events was consistently low, and the main reason for discontinuation was good disease evolution.

Conclusion: In this large, long-term, observational study, moderate-to-severe exacerbations decreased significantly from the first year of treatment with omalizumab. The beneficial effect was maintained in the long-term, along with a good safety profile. Our results position omalizumab as an effective long-term treatment in pediatric patients with severe persistent allergic asthma.

Keywords

Children, adolescents, severe asthma, omalizumab, anti-asthmatic agents, humanized monoclonal antibodies, observational study, real-life

Key message

Clinical trials have shown the benefits of omalizumab in pediatric patients with severe allergic asthma, but the follow-ups and/or number of patients included have been limited. Real-life studies are needed in order to check the results obtained in randomized clinical trials.

To our knowledge, this is the first observational study reporting outcomes for up to 6 years of omalizumab in a large cohort of pediatric patients with severe persistent allergic asthma. Our results come to support the long-term efficacy and safety of omalizumab in pediatric patients

with severe persistent allergic asthma who are unable to achieve disease control with conventional treatments. No tachyphylaxis seems to develop in the long term.

Introduction

Pediatric patients aged ≥ 6 years with severe persistent allergic asthma (SPAA) and unable to achieve disease control on Global Initiative for Asthma step 4 have the option to receive tiotropium bromide or targeted therapy with mepolizumab or omalizumab.¹ In line with the growing agreement on the need for pragmatic real-life data,² various prospective^{3–7} and retrospective^{8–12} studies have assessed omalizumab outcomes in real-life pediatric cohorts, but their follow-up, number of patients included or both have been limited. To determine the safety and effectiveness of omalizumab in real life, long-term follow up data from larger cohorts are needed. The study described herein follows this approach. The main objective was to describe the clinical evolution after initiating omalizumab. Other objectives included describing the patients' profile, and the effectiveness, safety, and rate and reasons for discontinuation of omalizumab.

Methods

ANCHORS (Asthma iN CHildren: Omalizumab in Real-life in Spain) was a multicenter, observational, database, retrospective cohort study conducted in 25 Pediatric Allergy and Pulmonology units in Spain with experience in severe asthma. All procedures were in accordance with the Declaration of Helsinki. A central ethics committee (Hospital Universitari i Politècnic La Fe, Valencia-Spain) approved the protocol, and granted a waiver for informed consent.

During the data collection period (August-October 2018), the participating units identified all patients <18 years who initiated omalizumab between 2006 and 2018, and included those who received omalizumab for the treatment of SPAA, after other respiratory disorders had been ruled out. Children <6 years received treatment on compassionate grounds, after obtaining informed consent from their parents. Data were collected from the year prior to omalizumab initiation (baseline period) until omalizumab discontinuation or the last available follow-up.

The primary outcome was the evolution of the annual number of moderate-to-severe exacerbations (MSE) compared to baseline. MSE were those requiring systemic corticosteroids, emergency visits, and/or hospitalizations. As secondary outcomes, we described the characteristics of patients and analyzed the annual evolution of several clinical parameters from baseline: number of non-serious exacerbations (requiring short-acting beta-agonists only); forced expiratory volume at first second (FEV₁, % predicted); fractional exhaled nitric oxide (FeNO); maximum mid-expiratory flow (MMEF, % predicted); absolute eosinophil count; number of healthcare encounters (unscheduled visits to primary care pediatricians and specialists, asthma-related emergency visits and hospitalizations, and pediatric intensive care unit [PICU] admissions); courses of systemic corticosteroids; concomitant chronic medications for asthma; and asthma control. Asthma control was assessed through validated tools (Asthma Control Questionnaire [ACQ], Asthma Control Test [ACT], and/or the Spanish Asthma Control in Children [CAN]).¹³⁻¹⁶ Finally, as secondary safety outcome, we described adverse events (AEs) and, as exploratory outcomes, the rate and reasons for omalizumab discontinuation.

Statistical analyses

Sample size considerations are described in the Appendix. Data extracted at each unit were pooled in a single anonymized database to conduct the statistical analyses (SAS software version 9.4). We present data and performed analyses for baseline demographic and clinical characteristics, MSE and other clinical parameters based on the effectiveness population (patients with data for the primary outcome at baseline and at least one year after omalizumab initiation). For safety outcomes, and rate and reasons for discontinuation, we used the safety population (patients who received ≥ 1 dose of omalizumab). To assess potential differences by age, demographics and clinical characteristics, evolution of MSE and main secondary outcome results (FeNO, FEV₁ and MMEF) were described by age group (≤ 6 years,

>6-12 years, >12 years). As the study population also included patients in whom omalizumab is not approved (≤ 6 years old), to subtract the effect of these patients we also described/analyzed outcomes for those >6 years separately.

We analyzed questionnaire scores (QS) as a continuous and categorical variable, by classifying patients as “controlled” and “uncontrolled” according to published thresholds.^{15–18} As the tool most used in Spain (CAN) as well as ACT only distinguish between “controlled” and “uncontrolled”, patients classified as “partially controlled” by ACQ were considered “uncontrolled” to harmonize the three tools. For patients with more than one score on a given year, we used the worst value.

We summarized and analyzed available data without imputing missing values. Annual changes versus baseline were assessed using paired t-tests or Wilcoxon signed rank tests (for continuous variables) and McNemar’s tests (for categorical). Comparisons between age groups were conducted through Kruskal Wallis tests (for continuous variables) or Chi-square or Fisher’s exact test (for categorical). The change in MSE over time (primary outcome) in the total study population and among age groups was also assessed through mixed models repeated measures (MMRM) analyses, using the baseline number of MSE as covariate, and either the year of follow-up as fixed effect, or the year of follow-up, age group and year of follow up-by-age group interaction as fixed effects. Pairwise comparisons were performed applying the Bonferroni correction, to account for multiplicity. All tests were two-sided, with a significance threshold of $p < 0.05$.

Results

Of the 484 patients included, all formed the safety population, while 426 formed the effectiveness population (Figure E1). Of the 484 patients, 101 (20.9%) reached six years of treatment. As only 20 (4.1%) patients continued treatment beyond this point, we present results for the first six years of follow-up, except for AEs and discontinuations. Clinical and demographic characteristics of the effectiveness population at omalizumab initiation (Table 1) did not differ substantially from those of the safety population. Characteristics for age subgroups are shown in Table E1.

Omalizumab dosage

In the effectiveness population, the mean $\pm$ standard deviation (SD) monthly dose of omalizumab was higher for patients present at baseline (524.5 ± 337.1 mg) compared with

patients on follow-up at each year of the study period, the lowest mean dose being observed at Year 6 (369.7 ± 276.6 mg). Conversely, the mean dosing interval was narrower at baseline (3.2 ± 1.1 weeks) and the widest interval was observed at Year 6 (4.0 ± 1.6 weeks).

Efficacy outcomes

The mean $\pm$ SD annual number of MSE decreased significantly from 7.9 ± 6.6 during baseline to 1.1 ± 2.0 during the first year of treatment with omalizumab (-80.2%, 95% confidence interval [CI] -84.5% to -75.8%). The number continued consistently low up to Year 6 (Figure 1A). The evolution was similar across age subgroups (Figure 1B). The MMRM analysis showed a significant least square mean (LSM) reduction in MSE from baseline at all years of follow-up, beginning at Year 1. Between-year pairwise comparisons only revealed significant LSM differences at Year 1 and Year 2 versus the rest (Table E2). When the age group and the year of follow-up-by-age group interaction were added to the MMRM model as fixed effects, the LSM reduction from baseline was found to be significant within each age group at each year of follow-up (Table E3). The model revealed a significant effect of age ($p=0.0046$), that according to pairwise comparisons between groups was due to a LSM difference of 0.36 MSE (95%CI 0.08 to 0.63) between the $>6-12$ and the >12 y age group ($p=0.0057$). The model still showed a significant effect of the year of follow-up ($p=0.0020$), consistent with the results above, while the year of follow-up-by age group interaction was not significant ($p=0.5248$).

During the first year of treatment, there was a significant reduction in the number of mild exacerbations (-64.4%, 95%CI -71.1% to -57.7%), which remained consistently low up to Year 6 (Figure E2). FeNO decreased and FEV₁ and MMEF increased significantly during the first year, remaining stable thereafter (Figure 2; see also Table E4 for age subgroups). The mean absolute eosinophil count progressively decreased as the follow-up progressed, reaching the lowest value versus baseline at Year 6 (-33.1%, 95%CI -49.1% to -17.1%) (Figure 3).

We describe disease control and evolution of QS for each tool in Figure E3. At baseline, 28/334 (8.4%) patients were controlled as per QS. This percentage improved significantly during the first year of treatment (148/329 [45.0%], $p<0.001$) and kept increasing up to Year 6 (75/84 [89.3%]).

After 1 year of omalizumab treatment, the number of all healthcare encounters decreased significantly, with no PICU admissions from Year 2 onwards (Figure 4). Mean $\pm$ SD courses

209 of rescue systemic corticosteroids decreased by 84.5% (95%CI -88.8% to -80.2%) from
210 baseline to Year 1 (4.1 ± 3.4 vs. 0.5 ± 1.1 , $p < 0.001$) and remained low thereafter (0.2 ± 0.7 during
211 Year 6).

212 The number of concomitant chronic medications was significantly reduced in Year 1 and
213 remained lower than baseline up to Year 6. There was an apparent increase in the proportion
214 of patients receiving ≥ 2 medications by the end of follow-up (Figure 5A). The proportion of
215 patients receiving each type of medication followed a similar pattern, with an apparent
216 increase from Year 5 in the use of inhaled corticosteroids (ICS) and long-acting beta-agonists
217 (LABA) (Figure 5B). There was a significant drop in the mean $\pm$ SD daily dose of ICS from
218 baseline to Year 1 (867.3 ± 474.5 vs. 663.4 ± 431.4 μg budesonide equivalent [b.e.]), that
219 continued over to Year 6 (350.2 ± 308.4 μg b.e., $p < 0.001$, -64.2% [95%CI -74.5% to -53.8%]
220 compared to baseline). In the subset of patients reaching Year 6, the proportion receiving ≥ 2
221 medications at baseline (93%) decreased to 69% after four years of follow-up and remained
222 rather constant thereafter (data not shown). The percentage receiving ICS and LABA at
223 baseline (100% and 93%) also decreased significantly (75% and 64% at Year 6, $p < 0.001$
224 both), as did the dose of ICS.

225 Main effectiveness results for the subset of patients > 6 years are available in Table E5.

226 *Adverse events*

227 Twenty-one of 484 (4.3%) patients experienced at least one AE. These included headache
228 ($n=8$, 1.7%), unspecific symptoms like malaise, fatigue, asthenia, low-grade fever, myalgia,
229 and/or flu-like syndrome ($n=5$, 1.0%), injection site pain/reaction ($n=4$, 0.8%), dizziness/loss
230 of consciousness/vasovagal syncope ($n=4$, 0.8%), transient urticaria ($n=2$, 0.4%),
231 anaphylaxis, Burkitt lymphoma, epistaxis, abdominal pain, immune thrombocytopenia, and
232 impaired wound healing ($n=1$ [0.2%] each). There were no deaths during omalizumab
233 treatment.

234 *Discontinuations*

235 Overall, 123/484 (25.4%) patients discontinued omalizumab. Discontinuations due to good
236 evolution of disease were the most common ($n=99$, 20.5%), and occurred for 0.2%, 1.2%,
237 2.5%, 2.1%, 3.9%, and 6.2% of patients between Years 1-6, and for 21.2% of patients
238 thereafter. Less common reasons were lack of efficacy ($n=17$, 3.5%), loss to follow-up ($n=13$,
239 2.7%), and patient decision ($n=3$, 0.6%). Seven (1.4%) patients discontinued due to

240 AEs/concomitant disease: malaise (n=2), headache, anaphylaxis, Burkitt lymphoma,
241 abdominal pain and immune thrombocytopenia (n=1 each). Reason was not reported in seven
242 (1.4%) patients. Discontinuations increased with age (≤ 6 years: 2.1%, >6-12 years: 43.8%,
243 >12 years: 54.1%).

244 Discussion

245 To our knowledge, ANCHORS is the first observational study reporting outcomes for up to 6
246 years of omalizumab in a large cohort of pediatric patients with SPAA. Many patients were
247 still on follow-up at Year 6, allowing for more precise estimates. Moreno-Galarraga et al¹¹
248 and Folque et al¹² have reported omalizumab outcomes for a maximum of approximately 6
249 years, but in 13 and 48 patients respectively.

250 Our cohort was clearly uncontrolled despite the high medication use, indicated by the number
251 of exacerbations, healthcare encounters, rescue corticosteroids use and QS during the
252 baseline period. Nevertheless, in the year after omalizumab initiation, the annual number of
253 MSE was reduced to 1.1. The MMRM analyses confirmed that the significant change in MSE
254 mainly occurred in the first year after omalizumab initiation, and that it stabilized (while
255 remaining significant from baseline) from this year onwards. The evolution of MSE over time
256 was similar regardless of age, as shown by the non-significant interaction between year of
257 follow-up and age group. This significant reduction in severe exacerbations during the first
258 year of omalizumab treatment has been also noted in previous prospective real-life study by
259 Deschildre et al¹⁹, in which exacerbations defined similar to our MSE decreased from 4.4 to
260 1.3. These patients had baseline FEV₁, MMEF and use of ICS similar to our cohort, while
261 duration of asthma and IgE levels were higher and ICS dose lower.

262 The effectiveness population in our study included patients who received omalizumab at a
263 younger age than allowed in the product label (≤ 6 years), reflecting the real-life clinical
264 practice. These patients showed a significantly higher number of MSE at baseline compared
265 to other age groups (probably motivating the off-label use of omalizumab), but the borderline
266 statistically significant effect of age found in the MMRM analysis was not due to differences
267 between these patients and the ones receiving omalizumab as per current indication (maybe
268 due to the relatively smaller size of this group), but to difference between the latter, as
269 revealed by pairwise comparisons. As the >6-12 years and >12 years age groups were solely
270 defined based on the current and former indication of omalizumab (respectively), the age
271 effect was due to a very small LSM difference in MSE, and there is not a validated minimal

272 relevant difference for this outcome,²⁰ the clinical significance of this finding seems unclear.
273 However, the fact that both patients >6-12 and >12 years old showed a significant
274 improvement of lung function, leads us to believe that the effect of age in omalizumab
275 outcomes is very limited. The lack of a significant and consistent improvement in lung
276 function observed for patients ≤6 years may be due to the comparatively better values at
277 baseline, as disease duration may have been too short to produce a significant decline, and to
278 the smaller number of patients in this subgroup.

279 As MSE, statistically significant improvements in secondary outcomes also occurred during
280 the first year. We did not evaluate earlier time points, but previous studies have found
281 significant amelioration after only 3-6 months of omalizumab.^{5,7,11,12} In our case,
282 improvements were maintained (or even continued) throughout 6 years of follow-up, as
283 reported by Moreno-Galarraga et al¹¹ and Folque et al.¹² Despite the shorter follow-up,
284 Deschildre et al also observed maintenance of omalizumab benefits for up to two years.³ As
285 commented for MSE, determining whether these statistically significant improvements
286 translated into clinically meaningful improvements can be difficult as, of variables assessed
287 in this study, minimal relevant differences have only been validated for some asthma control
288 questionnaires (0.5 points for ACQ, 2 points for ACT in pediatric patients and C-ACT).²⁰ In
289 our study, the improvements observed in mean ACQ, ACT and C-ACT scores widely
290 exceeded these values. Also, there was a progressive shift of scores from the uncontrolled
291 disease to the controlled disease score range. All this suggests a meaningful clinical effect of
292 omalizumab. Additionally, to our knowledge these are the longest follow-up data for disease
293 control reported in pediatric patients with SPAA, supporting a continued effectiveness of
294 omalizumab without development of tachyphylaxis. The rate of AEs in our cohort was very
295 low, and the most frequent were consistent with the safety profile of omalizumab. Few
296 patients discontinued due to AEs, one of them a Burkitt lymphoma. Although we cannot rule
297 out a causal relationship, systematic reviews and pooled analysis have not shown increased
298 risk of malignancies with omalizumab.²¹⁻²³

299 Although this evidence supports the long-term use of omalizumab, an earlier discontinuation
300 may be feasible in a considerable subset of patients. In our study, only 1.4% of patients
301 discontinued omalizumab due to good evolution during the first two years, but the percentage
302 increased to approximately 16.1% after six years of follow-up. Deschildre et al²⁴ reported a
303 similar percentage after only two years of follow-up, but the baseline number of

exacerbations and ICS dose were lower in their cohort, suggesting a better initial disease control.

Our results point at an indirect anti-eosinophilic effect of omalizumab. This was accompanied with a significant reduction in FeNO, also noted in prior studies.^{11,25} An elevated eosinophil count increases the risk of asthma exacerbations and, when coupled with an elevated FeNO, is associated to higher asthma morbidity.^{26,27} In severe asthma, high eosinophil levels may persist despite high-dose ICS therapy,²⁸ so our findings are particularly relevant in the population with SPAA.

The requirement for rescue corticosteroids and the use of ICS decreased from the first year. This corticosteroid-sparing effect confirms that reported in previous real-life studies,^{12,19,29} and is of major importance in children, as both the exposure to rescue corticosteroids and long-term use of ICS increase the risk of adrenal suppression,³⁰ and ICS have a dose-dependent negative effect on growth.³¹ The sparing effect extended to all other asthma medications. The apparent increase from Year 5 in the number of medications and the use of ICS and LABA may be a statistical artifact, as some patients had not reached Year 5 by the time of data collection. Another possible reason would be selection bias, as some patients discontinued omalizumab before Year 5 due to good evolution. In fact, patients who reached Year 6 were already receiving many treatments at baseline. In these patients, the dose of ICS decreased over time. The growing proportion of asthma control and discontinuations due to good evolution, along with the consistently low number of exacerbations and healthcare encounters, also exclude an upturn in asthma severity over time.

Our study has some limitations. The diagnosis of SPAA based on physicians' criteria may have led to the inclusion of patients with a range of disease status. However, baseline characteristics suggest that most included patients had indeed severe asthma. Also, in the context of a normal clinical practice, the mean time elapsed since diagnosis of severe asthma seems enough to determine persistence of symptoms, as well to assess and try to correct (when possible) secondary causes for lack of control (e.g. comorbidities, poor adherence, inhaler technique, social issues). Anyway, given the size of the effectiveness population, we believe that a potential small subset of misdiagnosed patients would have not affected the results substantially. Adherence, inhaler technique, and social issues other than tobacco smoke exposure (e.g. pets, suboptimal domestic hygiene) were not assessed as study variables, but we are aware that some of our pediatric patients initiated omalizumab before

these potential causes for lack of control had been corrected, mainly because parents were reluctant/uncapable to do so. This, however, reflects the need to adapt to the circumstances of these patients with severe symptomatology, and eventually the real-life nature of the study. During the period covered by the ANCHORS study, omalizumab was only intended to be administered by healthcare providers in specialized units, contrary to conventional treatments. This may improve adherence, by direct verification of drug administration and a closer follow-up. While this may have influenced outcomes in patients who initiated omalizumab for uncontrolled asthma despite being non-adherent to conventional treatment (through an improvement of adherence to asthma treatment), as explained previously we believe these patients were a minority in our cohort. Furthermore, some variables in our study continued to improve after the first year of follow-up, which cannot be explained by an early improvement of adherence at the time of omalizumab initiation. Regarding data quality, we pooled pre-existing databases which differed in the parameters recorded, time of assessments, and format/units used. In some variables, this required manual categorization and/or conversion of values in order to summarize and analyze them, which may have decreased data granularity. The high number of missing data observed in some variables may have biased results (e.g. mild exacerbations were less frequent than MSE, which points at an underestimation). Also, the expected high number of missing values for asthma control obliged us to pool data from various questionnaires, which differed in several aspects. Nevertheless, the conservative approach chosen to analyze asthma control most probably lead to underestimation. Finally, we cannot exclude some improvement due to surveillance bias, since patients were visited very frequently.

In conclusion, in our large real-life cohort, there was a significant reduction in the number of MSE and a significant improvement in all other clinical parameters assessed during the first year of treatment with omalizumab. The beneficial effect was maintained in the long-term, along with a good safety profile and a positive impact on medication use and healthcare encounters. Our results confirm those of prior observational studies, and position omalizumab as an effective long-term treatment in patients with SPAA unable to achieve disease control with non-biological treatment.

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Table 1. Demographic and clinical characteristics at omalizumab initiation

	Effectiveness population (n=426)
Sex (male), n (%)	263 (61.7)
Age (years)	11.1 (2.9)
Range	1.9-17.9
Time from asthma diagnosis (years) ^a	5.5 (3.6)
Time from severe asthma diagnosis (years) ^b	1.4 (2.0)
Total IgE (kU/L) ^c	976.5 (1196.8)
FeNO (ppb) ^d	44.5 (37.5)
FEV ₁ (% predicted) ^e	84.6 (18.1)
MMEF (% predicted) ^f	64.9 (37.6)
Absolute eosinophil count (cells/mm ³) ^g	640.1 (447.7)
MSE (annual number)	7.9 (6.6)
Mild exacerbations (annual number) ^h	4.9 (4.1)
Sensitizations, n (%) ⁱ	
House dust mites	299 (70.2)
Animal dander	150 (35.2)
Alternaria	147 (34.5)
Olive pollen	144 (33.8)
Grass pollen	105 (24.6)
Other pollen	105 (24.6)
Hen's egg	43 (10.1)
Nuts	40 (9.4)
Cow's milk	33 (7.7)
Other foods	50 (11.7)
Cockroach	10 (2.3)

	Effectiveness population (n=426)
Prior SIT, n (%) ^j	201 (47.2)
Good tolerance to prior SIT ^k	131 (65.2)
Current SIT, n (%) ^l	151 (35.4)
Tobacco smoke exposure, n (%)	22 (5.2)
Comorbidities, n (%) ⁱ	
Rhinoconjunctivitis	243 (57.0)
Atopic dermatitis	153 (35.9)
Food allergy	133 (31.2)
Eosinophilic esophagitis	38 (8.9)
Overweight/Obesity	30 (7.0)
Other	48 (11.3)

Values given as mean (SD) unless otherwise indicated. ^a Missing for 84 patients. ^b Missing for 83 patients. ^c Missing for 13 patients. ^d Missing for 149 patients. ^e Missing for 12 patients. ^f Missing for 64 patients. ^g Missing for 94 patients. ^h Missing for 152 patients. ⁱ Each patient may have more than one. ^j Missing for 52 patients. ^k Missing for 2 patients. ^l Missing for 32 patients. FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume at first second; MMEF, maximum mid-expiratory flow; ppb, parts per billion; MSE, moderate-to-severe exacerbations; SD, standard deviation; SIT, specific immunotherapy.

Figure 1. Annual evolution of MSE in the total effectiveness population (A) and by age group (B)

Bars and data labels represent the mean value. Whiskers represent the SD. * $p < 0.001$ versus baseline from this point onwards. † $p < 0.001$ versus baseline in Year 1, $p < 0.05$ versus baseline for Years 2 to 4. MSE, moderate-to-severe exacerbations; SD, standard deviation.

Figure 2. Annual evolution of FeNO (A), FEV₁ and MMEF (B) (effectiveness population)

Markers and labels represent the mean value. Whiskers represent the SD. In B, round markers/black line correspond to FEV₁ and square markers/grey line correspond to MMEF. * $p < 0.001$ versus baseline from Year 1 to Year 5; $p = 0.001$ at Year 6. † $p < 0.001$ versus baseline from this point onwards. FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume at first second; MMEF, maximum mid-expiratory flow; ppb, parts per billion; SD, standard deviation.

Figure 3. Annual evolution of absolute eosinophil count (effectiveness population)

Markers and labels represent the mean value. Whiskers represent the SD. * $p < 0.001$ versus baseline from this point onwards. SD, standard deviation.

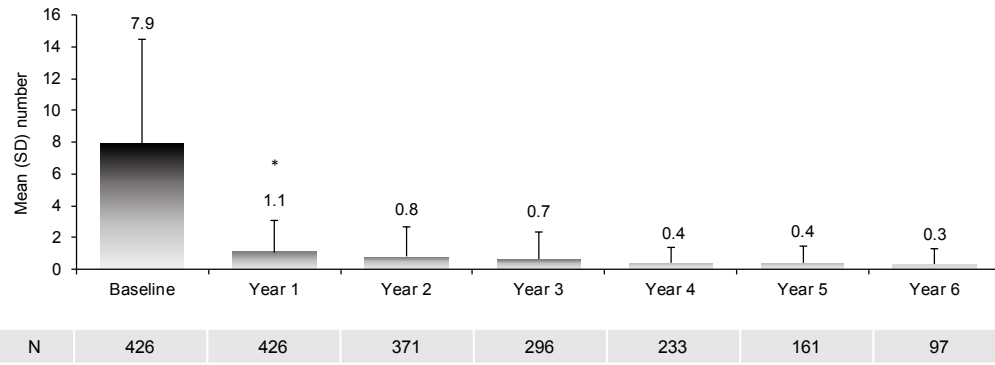
Figure 4. Annual evolution of healthcare encounters (effectiveness population)

Bars and labels represent the mean value. Whiskers represent the SD. * $p < 0.001$ versus baseline from this point onwards. † $p < 0.001$ versus baseline from Year 1 to Year 5; and $p < 0.05$ at Year 6. PICU, pediatric intensive care unit; SD, standard deviation.

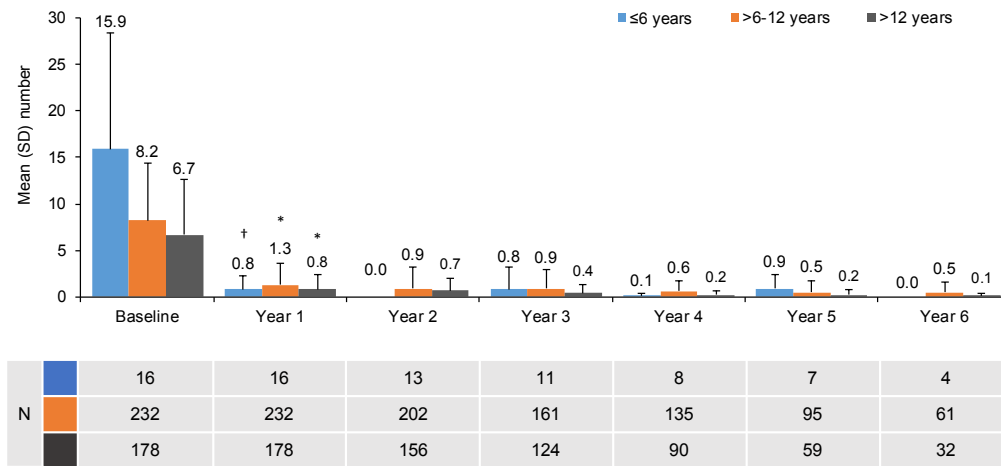
Figure 5. Annual evolution in the number (A) and type (B) of chronic concomitant medications (effectiveness population)

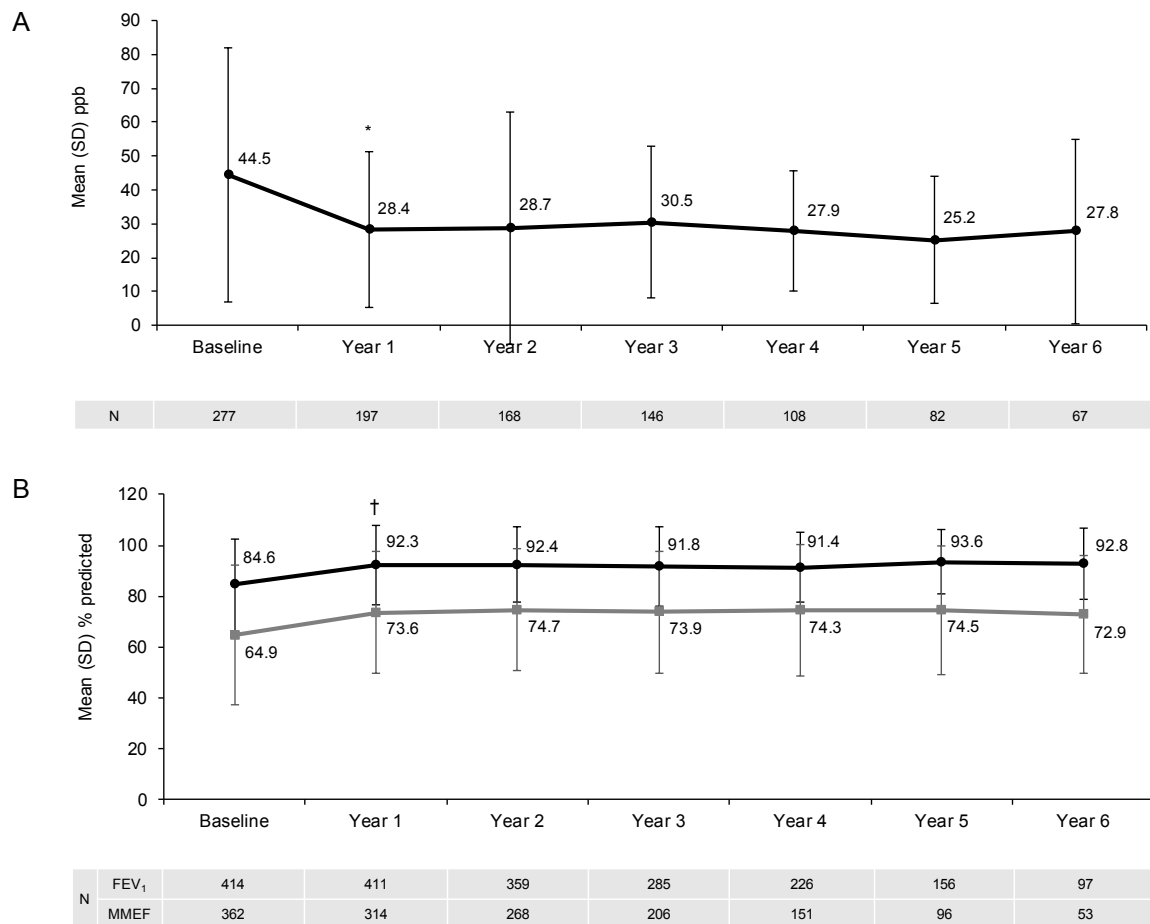
* $p < 0.001$ versus baseline from this point onwards. † $p < 0.001$ at Year 1 and Year 2, $p < 0.05$ at Year 3. p not estimable from Year 4 onwards. ‡ $p < 0.001$ at Years 1, 2 and 5; $p < 0.05$ at Year 3 and Year 4. Not significant at Year 6. ICS, inhaled corticosteroids; LABAs, long-acting beta-agonists; NA, not available.

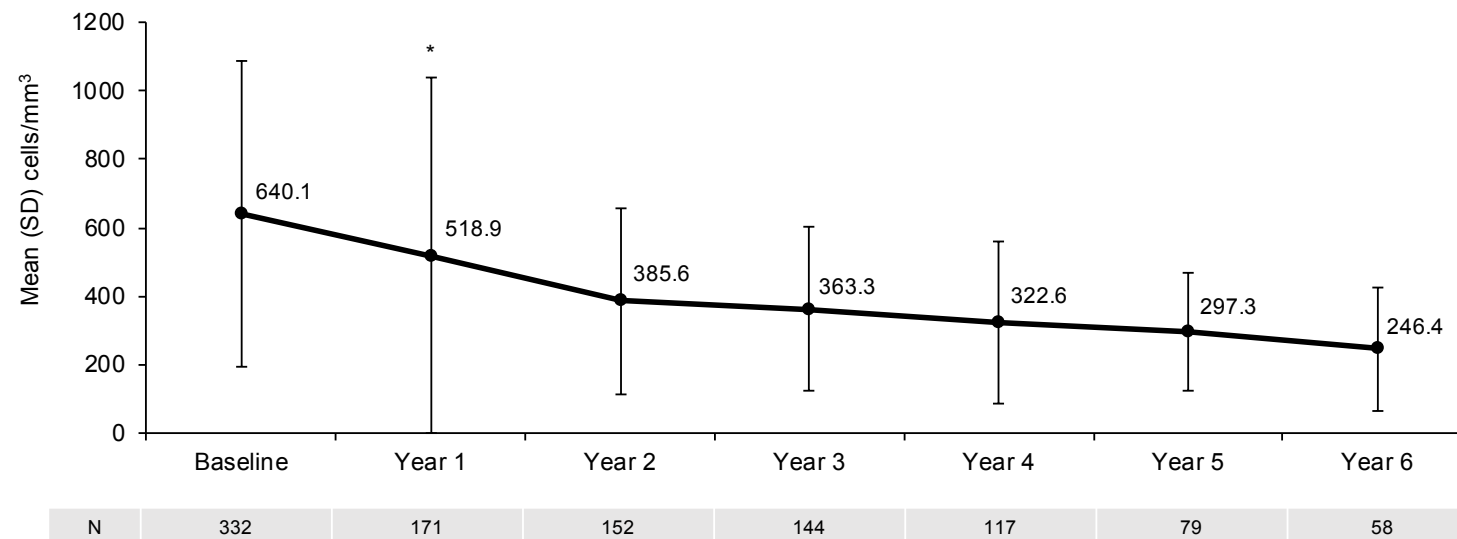
A

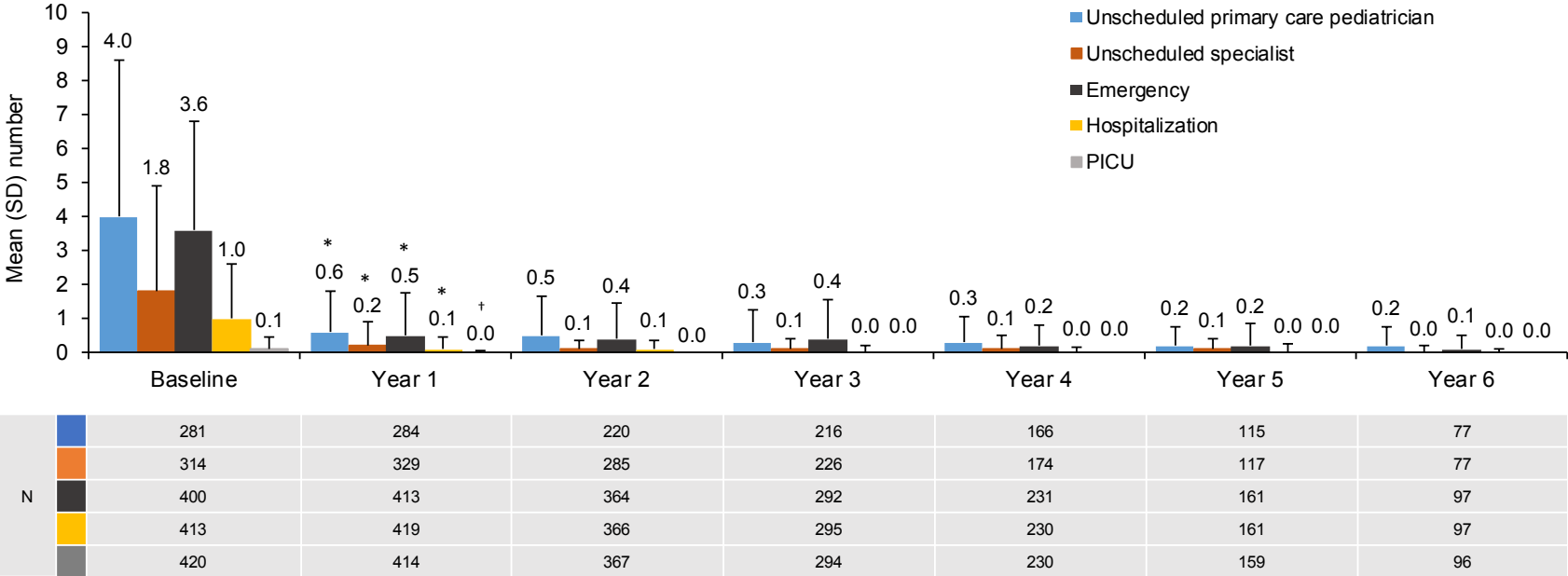


B

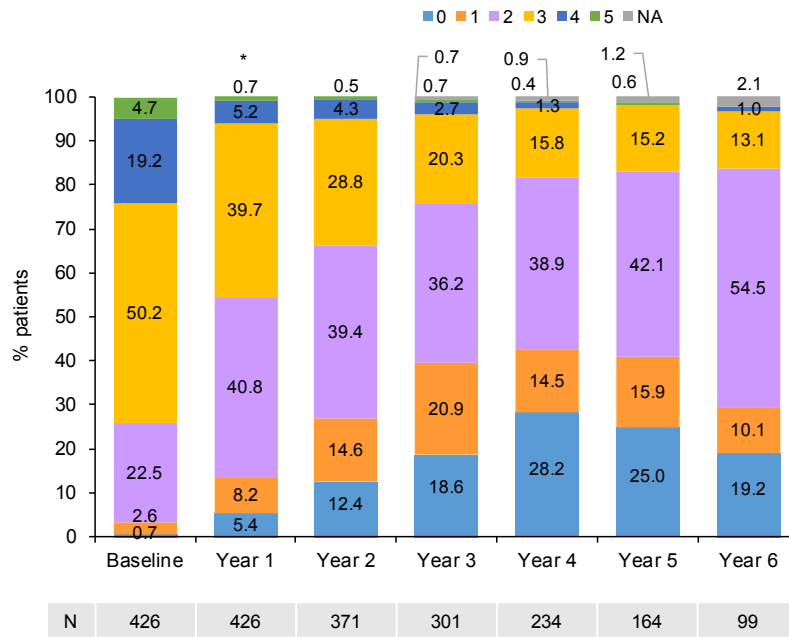




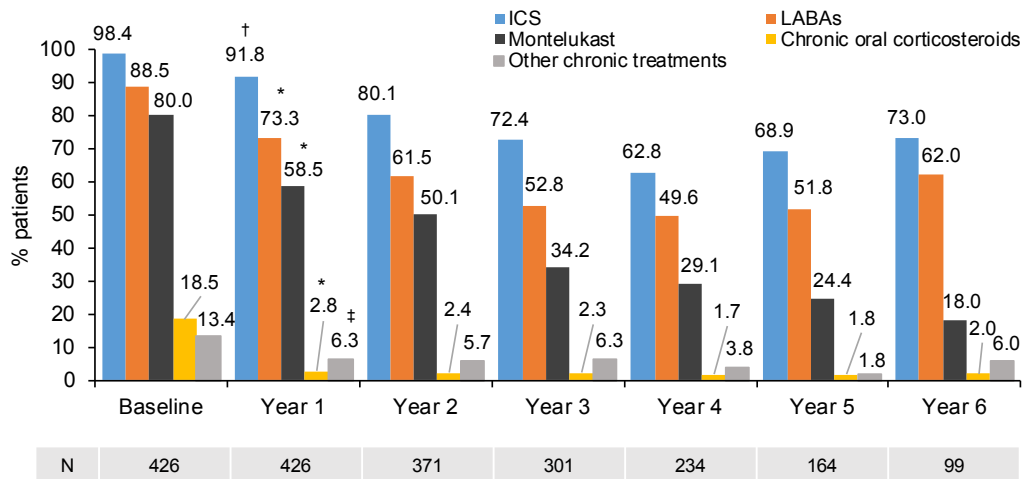




A



B



**Appendix to “Omalizumab outcomes for up to 6 years
in pediatric patients with severe persistent allergic asthma”**

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Supplementary methods

Sample size calculation

Due to the observational nature of the study, we did not conduct a formal sample size calculation. Nevertheless, we estimated that a minimum of 250 patients would retrieve, for quantitative variables, 95% confidence intervals equal to the sample mean $\pm$ 12% standard deviation (SD); and for qualitative variables, a maximum error margin of approximately 6%, for a confidence level of 95% and assuming maximum indetermination ($p=q=50$).

Tables

Table E1. Demographic and clinical characteristics by age at omalizumab initiation (effectiveness population)

	≤6 years (n=16)	>6-12 years (n=232)	>12 years (n=178)	>6 years* (n=410)
Sex (male), n (%)	13 (81.3)	138 (59.5)	112 (62.9)	250 (61.0)
Age (years)	4.7 (1.3)	9.5 (1.6)	13.9 (1.4)	11.4 (2.7)
Range	1.9-5.9	6.0-12.0	12.0-17.9	6.0-17.9
Time from asthma diagnosis (years) [†]	1.5 (1.3)	4.7 (2.8)	7.0 (4.0)	5.6 (3.5)
Time from severe asthma diagnosis (years) [‡]	0.2 (1.0)	1.1 (1.4)	1.8 (2.6)	1.4 (2.0)
Total IgE (kU/L) [§]	405.2 (428.8)	1029.8 (1284.0)	958.7 (1110.6)	999.6 (1212.2)
FeNO (ppb)	39.0 (44.4)	37.0 (29.8)	55.3 (43.6)	44.8 (37.3)
FEV ₁ (% predicted)**	94.5 (17.9)	85.0 (17.9)	83.4 (18.1)	84.3 (18.0)
MMEF (% predicted) ^{††}	72.1 (21.8)	67.2 (28.8)	61.4 (25.9)	64.7 (27.7)
Absolute eosinophil count (cells/mm ³) ^{‡‡}	738.3 (397.6)	680.8 (477.1)	571.4 (400.9)	635.7 (449.9)
MSE (annual number)	15.9 (12.5)	8.2 (6.2)	6.7 (5.9)	7.5 (6.1)
Mild exacerbations (annual number) ^{§§}	3.9 (5.9)	4.9 (4.2)	5.1 (3.7)	5.0 (4.0)
Sensitizations, n (%)				
House dust mites	8 (50.0)	172 (74.1)	119 (66.9)	291 (71.0)
Animal dander	5 (31.3)	80 (34.5)	65 (36.5)	145 (35.4)
Alternaria	5 (31.3)	75 (32.3)	67 (37.6)	142 (34.6)
Olive pollen	3 (18.8)	73 (31.5)	68 (38.2)	141 (34.4)

	≤6 years (n=16)	>6-12 years (n=232)	>12 years (n=178)	>6 years* (n=410)
Grass pollen	2 (12.5)	51 (22.0)	52 (29.2)	103 (25.1)
Other pollen	1 (6.3)	55 (23.7)	49 (27.5)	105 (24.6)
Hen's egg	2 (12.5)	29 (12.5)	12 (6.7)	41 (10.0)
Nuts	2 (12.5)	23 (9.9)	15 (8.4)	38 (9.3)
Cow's milk	3 (18.8)	19 (8.2)	11 (6.2)	30 (7.3)
Other foods	2 (12.5)	29 (12.5)	19 (10.7)	48 (11.7)
Cockroach	0 (0.0)	6 (2.6)	4 (2.2)	10 (2.4)
Prior SIT, n (%)***	8 (50.0)	100 (43.1)	93 (52.2)	193 (47.1)
Good tolerance to prior SIT†††	5 (62.5)	68 (68.0)	58 (62.4)	126 (65.3)
Current SIT, n (%)‡‡‡	7 (43.8)	88 (37.9)	56 (31.5)	144 (35.1)
Tobacco smoke exposure, n (%)	0 (0.0)	14 (6.0)	8 (4.5)	22 (5.4)
Comorbidities, n (%)‡‡‡				
Rhinoconjunctivitis	5 (31.3)	127 (54.7)	111 (62.4)	238 (58.0)
Atopic dermatitis	7 (43.8)	89 (38.4)	57 (32.0)	146 (35.6)
Food allergy	5 (31.3)	78 (33.6)	50 (28.1)	128 (31.2)
Eosinophilic esophagitis	0 (0.0)	24 (10.3)	14 (7.9)	38 (9.3)
Overweight/Obesity	1 (6.3)	17 (7.3)	12 (6.7)	29 (7.1)
Other	1 (6.3)	32 (13.8)	15 (8.4)	47 (11.5)

Values given as mean (SD) unless otherwise indicated. * Subgroup >6-12 years plus subgroup >12 years. † Missing for 1, 44, 39 and 83 patients respectively. ‡ Missing for 1, 46, 36 and 82 patients respectively. § Missing for 0, 4, 9 and 13 patients respectively. || Missing for 6, 78, 65 and 143 patients respectively. ** Missing for 4, 4, 4 and 8 patients respectively. †† Missing for 7, 30, 27 and 59 patients respectively. ‡‡ Missing for 2, 45, 47 and 92 patients respectively. §§ Missing for 2, 83, 67 and 150 patients respectively. ||| Each patient may have more than one. *** Missing for 0, 30, 22 and 52 patients respectively. ††† Missing for 0, 1, 1 and 2 patients respectively. ‡‡‡ Missing for

1, 17, 14 and 31 patients respectively. FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume at first second; MMEF, maximum mid-expiratory flow; MSE, moderate-to-severe exacerbations; ppb, parts per billion; SD, standard deviation; SIT, specific immunotherapy.

Table E2. LSM reduction in the number of MSE from baseline to each year of follow-up and pairwise comparisons between years (MMRM - year of follow-up as fixed effect)

		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
LSM reduction from baseline (95% CI)		-7.42 (-7.61, -7.23)	-7.76 (-7.95, -7.57)	-7.92 (-8.10, -7.75)	-8.13 (-8.25, -8.01)	-8.15 (-8.31, -8.00)	-8.19 (-8.36, -8.02)
p-value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Pairwise comparisons (LSM difference [95%CI]; p-value)	Year 2	0.34 (0.16, 0.52); 0.005	-	-	-	-	-
	Year 3	0.50 (0.32, 0.68); <0.001	0.16 (0.00, 0.33); 0.802	-	-	-	-
	Year 4	0.71 (0.52, 0.90); <0.001	0.37 (0.20, 0.54); <0.001	0.21 (0.04, 0.37); 0.243	-	-	-
	Year 5	0.73 (0.50, 0.96); <0.001	0.39 (0.17, 0.61); 0.008	0.23 (0.03, 0.43); 0.325	0.02 (-0.14, 0.19); >0.999	-	-
	Year 6	0.77 (0.53, 1.00); <0.001	0.43 (0.20, 0.66); 0.004	0.27 (0.03, 0.50); 0.385	0.06 (-0.11, 0.23); >0.999	0.04 (-0.14, 0.21); >0.999	-

Baseline effect p<0.0001; Year of follow-up effect p<0.0001.

CI, confidence interval; LSM, least square mean; MMRM, mixed model repeated measures; MSE, moderate-to-severe exacerbations.

Table E3. LSM reduction in the number of MSE from baseline to each year of follow-up (MMRM - year of follow-up, age group and year of follow-up-by-age group interaction as fixed effects)

	Year 1			Year 2			Year 3		
	≤6 y	>6-12 y	>12 y	≤6 y	>6-12 y	>12 y	≤6 y	>6-12 y	>12 y
LSM mean reduction	-7.81	-7.22	-7.65	-8.57	-7.61	-7.89	-7.79	-7.74	-8.17
95%CI	-8.79, -6.83	-7.47, -6.96	-7.94, -7.36	-9.56, -7.58	-7.86, -7.36	-8.18, -7.60	-8.71, -6.89	-7.98, -7.51	-8.44, -7.89
p-value (vs. baseline)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

	Year 4			Year 5			Year 6		
	≤6 y	>6-12 y	>12 y	≤6 y	>6-12 y	>12 y	≤6 y	>6-12 y	>12 y
LSM mean reduction	-8.58	-7.96	-8.23	-7.94	-8.06	-8.31	-8.71	-8.02	-8.41
95%CI	-9.24, -7.93	-8.12, -7.81	-8.51, -8.13	-8.70, -7.17	-8.26, -7.87	-8.56, -8.06	-9.59, -7.83	-8.24, -7.80	-8.71, -8.12
p-value (vs. baseline)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Baseline effect p<0.0001; Year of follow-up effect p=0.0020; Age group effect p=0.0046; Year of follow-up*age group interaction effect p=0.5248.

Pairwise comparisons: ≤6 years vs. >6-12 years, LSM mean difference -0.46 (95%CI -1.2 to 0.27; p = 0.3916); ≤6 years vs. >12 years, LSM mean difference -0.10 (95%CI -0.85 to 0.64; p > 0.9999); >6-12 years vs. >12 years, LSM mean difference 0.36 (95%CI 0.08 to 0.63; p=0.0057).

CI, confidence interval; LSM, least square mean; MMRM, mixed model repeated measures; MSE, moderate-to-severe exacerbations; y, years.

Table E4. Annual evolution of FeNO, FEV₁ and MMEF across age subgroups (effectiveness population)

	≤6 years (n=16)	>6-12 years (n=232)	>12 years (n=178)
FeNO (ppb)			
Baseline	39.0 (44.4)	37.0 (29.8)	55.3 (543.6)
Year 1	19.0 (11.6)	27.3 (21.8)*	31.3 (25.3)*
Year 2	19.9 (6.3)	26.4 (20.9) [†]	32.5 (46.7)*
Year 3	20.8 (15.4)	27.4 (18.4)	35.8 (26.7)*
Year 4	18.0 (12.7)	28.3 (18.1)	28.4 (17.9)*
Year 5	20.2 (10.7)	26.3 (20.1)	24.1 (15.6)*
Year 6	35.4 (30.3)	28.1 (31.3)	26.4 (21.1) [†]
FEV₁ (% predicted)			
Baseline	94.5 (17.9)	85.0 (17.9)	83.4 (18.1)
Year 1	100.4 (19.6)	93.4 (15.3)*	90.2 (15.8)*
Year 2	103.5 (11.3)	92.6 (14.5)*	91.5 (15.0)*
Year 3	96.8 (18.6)	93.2 (15.4)*	89.7 (15.7)*
Year 4	95.2 (19.2)	91.7 (13.6)*	90.7 (13.5)*
Year 5	95.1 (13.3)	94.0 (13.2)*	92.9 (12.2)*
Year 6	90.8 (13.2)	91.4 (14.2)*	90.5 (13.5)
MMEF (% predicted)			
Baseline	72.1 (21.8)	67.2 (28.8)	61.4 (25.9)
Year 1	77.0 (23.7)	75.1 (23.6)*	71.3 (24.8)*
Year 2	90.3 (19.7)	75.1 (24.3)*	73.4 (23.8)*
Year 3	72.5 (28.5)	74.4 (24.5) [†]	73.4 (23.1)*
Year 4	76.0 (38.2)	75.2 (27.3)*	72.9 (23.1)*
Year 5	78.8 (30.1)	75.0 (27.0) [†]	73.0 (21.2)*
Year 6	96.5 (2.1)	71.7 (24.0)*	72.8 (21.2)

Values presented as mean (SD). * p<0.001 versus baseline. [†] p<0.05 versus baseline. FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume at first second; MMEF, maximum mid-expiratory flow; ppb, parts per billion; SD, standard deviation.

Table E5. Primary and main secondary effectiveness outcomes for patients >6 years (effectiveness population, n=410)

Outcome	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
MSE (annual number)*	7.5 (6.1)	1.1 (2.0)	0.8 (1.9)	0.6 (1.7)	0.4 (1.0)	0.4 (1.0)	0.3 (1.0)
Mild exacerbations (annual number)*	5.0 (4.0)	1.5 (2.3)	1.0 (1.6)	0.8 (1.5)	0.6 (1.2)	0.5 (1.0)	0.7 (1.5)
FeNO (ppb) [†]	44.8 (37.3)	28.9 (23.3)	29.1 (34.9)	31.0 (22.6)	28.3 (17.9)	25.4 (18.4)	27.4 (27.3)
FEV ₁ (% predicted)*	84.3 (18.0)	92.0 (15.6)	92.1 (14.7)	91.6 (15.6)	91.3 (13.5)	93.6 (12.8)	92.9 (14.0)
MMEF (% predicted)*	64.7 (27.7)	73.5 (24.1)	74.4 (24.0)	73.9 (23.8)	74.3 (25.6)	74.3 (24.9)	72.0 (23.0)
Absolute eosinophil count (cells/mm ³)*	635.7 (449.9)	525.2 (528.4)	387.5 (277.1)	362.9 (243.7)	323.6 (237.6)	298.5 (173.6)	249.8 (182.0)
Controlled patients, n (%)	28 (8.4)	148 (45.0)	168 (57.3)	146 (59.8)	138 (70.4)	103 (75.5)	75 (89.3)
Healthcare encounters (annual number)							
Unscheduled primary care pediatrician*	3.9 (3.7)	0.6 (1.2)	0.5 (1.2)	0.3 (1.0)	0.3 (0.8)	0.2 (0.6)	0.2 (0.6)
Unscheduled specialist*	1.8 (3.1)	0.2 (0.7)	0.1 (0.3)	0.1 (0.3)	0.1 (0.4)	0.1 (0.3)	0.0 (0.2)
Emergency room visits*	3.5 (3.1)	0.6 (1.3)	0.4 (1.1)	0.4 (1.2)	0.2 (0.6)	0.2 (0.6)	0.2 (0.4)
Ward hospitalization*	0.9 (1.5)	0.1 (0.4)	0.1 (0.3)	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)	0.0 (0.1)
PICU admissions [†]	0.1 (0.4)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Rescue systemic corticosteroids (courses)*	4.0 (3.1)	0.5 (1.1)	0.4 (1.0)	0.3 (0.8)	0.2 (0.6)	0.2 (0.5)	0.2 (0.7)
Number of patients according to the number of other concomitant chronic medications received for asthma, n (%)*							
0	3 (0.7)	22 (5.4)	45 (12.6)	53 (18.3)	63 (27.9)	39 (25.0)	18 (18.9)
1	11 (2.7)	35 (8.5)	52 (14.5)	59 (20.3)	32 (14.2)	24 (15.4)	9 (9.5)

Outcome	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
2	93 (22.7)	165 (40.2)	141 (39.4)	105 (36.2)	88 (38.9)	66 (42.3)	52 (54.7)
3	205 (50.0)	163 (39.8)	102 (28.5)	61 (21.0)	37 (16.4)	25 (16.0)	13 (13.7)
4	78 (19.0)	22 (5.4)	16 (4.5)	8 (2.8)	3 (1.3)	0 (0)	1 (1.1)
5	20 (4.9)	3 (0.7)	2 (0.6)	2 (0.7)	1 (0.4)	1 (0.6)	0 (0)
Number of patients according to the type of other concomitant chronic medications received for asthma, n (%)							
ICS*	403 (98.3)	376 (91.7)	287 (80.2)	213 (73.4)	143 (63.3)	109 (69.9)	71 (74.7)
LABA*	364 (88.8)	306 (74.6)	222 (62.0)	156 (53.8)	114 (50.4)	83 (53.2)	60 (63.2)
Montelukast*	326 (79.5)	237 (57.8)	175 (48.9)	99 (34.1)	66 (29.2)	38 (24.4)	17 (17.9)
Chronic oral corticosteroids*	77 (18.8)	12 (2.9)	9 (2.5)	7 (2.4)	4 (1.8)	3 (1.9)	2 (2.1)
Other [‡]	54 (13.2)	26 (6.3)	21 (5.9)	19 (6.6)	9 (4.0)	3 (1.9)	6 (6.3)
Dose of ICS (µg b.e.)*	873.0 (474.3)	669.1 (433.2)	639.3 (446.9)	558.9 (451.6)	453.6 (348.9)	464.4 (376.9)	354.4 (311.7)

Values given as mean (SD) unless otherwise indicated. * p<0.001 versus baseline from Year 1 onwards. [†] p<0.001 versus baseline from Year 1 onwards except for Year 6 (p <0.05). [‡] p<0.001 at Years 1, 2 and 5, p<0.05 at Years 3 and 4, p=0.09 at Year 6. b.e.: budesonide equivalent; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume at first second; ICS, inhaled corticosteroids; LABA, long-acting beta-agonists; MMEF, maximum mid-expiratory flow; MSE, moderate-to-severe exacerbations; PICU, pediatric intensive care unit; SD, standard deviation.

Figure E1. Patient flow

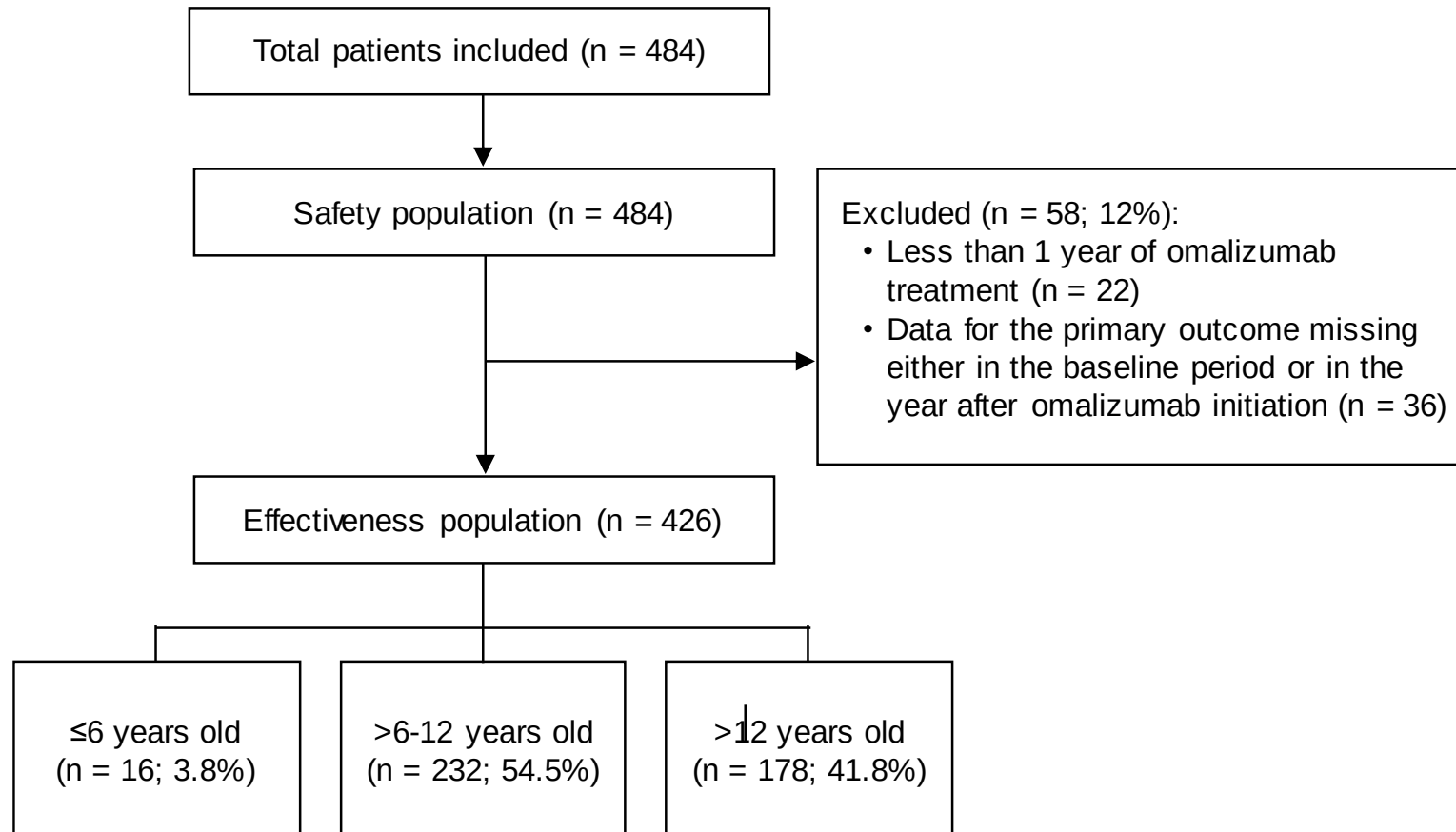
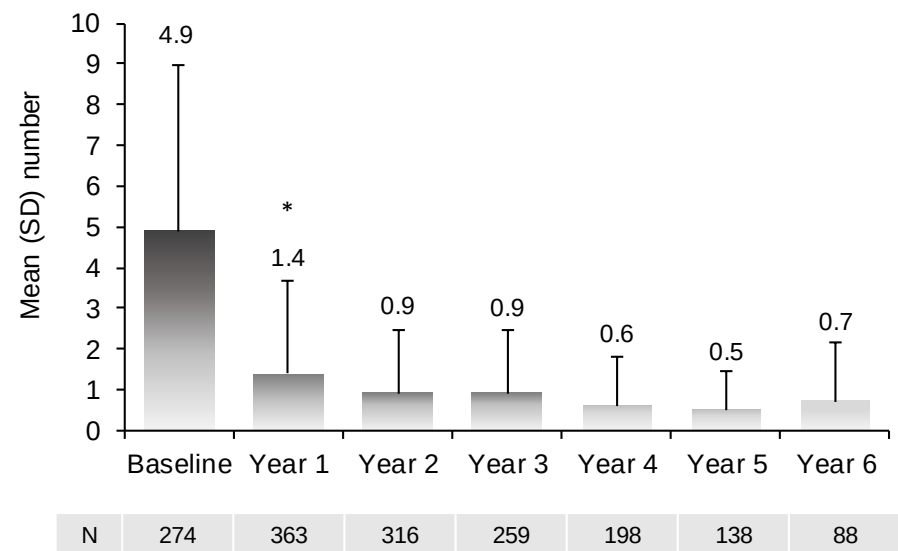
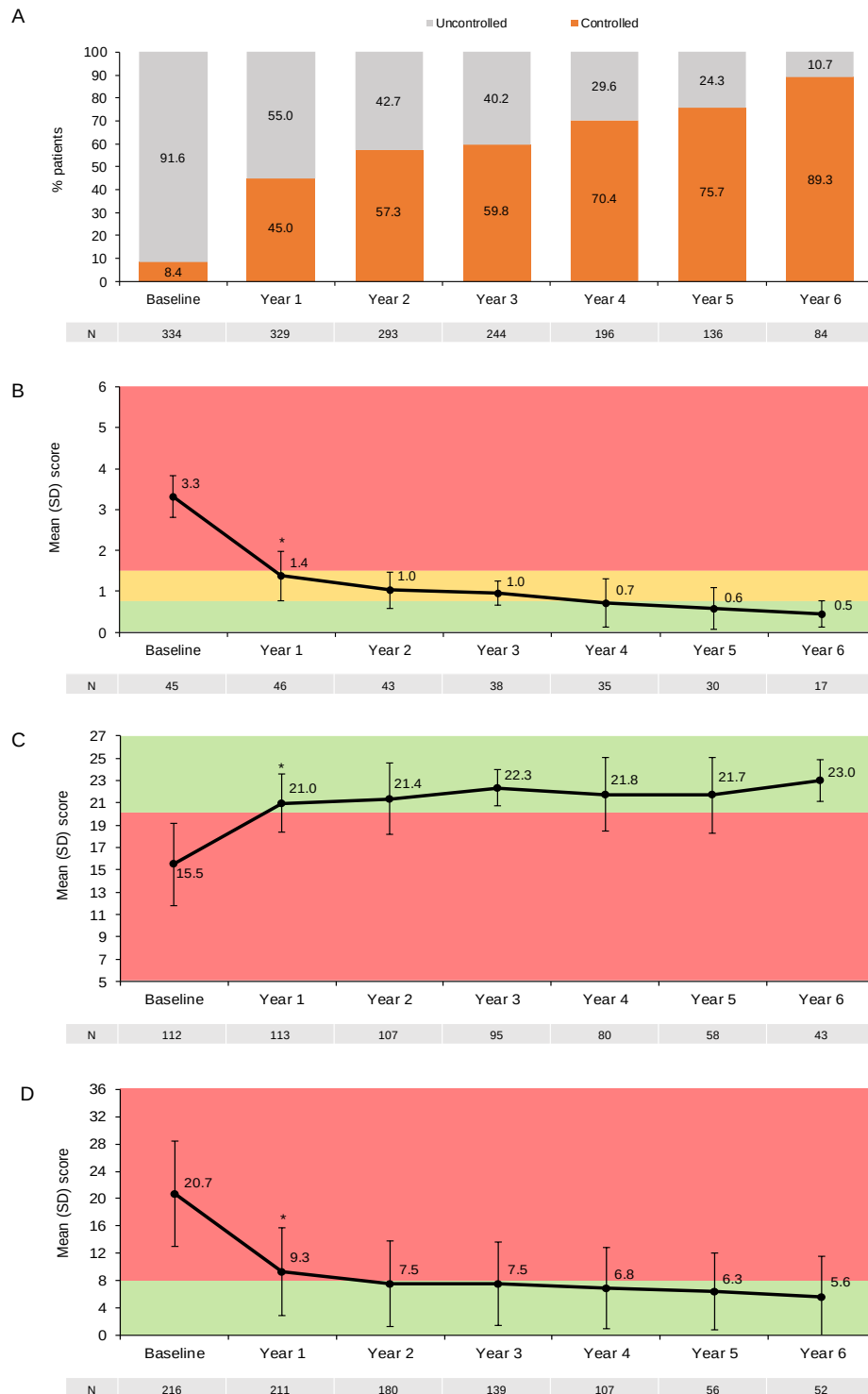


Figure E2. Annual evolution of mild exacerbations (effectiveness population)



* p<0.001 versus baseline from this point onwards. SD, standard deviation.

Figure E3. Annual evolution of asthma control (A), ACQ (B), ACT/C-ACT (C), and CAN (D) scores (effectiveness population)



* $p < 0.001$ versus baseline from this point onwards. ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; C-ACT, Asthma Control Test in Children; CAN, Asthma Control in Children. Total ACQ score ranges from 0 (totally controlled) to 6 (severely uncontrolled). Patients scoring ≤ 0.75 are considered well controlled, $>0.75 - <1.5$ partly controlled, and ≥ 1.5 not controlled (1). Total ACT/C-ACT score ranges from 5 (poor control) to 25/27 (complete control). A score ≥ 20 indicates good control in both questionnaires (2, 3). The total CAN score ranges from 0 (best control) to 36 (worst control). Patients scoring <8 points are considered well controlled (4). In panels B, C and D, these scores ranges are shown as background red (“uncontrolled”), yellow (“partially controlled”) and green (“controlled”) bands.

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