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Systematic literature review of the clinical, humanistic, and economic burden associated with asthma uncontrolled by GINA Steps 4 or 5 treatment

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DECLARATION OF FINANCIAL/OTHER RELATIONSHIPS

Stephanie Chen, Sarowar Golam, and Xiao Xu are employees of AstraZeneca. Julie Myers, Chris Bly, and Harry Smolen are employees of Medical Decision Modeling, Inc. Peer reviewers on this manuscript have received an honorarium from CMRO for their review work, but have no other relevant financial relationships to disclose.

AUTHOR CONTRIBUTIONS

Julie Myers, Chris Bly, and Harry Smolen were involved in the design of the systematic literature review, together with the collection and interpretation of the data. Stephanie Chen, Sarowar Golam, and Xiao Xu were involved in the study design and data interpretation. All authors were involved in the critical evaluation of the manuscript content, approved the final version, and agree to be accountable for all aspects of the work.

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ABSTRACT

Objective: We sought to characterize the epidemiologic, clinical, humanistic, and economic burden of patients with asthma uncontrolled by GINA Steps 4 or 5 treatment (severe, uncontrolled asthma [SUA]).

Methods: A systematic literature review adhering to PRISMA guidelines was performed. We searched for relevant publications in MEDLINE and EMBASE from January 2004 to September 2016 and in a conference proceedings database from January 2012 to October 2016. Studies were screened using the Population, Intervention, Comparator, Outcomes, Study Design, and Time (PICOS-T) framework. Studies of SUA with observational (prospective and retrospective), randomized, or nonrandomized study designs; adult patient populations; sample sizes ≥ 20 patients; epidemiologic or clinical outcomes, patient-reported outcomes (PROs), or economic outcomes were included. For our analysis, SUA was defined as inadequate control of asthma despite the use of medium- to high-dosage inhaled corticosteroids and at least one additional treatment.

Results: A total of 195 articles reporting unique study populations were included. Prevalence of SUA was as great as 87.4% for patients with severe asthma, although values varied depending on the criteria used to define asthma control. Compared with patients with severe asthma who were controlled, patients with SUA experienced more symptoms, night-time awakenings, rescue medication use and worse PROs. SUA-associated costs were 3-times greater than costs for patients with severe, controlled disease.

Conclusion: Despite the availability of approved asthma treatments, this literature analysis confirms that SUA poses a substantial epidemiologic, clinical, humanistic, and economic burden. Published data are limited for certain aspects of SUA, highlighting a need for further research.

Keywords: Severe, uncontrolled asthma; economic burden; epidemiology; clinical burden; humanistic

INTRODUCTION

Asthma is a chronic disorder of the airways characterized by inflammation associated with bronchial hyperreactivity and spasm, resulting in airflow obstruction. Features of asthma include wheezing, chest tightness, breathlessness, and coughing. More than 300 million individuals worldwide are affected by asthma, and this number is projected to exceed 400 million by 2025.¹ Asthma occurs in all countries irrespective of socioeconomic level, but intercountry prevalence varies. In the United States, the prevalence of asthma is 7.6% and 8.4% for adults and children, respectively²; in the European Union, the prevalence is 8.2% and 9.4%, respectively.^{3,4}

Asthma presents with varying degrees of severity, from mild and moderate to severe disease. Severe asthma can be debilitating and even life-threatening. Previously based on symptoms, the definition of asthma severity now has evolved to one that is focused on the intensity of treatment required to achieve good symptom control.^{1,5} According to international guidelines such as the Global Initiative for Asthma (GINA), asthma is severe if, despite the elimination of modifiable factors (e.g., poor inhaler technique/adherence, persistent environmental exposures), it requires high-dosage inhaled corticosteroids (ICS) plus a second controller with or without oral corticosteroids (OCS; GINA Steps 4 or 5) to prevent it from becoming uncontrolled or remains uncontrolled despite this treatment.⁵ Patients are assessed as having uncontrolled disease if they have at least three of the following: daytime symptoms (more than twice a week), night-time symptoms, activity limitation, or the need for rescue medication more than twice a week.⁵ Patients with asthma uncontrolled by GINA Step 4 or 5 treatment (subsequently described as severe, uncontrolled asthma [SUA]) respond poorly to standard therapies and often rely on regular intake of OCS for symptom control.⁵ SUA accounts for a disproportionate use of asthma-related health care resource utilization, including inpatient care, and remains a significant unmet need in respiratory medicine.^{6,7}

We conducted a systematic literature review (SLR) to further understand the burden of SUA and to identify unmet needs associated with this disease. The following aspects of SUA were evaluated: epidemiology, clinical burden (including clinical outcomes of pharmacologic treatments, consequences of long-term/frequent OCS use), humanistic burden (patient-reported outcomes [PROs]), and economic burden (including direct and indirect costs). Data for the overall SUA population were obtained from the literature and are summarized in this review.

METHODS

We performed an SLR adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.⁸ MEDLINE, via PubMed, and EMBASE were searched for relevant studies published from January 1, 2004 (to capture publications following approval of the first biologic therapy for severe, uncontrolled asthma) to September 12, 2016. The search algorithm included keywords for SUA paired with outcome terms of interest (Supplementary

Tables 1–4). We manually checked the bibliographies of relevant SLRs and meta-analyses published since 2010 contained within both databases to confirm comprehensive retrieval of literature of interest.

In addition to MEDLINE and EMBASE, scientific conference proceedings published from January 2012 through October 2016 were reviewed to identify potential studies of interest using MedMeme Online Portal for Clinical Intelligence database. Supplementary Table 5 shows the terms used for this search.

Study Selection

Inclusion criteria

Studies of asthma uncontrolled by GINA Step 4 or 5 treatment with the following characteristics were included: observational (prospective and retrospective), randomized, or nonrandomized study designs; adult patient populations; sample sizes ≥ 20 patients; and epidemiologic, clinical, patient-reported, and/or economic outcomes. For our review summary, uncontrolled asthma was defined as asthma that was inadequately controlled despite the use of medium- to high-dosage ICS and at least one additional treatment, such as a long-acting β_2 -agonist (LABA), as specified in the 2016 GINA guidelines (referred to as severe, uncontrolled asthma [SUA]).⁵ Criteria for defining asthma control varied between studies and included exacerbation/hospitalization history or validated symptom questionnaires. To gain insights from a global perspective, we included studies published in English, Chinese, Dutch, French, German, Italian, Japanese, Portuguese, Russian, and Spanish languages.

Exclusion criteria

We excluded studies with only pediatric or adolescent patients (as disease characteristics differ from those of adults) and studies of seasonal asthma, genetics of asthma, and nonpharmacologic treatments for asthma. Animal studies, studies using *in vitro* models, and data from published letters, commentaries, editorials, and narrative reviews were excluded.

Review Process

Following the literature search, a single reviewer manually screened all titles and abstracts identified from MEDLINE, EMBASE, and the scientific congress proceedings databases against the inclusion and exclusion criteria using the PICOS-T (Population, Intervention, Comparator, Outcomes, Study Design, and Time) framework.⁹ The full-text articles of accepted studies passing abstract screening were retrieved, and an investigator screened them using the same inclusion and exclusion criteria that had been applied at the abstract level. All excluded studies were confirmed by a second, senior investigator. Any discrepancies between the two investigators were resolved by a third investigator. Full-text articles published in non-English languages were translated into English and reviewed following the above-described process to determine their eligibility for inclusion in the review.

Data Abstraction

We performed data abstraction of the included studies using an evidence table template. For each study, data were abstracted into a data input grid by two investigators independently trained in the critical assessment of evidence. A senior investigator resolved any discrepancies.

Quality Assessment of Included Studies

We evaluated all selected publications to determine the quality of the studies according to criteria modified from the University of Oxford's Centre for Evidence-Based Medicine (CEBM).¹⁰ CEBM ratings were only given to studies published in the peer-reviewed literature (i.e., MEDLINE and EMBASE).

RESULTS

Study Selection

The MEDLINE (via PubMed) and EMBASE searches for literature were performed on September 12, 2016, and yielded 4,986 publications from MEDLINE and 6,067 from EMBASE, with overlap between the two databases. After removing duplicate publications, we identified 8,187 unique articles and screened them at the abstract level, selecting 1,718 for further review of the full text. Of these, 169 primary studies were accepted for inclusion in the SLR.

A review of the conference proceedings identified 59 additional meeting abstracts, resulting in 228 included studies. Thirty-three of these reported data on the same study population and were designated "related publications" to avoid counting patients multiple times in the review's results. Many of the related publications were either subgroup analyses or conference abstracts that were also available as full publications. When accounting for the presence of related publications, 195 articles on unique study populations were included for summary in the SLR. Figure 1 presents a summary of study attrition at each level of the SLR.

Epidemiology of Asthma Uncontrolled by GINA Step 4 or 5 Treatment

Our SLR identified 83 primary studies with epidemiology data relevant to SUA; all were observational studies. Three studies were international (involving multiple countries from different continents),^{11–13} and the remaining studies were from Asia,^{14–19} Australia,^{20,21} Germany,^{22,23} France,^{24–27} Italy,^{28–35} Spain,^{36–40} the United Kingdom,^{6,41–48} Europe (other),^{49–68} the Middle East,^{69,70} South America,^{71–75} and the United States.^{76–90} Table 1 shows a summary of the epidemiology of SUA, and Supplementary Table 6 provides details of the study designs and main results. Of the identified studies, only one study reported on severe asthma-related mortality; however, this study reported risk factors for mortality in severe asthma patients rather than the prevalence of mortality from severe disease.⁹¹ All other epidemiologic studies reported on the prevalence of SUA, most often in the asthma patient population. These studies reported that a small but clinically important segment of patients with severe asthma often has uncontrolled symptoms, despite available maintenance therapies (high-dosage ICS/LABA).

Prevalence of severe, uncontrolled asthma

The prevalence of SUA within the general population was reported as 0.03% in a study from the United States in which SUA was defined by ≥ 2 exacerbations per year.⁹² The prevalence of SUA as a percentage of all asthma varies among studies and countries, largely because of variation between clinical and epidemiologic definitions of SUA. In identified studies, criteria used to define asthma severity and control included GINA⁴ or British Thoracic Society⁹³ guidelines, Asthma Control Test (ACT)⁹⁴ score cutoff of 16–19 (not well controlled) or <15 (very poorly controlled), Asthma Control Questionnaire (ACQ)⁹⁵ score >1.5 (uncontrolled), clinician judgement, and patient self-assessment. The percentage of the overall asthma patient population with SUA reported in these identified publications ranged from 0.7%⁵³ in the Netherlands, where SUA was defined by hospitalization/short course of OCS, to 49.2% in the United States, where SUA was defined by ACT <20 at baseline and 6 months.⁷⁹ Studies using GINA guidelines criteria reported an SUA prevalence of 1.8³⁷ to 38.9%⁷² within the asthma patient population. Among eight large population studies (sample size ranging from 4,755–36,649 patients), the percentage of all patients with asthma with SUA ranged from 3.2% in France²⁶ to 10% in the US TENOR study population⁸¹ for studies with the same definition of disease (treatment with GINA Step 4 or 5 [or equivalent]; uncontrolled status assessed using a standard questionnaire).

Studies reporting the percentages of patients with severe asthma and uncontrolled disease used varying criteria to determine the degree of control. These criteria included exacerbation history, GINA guideline definition, and use of validated asthma control questionnaires. For patients with severe asthma, up to 87.4% were reported to have SUA (French study, asthma control defined by adapted GINA guidelines).²⁴ As in the overall asthma population, the prevalence of SUA in patients with severe asthma varied greatly depending on the criteria used. For example, in a Brazilian study, the prevalence of SUA increased from 8% when using self-assessment to 38.8% when control was assessed using the ACQ-6.⁷¹

Patient characteristics and risk factors for severe, uncontrolled asthma

The SLR identified only one study that assessed mortality associated with SUA. It was a nested case-control study of patients in Brazil with severe asthma.⁹¹ Multivariate analysis identified male sex, uncontrolled asthma in the past year, number of asthma exacerbations in the past year, and prebronchodilator forced expiratory volume in 1 second (FEV₁) $<60\%$ as significant and independently associated risk factors for mortality for the population with severe asthma. This study suggested that the risk of respiratory-related mortality was approximately 8-times greater for patients with SUA than patients with controlled disease.⁹¹

Approximately 50% of patients who had SUA despite the use of high-dosage ICS had elevated blood eosinophil counts (≥ 300 cells/ μL).⁹² For patients with SUA, greater eosinophil counts were significantly associated with persistent airway obstruction, absence of atopy, late-onset asthma, and age younger than 65 years.⁴² Patients' body mass index had an inverse relationship with both sputum and blood eosinophil counts.^{32,35,65}

Clinical Burden of Asthma Uncontrolled by GINA Step 4 or 5 Treatment

Our SLR identified 113 publications that included data related to the clinical burden of SUA. Twenty-three of these studies, reported in 21 publications, were international studies^{13,96–115}; others reported data from Asia,^{14–16,19,116–124} Australia,^{21,125} Germany,^{22,126–129} France,^{50,54,113,130–133} Italy,^{29–31,34,134,135} Spain,^{37,39,40,136–138} the United Kingdom,^{6,41–48,139–146} Europe (other),^{56,62,64,67,68,122,131,147–155} Mexico,^{156,157} South America,¹⁵⁸ the Middle East,^{159–164} Africa,¹⁶⁵ the United States,^{77–79,88,92,115,166–171} Canada,¹⁷² and the United States and Canada combined.^{173,174} These studies evaluated asthma exacerbation rates and the effect of active treatment on asthma exacerbation rates, lung function, and asthma medication use. Supplementary Table 6 provides details of the study designs and main results.

Our review found that, as expected, exacerbations were common for people with SUA, and patients with severe asthma had more than twice as many asthma-related hospitalizations as those with non-severe disease.⁹² However, estimates of annual asthma exacerbation rates varied depending on inclusion and exclusion criteria and the definition of asthma exacerbation used by the reporting studies. Consistent with current treatment guidelines,^{5,175} most of the studies defined exacerbation by the need for corticosteroid use and/or emergency department (ED) visit or hospital admission. The annualized exacerbation rate from observational studies of patients with SUA ranged from 0.48 in Japan (N=54)¹⁴ to 6.96 in Ireland (N=30),⁶² and the differences in these reported ranges reflect significant variations in study designs and inclusion criteria. The exacerbation rate identified for patients from Ireland was reported before the availability of omalizumab as a treatment option. Omalizumab also was not available for a portion of the time period covered in the report from Japan.¹⁴ The rate of severe exacerbations was more consistent across studies, with an annualized rate of 2.27 in Greece (N=60)⁶⁴ to 3.60 in Spain (N=263).^{39,40} Exacerbation rates were provided as a 12-month prevalence percentage in two studies and ranged from 19.6% for Denmark¹⁷⁶ (N=61,583) to 31.2% for Taiwan (N=282).¹¹⁶ No nontreatment-associated observational studies were identified that reported on the lung function status of patients with SUA.

Impact of biologic therapies on clinical burden

Omalizumab treatment was approved for the treatment of patients with severe asthma for a substantial period covered by this review. We identified 58 publications of reports of omalizumab from clinical trials and observational settings.^{15,19,21,22,27,29–31,34,39,40,48,56,62,64,67,68,79,98,99,104,117,122,124–131,134,136,138,139,146,149,152,153,156–158,160–164,167–169,174,177–182} Of these publications, most trials and all observational studies showed a reduction in exacerbations with treatment.^{29,30,39,48,98,127,128,177,178,183} Two German studies reported the greatest and the smallest change in annual exacerbation rates after omalizumab treatment; the greatest change was a 93% reduction,¹²⁷ and the smallest was a 22% reduction (although this analysis only included patients 50 years or older).²² However, trials of omalizumab showed inconsistent results for improvement in lung function.^{56,64,96,100,131,152,153,156,157} Omalizumab treatment was associated with a decrease in the use and dosage of other asthma medications, including a reduction in OCS use^{48,116,124,129,136,138,139,146,177} and ICS use.^{62,64,136,168} Omalizumab therapy also reduced rescue medication use in several trials.^{15,40,62,136} Although overall the

extensive studies reporting on the treatment of severe asthma with omalizumab show this drug to be effective, not all patients with SUA are suitable for treatment with omalizumab, and not all those identified as candidates respond to treatment.¹⁷⁵

The impact of active treatment on the risk of exacerbations with other biologic treatments varied. Reductions in annual exacerbations were observed in randomized controlled trials (RCTs) of benralizumab (reduction vs. placebo: 29–70%^{97,102,114}), mepolizumab (reduction vs. placebo: 47–52%,¹¹¹ 39–52%¹¹⁰ [depending on dosage and administration route]), dupilumab (reduction vs. placebo: 33–87%^{13,171} [depending on treatment schedule]), and reslizumab (reduction vs. placebo: 46%¹¹³). In contrast, there were no significant differences between the effects of placebo and active treatment exacerbations for trials of golimumab,¹¹² etanercept,¹⁸⁴ KB003,¹⁰⁸ or tralokinumab.¹⁰⁰

Improvements in lung function were observed only with certain active biologic treatments and not consistently in all studies of each treatment. Improvements in lung function compared with placebo, although not statistically significant in all cases, were reported in RCTs for dupilumab,^{13,171} benralizumab,^{97,102,114} and reslizumab.¹¹³ Golimumab¹¹² and etanercept¹⁸⁴ were not significantly more effective than placebo at improving lung function outcomes in any trial reported. Tralokinumab showed inconsistent results, with significant improvements in some, but not all, lung function measures associated with active treatment.¹⁰⁰

The impact of treatment on medication use (asthma and rescue medication) varied for patients with SUA. As discussed previously, omalizumab treatment was associated with a decrease in the use and dosage of other asthma medications, including rescue medication. Dupilumab¹⁷¹ treatment also reduced rescue medication use, while golimumab¹¹² treatment, compared with placebo, did not. During the review period covered by this SLR, the impact of newer biologic treatments on OCS use was not reported.

Impact of nonbiologic therapies on clinical burden

Identified studies reported no significant differences between the effects of placebo and active treatment on exacerbations in trials of masitinib,¹⁸⁵ AZD5069,¹⁰⁹ or mometasone furoate.¹⁴⁴ Improvements in lung function compared with placebo, although not statistically significant in all cases, were reported in RCTs of prednisolone.¹⁵¹ In observational studies, lung function improved significantly for patients receiving mycophenolate mofetil,¹⁴⁴ tiotropium with salmeterol/fluticasone,¹⁵⁴ and pranlukast.¹¹⁹ Azithromycin,¹⁴⁷ mometasone furoate,¹⁵⁴ and sodium cromoglicate¹²¹ were not significantly more effective than placebo at improving lung function outcomes in any trial reported. Ciclesonide demonstrated inconsistent results, with significant improvements in some lung function measures associated with treatment.⁹⁶

Humanistic Burden of Asthma Uncontrolled by GINA Step 4 or 5 Treatment

We identified 103 primary studies that included data related to PROs for patients with SUA.

Twenty-three international studies in 19 publications were identified.^{11,13,97,98,100–102,104–114,132}

Additional studies were from Asia,^{15,16,18,19,117,119–124} Australia,^{21,125} Germany,^{126–129,186}

France,^{179,181,187} Italy,^{34,183} Spain,^{39,40} the United Kingdom,^{41–43,45,46,48,139–142,144–146,177,182,184,188,189}

Europe (other),^{50,51,55–57,59–61,64,69,147–150,152,153,161–163,184,190} the Middle East,¹⁶⁷ South America,^{73,158} the United States,^{77,81,87,115,147,167,191} Canada,^{173,174} and Africa.¹⁶⁵ Validated questionnaires used in these studies to measure PROs included Asthma Quality of Life Questionnaire (AQLQ),¹⁹² ACT,⁹⁴ and ACQ, and the minimally clinically important differences were 0.5, 3, and 0.5 points, respectively.⁹⁵ Supplementary Table 6 provides details of study designs and main results. Observational studies reported that, compared with patients with controlled disease, patients with SUA experienced more symptoms, night-time awakenings, and rescue medication use, as well as worse health-related quality of life (HRQOL).^{37,132} In the identified observational publications, HRQOL was most often assessed by AQLQ score, but some studies also used the European Quality of Life-Five Dimensions Questionnaire and the St. George's Respiratory Questionnaire. Compared with patients with moderate to severe, controlled disease, patients with SUA scored an average of 1.4 points greater (worse control) on the ACQ,³⁷ 7 points greater (worse control) on the ACT,³⁴ and 1.3 points lower (worse HRQOL) on the AQLQ.³⁷

In RCTs of treatments for patients with SUA, patient questionnaires were frequently used to assess treatment-associated improvements in PROs. RCTs have reported statistically significant treatment improvements in HRQOL for patients with immunoglobulin E (IgE)-mediated allergic SUA, as assessed by the AQLQ for patients treated with mometasone furoate (nonbiologic) or omalizumab (biologic).^{15,104,117,145,150,174} No significant effects on HRQOL were reported in the identified publications for patients treated with the biologic therapies etanercept¹⁸⁴ and golimumab,¹¹² or the nonbiologic AZD5069.¹⁰⁹ Mixed results were seen for trials of patients treated with the biologic therapies reslizumab,¹¹³ benralizumab,^{97,102} tralokinumab,¹⁰⁰ dupilumab,¹³ and mepolizumab,^{11,111,145,150} and the nonbiologic tiotropium.^{106,150}

In the publications we identified, prospective cohort studies reported significant improvements in disease control associated with omalizumab biologic treatment using the ACQ, and several RCTs across geographic areas reported significant treatment effects on PROs for omalizumab.^{15,21,48,98,124,126,138,181} RCTs evaluating other biologic treatments, including benralizumab^{97,102} and dupilumab,^{13,171} and the nonbiologic masitinib,¹⁸⁵ also found significant effects of treatment on symptom control, as assessed by ACQ score. However, RCTs evaluating the biologics reslizumab,^{113,173} mepolizumab,^{110,111} and golimumab¹¹² and the nonbiologics AZD5069¹⁰⁹ and azithromycin¹⁴⁷ found no significant treatment effects on ACQ score. Trials evaluating tiotropium (nonbiologic)^{105,106} and tralokinumab (biologic)¹⁰⁰ did not report consistent results. RCTs and several cohort studies reported an association between omalizumab therapy and beneficial changes on the ACT scores of patients with SUA (including for those with IgE-mediated allergic SUA).^{23,36,39,64,71,145,147,173,178,179,193}

Overall, the results of these studies highlight that there is a considerable, worldwide humanistic burden associated with SUA. In many studies, there was evidence that this burden remained after treatment. Although treatment was associated with some improvements in PROs, these improvements were not consistently statistically significant compared with placebo for all outcomes measured and across studies.

Economic Burden of Asthma Uncontrolled by GINA Step 4 or 5 Treatment

We identified 65 primary studies that included data related to the economic burden of SUA. Nine international studies were identified,^{97,98,102,104,105,111,112,114,194} as well as studies from Africa,¹⁶⁵ Asia,^{19,116,122,124,195} Australia,¹²⁵ Canada,¹⁹⁶ France,^{27,178,179} Germany,^{22,127,128} Italy,^{30–32,34,197} Spain,^{37,39,40,138} the United Kingdom,^{6,41,42,44,46,48,80,139–142,145,146,184,189,198,199} Europe (other),^{49,51–53,55,62,63,68,131,147–149,152,200,201} Mexico,^{156,157} the Middle East,^{159,164} South America,^{71,73,202} and the United States.^{71,73,76,77,84,85,87,88,92,166–169,171,202–204} Supplementary Table 6 provides details of study designs and main results.

Across studies, this review identified that a substantial economic burden was associated with SUA, which was reduced but not eliminated by treatments approved for SUA. This burden was measured most often by health care resource utilization, such as hospitalizations, ED visits, and intensive care unit (ICU) admissions, as well as unscheduled and scheduled physician appointments (typically asthma exacerbation/symptom worsening related). Patients with SUA had an average of 3–3.5 office visits, 0.6–2.0 ED visits, and 0.5–0.6 hospitalizations annually.^{37,179} More than 80% of studies reported that ≥17% of patients with SUA had been hospitalized in the year prior to study entry.

A Canadian study (1996–2000) reported that patients with SUA accounted for 60% of total asthma-related health care costs, estimated at \$25 million per year (inflation-adjusted 2006 Canadian Dollars) in British Columbia, Canada.¹⁹⁶ A European study performed in The Netherlands reported that total direct medical costs per patient year for all patients with SUA were 3-times as high as for patients with severe asthma but whose disease was controlled.⁵³ Overall, for a representative population of patients with asthma from The Netherlands (N=32,163), medication and hospitalization costs for all patients with severe asthma (n=1,518) totaled €1.6 million in 2004. Above standard maintenance costs, therapy drug costs totaled roughly €700 per patient per year for patients with SUA with hospitalization and €300 per patient per year for patients with SUA with multiple courses of OCS. Costs for patients with SUA requiring hospitalization (including admission- and drug-associated costs) were more than €10,000 per patient per year.⁵³ Patients with SUA received frequent or long-term OCS, with an average of 43% greater associated direct health care treatment costs than patients not receiving maintenance OCS.⁶ Other studies nonspecific to SUA have associated OCS treatment with short- and long-term detrimental adverse effects, including diabetes, osteoporosis, high blood pressure, skeletal complications, ocular complications, and Cushingoid features.^{205,206}

Identified studies reported that SUA severely impaired quality of life and was associated with substantially greater health care resource use.⁹² A US study evaluating SUA-associated health care costs reported that a subset of patients with severe eosinophilic asthma (defined as ≥1 laboratory result with a blood eosinophil count ≥300 cells/μL) incurred greater costs than patients with severe asthma without an elevated blood eosinophil count. Persistent asthma was defined as asthma that was inadequately controlled, and severe, persistent asthma was

defined as asthma in patients who had evidence of ≥ 2 exacerbations during the study period (Figure 2).⁹²

SUA also was associated with greater indirect costs. In RCTs of omalizumab from France and the United Kingdom, patients with SUA had mean baseline annual days of absenteeism of 14.6 and 49.4 days, respectively.^{48,179} A small (N=92) study from Korea found that for patients with severe asthma, the indirect costs were 3.5-times greater for those with uncontrolled versus well-controlled disease (\$4,909.50 vs. \$1,217.80 per year).¹⁹⁵ In a cross-sectional study from the European Network for Understanding Mechanisms of Severe Asthma, which included patients from nine European countries, patients with SUA reported that work affected their breathing and that they often had to change jobs due to their asthma. In addition, fewer patients with SUA were employed at the time of the study than patients who had mild disease (odds ratio, 0.39).⁵⁵

DISCUSSION

This SLR provides a broad overview of the burden associated with SUA (defined as asthma uncontrolled by GINA Step 4 or 5 treatment), including epidemiologic, clinical, humanistic, and economic outcomes. In the identified literature, the prevalence of SUA varied widely based on the definition of asthma control used and the study population. Historical differences in the criteria used to define SUA, patient and physician perceptions of control, and the application of the GINA guidelines all may have contributed to the variation in reported estimates. Bearing in mind these limitations, from the available literature identified, the reported prevalence of SUA ranged from 0.7%⁵³ to 49.2%⁷⁹ within the asthma patient population,⁸¹ and was up to 87.4% within the severe asthma patient population.²⁴ The prevalence of SUA within the asthma patient population tended to be smaller for larger population studies (>2,000 patients) and greater for studies that defined SUA according to GINA guidelines. Clinician and patient self-assessments tended to overestimate the degree of patients' asthma control.

Our review identified a large body of evidence confirming that patients with SUA have a significant burden of disease, characterized by poorly controlled symptoms and frequent exacerbations, reduced HRQOL, and substantial health care-associated costs. This indicates that SUA is associated with a significant impediment to patients' everyday lives. Compared with patients with moderate to severe disease, those with SUA have more persistent symptoms, more frequent exacerbations, and a greater number and rate of comorbidities. Identified studies also reported that SUA is associated with a reduced HRQOL, which was most frequently assessed using the AQLQ, a patient questionnaire designed to evaluate the physical, emotional, social, and occupational burden of patients with asthma. Overall, the studies we identified indicate that the symptom burden associated with SUA is considerable, globally consistent, and persists even after treatment. These results are consistent with the results of another review that demonstrated that many patients treated according to the GINA guidelines continue to have symptoms that adversely affect their HRQOL.²⁰⁷

We identified 40 studies evaluating the efficacy of omalizumab for the treatment of SUA. Omalizumab, the first targeted biological therapy for the treatment of SUA, was first approved in 2003. The extent of the literature evaluating its use is not unexpected. The identified studies, which were published from 2004–2016, included observational studies and RCTs. Omalizumab was associated with a reduction in exacerbations in all observational studies and most RCTs, but results for lung function were inconsistent between studies (both observational and RCTs). Overall, these results provide evidence that SUA continues to contribute a significant clinical and economic burden despite the introduction of omalizumab. Reports in the literature of more recently approved targeted biological therapies, such as mepolizumab, reslizumab, and benralizumab, are mostly restricted to RCTs. As these therapies become more widely used over time, it will be interesting to see if and how they affect the clinical, humanistic, economic burden associated with SUA at the population level.

The identified studies reporting on the economic burden of SUA most often assessed health care resource utilization by analyzing the frequency of patient hospitalizations, ED visits, ICU admissions, and physician appointments. These studies reported a considerable economic burden associated with SUA compared with controlled asthma. This is in agreement with a recent report from the United Kingdom, which stated that mean per-patient health care resource and associated costs were 4-times greater for patients with eosinophilic SUA than the general asthma patient population.²⁰⁸ SUA also has been associated with a greater risk of exacerbations, hospitalizations, deaths, and OCS dependency.²⁰⁹ Improved asthma control would decrease the need for hospitalizations and lower the overall costs associated with SUA.

Our review identified several data gaps in the available literature relating to SUA. In particular, data were lacking for the mortality associated with SUA and the SUA-related indirect costs caused by patient loss of productivity, work absenteeism, and caregiver burden.

Limitations

As is the case for all SLRs, this review has certain limitations. For example, it was subject to selection bias, although this was minimized by using a stringent case definition of SUA (i.e., inadequate control of asthma despite the use of medium- to high-dosage ICS and at least one additional treatment). However, during the timeframe of studies included in this review, the generally accepted definition of SUA changed from symptom-based to treatment-based. Although we made every attempt to standardize the definition of SUA, it is possible that unidentified misclassifications were present in our results. For the assessment of PROs, variation existed between studies on how clearly outcomes were described and whether actual values, relative change from baseline, or differences between treatment and placebo were reported. Furthermore, many reports from RCTs provided limited details on the methods of administering the instruments and how estimates of results were derived. There also was inconsistent reporting of how patient discontinuations and missing data were handled. This could significantly impact the reported results, because for some studies, dropout rates were significant and may have been conceivably greater for placebo study arms.

CONCLUSIONS

This SLR identified a substantial epidemiologic burden, as well as a clinical, humanistic, and economic burden, associated with SUA, despite the availability and use of current treatments. Although this review is subject to limitations, most notably the lack of a consistent definition of severe, uncontrolled asthma, it highlights the considerable unmet need worldwide for patients with SUA. This is important, because many of the 250,000 annual asthma-related deaths worldwide can be attributed to avoidable factors (e.g., lack of referral for specialist care).^{210–212} Thus, clinicians should understand the heterogeneous nature of asthma and improve treatment and HRQOL for patients with SUA.

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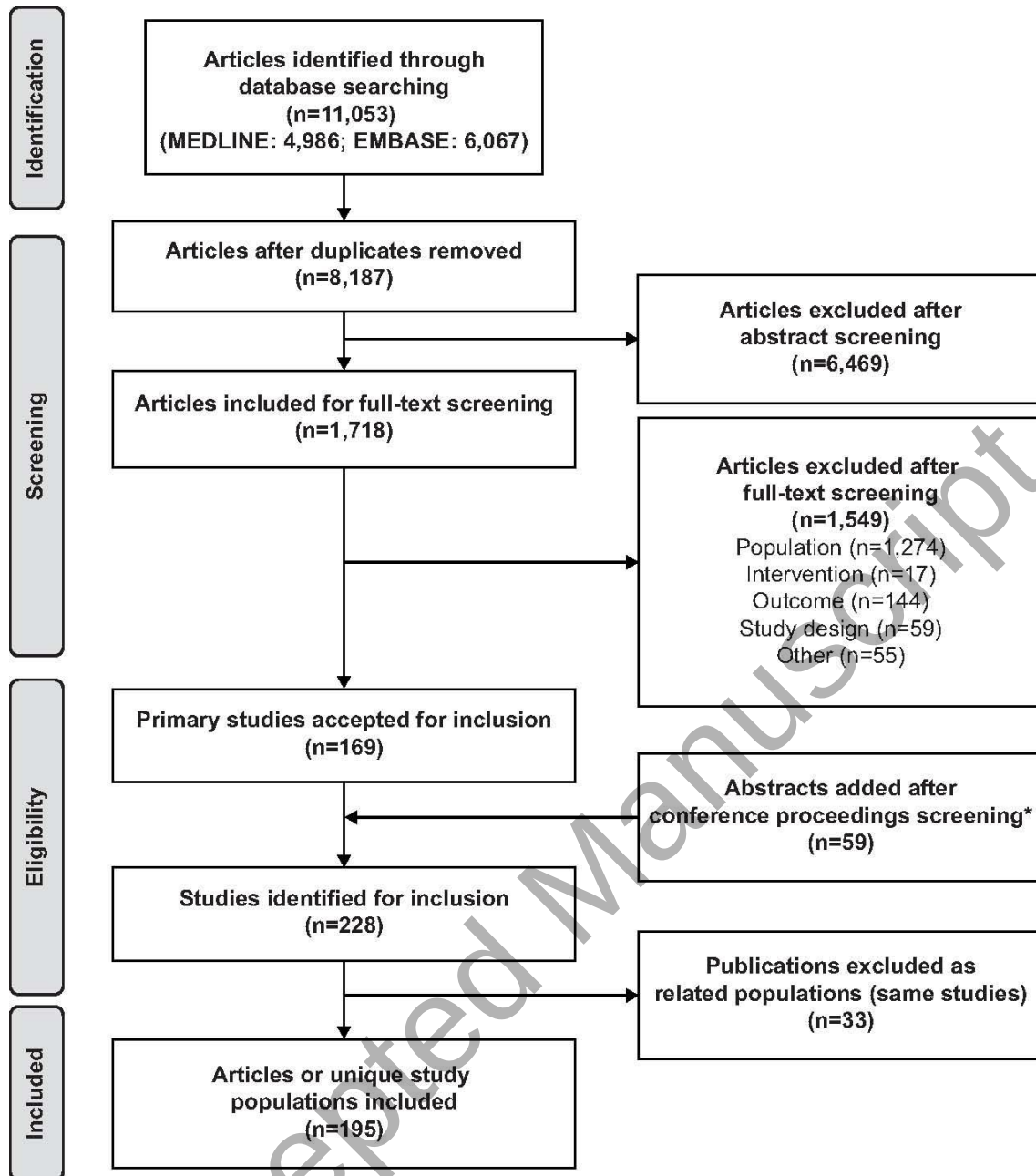
FIGURES

Figure 1. Study Selection

*Conference proceedings identified from the MedMeme Online Portal for Clinical Intelligence Database.

Figure 2. Mean All-Cause and Asthma-Related Costs for Patients with Persistent Severe, Uncontrolled; and Severe, Eosinophilic Asthma⁹⁰

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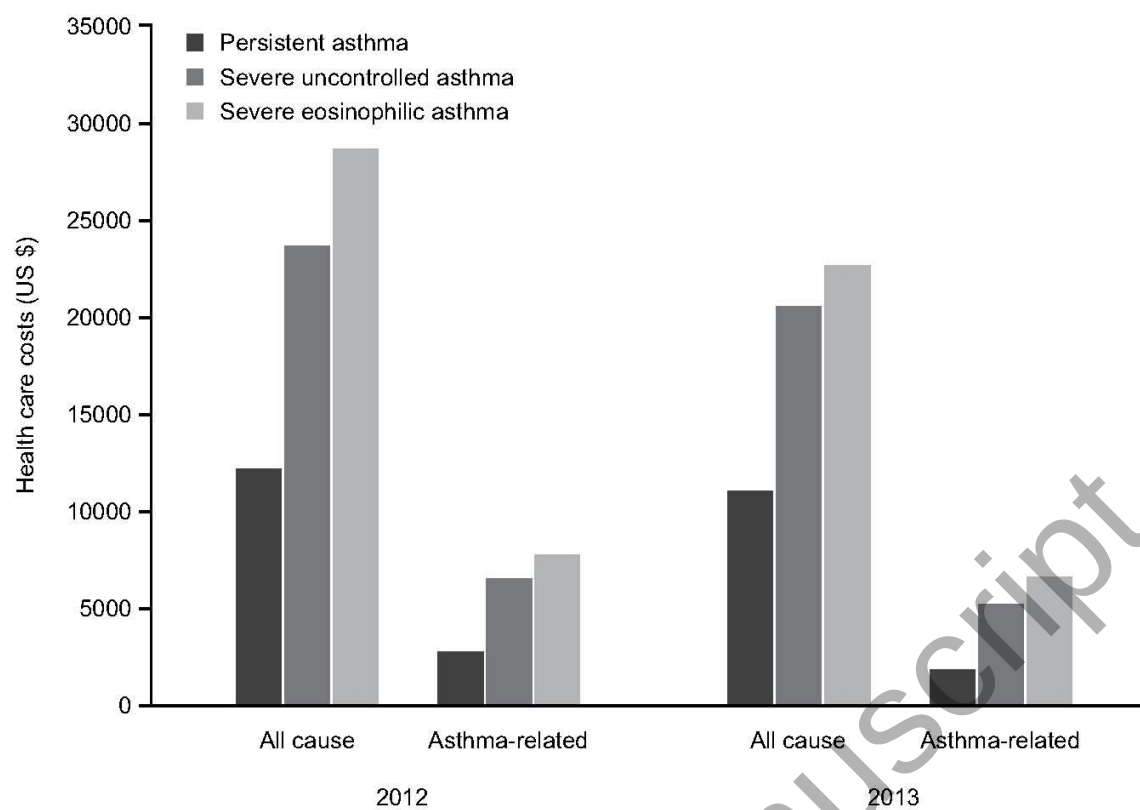


Table 1. Summary of Key Studies Reporting the Prevalence of Asthma

**Uncontrolled by GINA Step 4 or 5 Treatment (Severe, Uncontrolled Asthma
[SUA])**

Country	Number of studies (number of patients)	How asthma control was defined	SUA in asthma population	SUA in uncontrolled asthma	SUA in severe asthma	Prevalence in the general population
International (France, Germany, Italy, Spain, UK, US) ¹²	1 (N=9,734)	ACT <20	10.0%	NR	79.0%	NR
US ^{76,78,79,83,85,81,89}	7 (N=320–12.6 million)	Self-assessment of control in the previous 4 weeks; EPR-3 definition: the presence of either risk or impairment; ACT<20 at baseline and 6 months; ≥2 exacerbations ^a ; ACT <20 at baseline and every 6 months to 24 months; ≥2 exacerbations ^a and high-dosage therapy; ≥3 exacerbations ^a ; NAEPP guidelines	1.06% (EPR-3)–49.2% (ACT)	29.9 (EPR-3)–88.0% (≥3 exacerbations)	19.9 (≥2 exacerbations)–49.2% (ACT)	0.03 (≥2 exacerbations)
UK (Scotland) ⁴⁵	1 (N=267)	BTS guideline	16.9%	NR	NR	NR
France ^{24,25,26}	2 (N=491–15,534)	ACT score (<15 very poorly controlled; 15–20 poorly controlled);	3.2% (ACT)–18.4%	51.2% (GINA)	26.6 (patient judgment)–87.4%	NR

		ANAES (French adaptation of the GINA guidelines); GINA 2006 classification; patient judgment	(GINA)		(ANAES)	
Germany ²³	1 (N=150)	GINA 2009 classification	30.0%	66.2%	38.1%	NR
Italy ²⁸	1 (N=2,835)	ACT ≤ 15	NR	34.6%	14.2%	NR
Spain ^{36,37}	2 (N=1,224–36,649)	ACQ >1.5; clinician judgment; GINA guidelines	1.8% (GINA)– 3.9% (clinical judgment)	NR	55.7% (ACQ)	NR
Denmark ¹⁷⁶	1 (N=61,583)	High SABA use (≥ 600 doses of SABA) and/or at least 1 exacerbation in the 1-year period of observation	3.0%	11.7%	36.4%	NR
The Netherlands ⁵³	1 (N=32,163)	Hospitalization for asthma or use of more than one short (<30 days) course of oral corticosteroids in 2004	0.7%– 0.8%	NR	17%	NR
Brazil ^{71,72,75}	3 (N=275–183 million)	Patient self-assessment; ACQ ≥ 1.5 ; GINA 2006 classification	38.9% (GINA)	69.9% (GINA)	8.0 (self-assessment)– 74.3% (GINA)	
South Korea ¹⁷	1 (N=2,298)	ATS criteria for refractory asthma	4.3%	NR	NR	NR

Israel ⁷⁰	1 (N=123)	GINA 2006 classification	NR	NR	43.9%	NR
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ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; ANAES, L'Agence Nationale d'Accreditation et d'Evaluation en Sante; ATS, American Thoracic Society; BTS, British Thoracic Society; EPR-3, The Expert Panel Report 3; GINA, Global Initiative for Asthma; NAEPP, National Asthma Education and Prevention Program; NR, not reported; SABA, short-acting β_2 -agonist.

^aExacerbations per year.

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Systematic Literature Review of the Clinical, Humanistic, and Economic Burden Associated with Asthma Uncontrolled by GINA Steps 4 or 5 Treatment

APPENDIX

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Supplementary Table 1: MEDLINE (via PubMed) Search Algorithm on the Disease Burden of Asthma Uncontrolled by GINA Step 4 or 5 Treatment

Topic		MEDLINE Search Algorithm	Hits
Severe asthma	1	("Asthma"[MeSh] OR asthma OR asthmatic) AND (severe OR persistent OR uncontrolled OR severity OR "poor control" OR refractory OR recurrent OR "poorly controlled" OR "inadequately controlled")	8,465
Humanistic burden	2	"quality of life" OR "quality-of-life" OR QoL OR HRQoL OR "health-related quality of life" OR "patient reported outcome" OR "patient-reported outcome" OR "patient reported outcomes" OR "patient-reported outcomes" OR satisfaction OR "health utility" OR "health utilities" OR disab* OR "functional status" OR "physical function" OR sleep OR "health status" OR "Asthma Quality of Life Questionnaire" OR AQLQ OR "Asthma Life Impact Scale" OR SGRQ OR "St George's Respiratory Questionnaire" OR "limitation of activities" OR "activities of daily living" OR "emotional dysfunction" OR "caregiver burden" OR humanistic OR "quality of life"[MeSH] OR "Patient Satisfaction"[MeSh] OR "Activities of Daily Living"[MeSH]	356,224
Epidemiology	3	"epidemiology"[MeSH] OR "Comorbidity"[MeSH] OR "incidence"[MeSH] OR "prevalence"[MeSH] OR "risk factor"[MeSH] OR "mortality"[MeSH] OR "survival"[MeSH] OR "Disease Progression"[MeSH] OR epidemiol* OR incidence OR incident OR prevalence OR prevalent OR "risk factor*" OR mortality OR exacerbation OR comorbid*	1,160,677
Economic burden	4	cost* OR budget* OR expenditure* OR resource utili* OR economic* OR pharmacoeconomic* OR productivity OR price* OR pricing OR reimbursement OR fee OR fees OR ((hospital* OR hospital OR	1,462,071

		hospitalization OR hospitalisation) AND (cost OR costs OR fee OR fees)) OR ((work AND (loss OR lost)) OR "work disability" OR absenteeism OR "sick leave" OR "sick day" OR "sick leave"[MeSH] OR "Costs and cost analysis"[MeSH] OR "Cost of illness"[MeSH] OR economics[MeSH] OR economics, nursing[MeSH] OR economics, pharmaceutical[MeSH] OR economics, hospital[MeSH] OR "Quality-adjusted life year"[MeSH] OR "direct cost" OR "direct costs" OR "direct medical cost" OR "direct medical costs" OR "medical direct cost" OR "medical direct costs" OR "direct non medical cost" OR "direct non medical costs" OR "non medical direct cost" OR "non medical direct costs" OR "indirect cost" OR "indirect costs" OR "total cost" OR "total costs" OR "cost per patient treated" OR "health expenditures"[MeSH] OR ("health resources" OR "health care" OR "medical resources")) AND (use OR utilization OR utilization OR service OR consumption)) OR Hospital Costs"[MeSH] OR "Health Expenditures"[MeSH] OR "Employer Health Costs"[MeSH]	
Clinical burden	5	"standard of care" OR treatment* OR therapy* OR "Long-acting beta agonists" OR "Long acting beta agonists" OR LABA OR salmeterol OR formoterol OR "inhaled corticosteroids" OR LAMA OR 'long-acting muscarinic antagonist' OR 'long acting muscarinic antagonist' OR fluticasone OR budesonide OR mometasone OR ciclesonide OR flunisolide OR beclomethasone OR omalizumab OR ipratropium OR montelukast OR salbutamol OR mepolizumab OR Nucala OR reslizumab OR benralizumab OR Cinqair OR cinquil OR Cinqaero OR prednisone OR dexamethasone OR methylprednisolone OR prednisolone OR "systemic corticosteroids" OR "Therapeutics"[MeSH] OR "therapy" [Subheading] OR "Treatment Failure"[MeSH] OR "Treatment Outcome"[MeSH]	1,729,371
Overall	6	#1 AND (#2 OR #3 OR #4 OR #5)	6,436

Population	7	(#6 NOT (adolescent[MeSH] OR children[MeSH] OR infant[MeSH] OR animals[MeSH])) OR ((#6 AND (adolescent[MeSH] OR children[MeSH] OR infant[MeSH]) AND adult[MeSH])	4,568
Total yield	8	#7 NOT (editorial[ptyp] OR case reports[ptyp] OR comment[ptyp] OR news[ptyp] OR review[ptyp]	3,790

AQLQ, Asthma Quality of Life Questionnaire; HRQOL, health-related quality of life; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; MeSH, medical subject headings; QOL, quality of life; SGRQ, St. George's Respiratory Questionnaire.

Supplementary Table 2: MEDLINE (Via PubMed) Search Algorithm for Systematic Reviews on Asthma Uncontrolled by GINA Step 4 or 5 Treatment

Topic		MEDLINE Search Algorithm	Hits
Severe asthma	1	("Asthma"[MeSH] OR asthma OR asthmatic) AND (severe OR persistent OR uncontrolled OR severity OR "poor control" OR refractory OR recurrent OR "poorly controlled" OR "inadequately controlled")	8,465
Total yield	3	#1 AND ("systematic review" OR meta-analysis OR Systematic Reviews[ptyp] OR Meta-Analysis[ptyp] OR meta analysis[MeSH])	321

MeSH, medical subject headings.

**Supplementary Table 3: Embase Search Algorithm on the Disease Burden of Asthma
Uncontrolled by GINA Step 4 or 5 Treatment**

Topic		Embase Search Algorithm	Hits
Severe asthma	1	('severe persistent asthma'/exp) OR (('asthma'/exp OR 'asthmatic'/exp OR asthma:ab,ti OR asthmatic:ab,ti) AND ((severe OR refractory OR recurrent OR persistent OR "poor control" OR "inadequate control" OR severity OR uncontrolled OR 'poorly controlled' OR 'inadequately controlled'):ab,ti))	56,607
Humanistic burden	2	((('quality of life' OR 'quality-of-life' OR QoL OR HRQoL OR 'health-related quality of life' OR 'patient reported outcome' OR 'patient-reported outcome' OR 'patient reported outcomes' OR 'patient-reported outcomes' OR satisfaction OR 'health utility' OR 'health utilities' OR disab* OR 'functional status' OR 'physical function' OR sleep OR 'health status' OR 'Asthma Quality of Life Questionnaire' OR AQLQ OR 'Asthma Life Impact Scale' OR SGRQ OR 'St George's Respiratory Questionnaire' OR 'limitation of activities' OR 'activities of daily living' OR 'emotional dysfunction' OR 'caregiver burden' OR humanistic OR symptoms OR diary OR 'asthma control questionnaire' OR ACQ OR 'asthma control test' OR ACT OR 'health utility index' OR HUI OR HUI2 OR HUI3 OR 'Asthma Symptom Severity score' OR 'Wasserfallen asthma symptom score' OR 'euroqol 5-dimension questionnaire' OR 'euroqol 5D'):ab,ti) OR ('quality of life'/exp OR 'patient satisfaction'/exp OR 'disabled person'/exp OR 'daily life activity'/exp OR 'outcome assessment'/exp OR 'health status'/exp)	2,963,655
Epidemiology	3	('epidemiology'/exp OR 'incidence'/exp OR 'prevalence'/exp OR 'risk factor'/exp OR 'mortality'/exp OR 'comorbidity'/exp) OR ((epidemiol* OR exacerbation OR incidence OR incident OR	4,906,831

		prevalence OR prevalent OR "risk factor*" OR mortality OR comorbid* OR morbidity):ab,ti)	
Economic burden	4	('cost'/exp OR 'hospitalization cost'/exp OR 'hospital cost'/exp OR 'health care cost'/exp OR 'cost control'/exp OR 'drug cost'/exp OR 'budget'/exp OR 'productivity'/exp OR 'reimbursement'/exp OR 'fee'/exp OR 'hospitalization'/exp OR 'work disability'/exp OR 'absenteeism'/exp OR 'sick leave'/exp OR 'cost of illness'/exp OR 'economics'/exp OR 'hospital admission'/exp OR 'inpatient'/exp OR 'outpatient'/exp) OR ((cost OR costs OR expenditure OR expenditures OR 'resource utilization' OR 'resource utilisation' OR economic* OR pharmacoeconomic* OR price OR prices OR pricing OR 'work loss' OR 'work lost' OR 'sick day' OR 'cost offset' OR qaly OR qalys OR hru OR hcru OR 'emergency room visit' OR 'emergency room visits' OR 'direct cost' OR 'direct costs' OR 'direct medical cost' OR 'direct medical costs' OR 'medical direct cost' OR 'medical direct costs' OR 'direct non medical cost' OR 'direct non medical costs' OR 'non medical direct cost' OR 'non medical direct costs' OR 'indirect cost' OR 'indirect costs' OR 'total cost' OR 'total costs' OR 'cost per patient treated' OR 'health resource use' OR 'health resource utilisation' OR 'quality-adjusted life year' OR 'quality-adjusted life years' OR 'health resource consumption' OR 'health care consumption' OR 'medical resource use' OR 'medical resource utilization' OR 'medical resource consumption' OR 'health care use' OR 'health care utilization' OR 'health care utilisation' OR 'health resource utilization'):ab,ti)	1,821,493
Clinical burden	5	'standard of care' OR treatment* OR therapy* OR 'Long-acting beta agonists' OR 'Long acting beta agonists' OR LABA OR salmeterol OR formoterol OR "inhaled corticosteroids" OR "oral corticosteroids" OR fluticasone OR budesonide OR mometasone	8,931,836

		OR ciclesonide OR flunisolide OR beclomethasone OR LAMA OR 'long-acting muscarinic antagonist' OR 'long acting muscarinic antagonist' OR omalizumab OR Xolair OR ipratropium OR montelukast OR salbutamol OR mepolizumab OR Nucala OR Benralizumab OR reslizumab OR Cinqair OR cinquil OR Cinqaero OR prednisone OR dexamethasone OR methylprednisolone OR prednisolone OR "systemic corticosteroids"):ab,ti OR ('corticosteroid'/exp OR 'beta adrenergic receptor stimulating agent'/exp OR 'salmeterol'/exp OR 'budesonide plus salmeterol'/exp or 'fluticasone propionate plus salmeterol'/exp or 'salmeterol xinafoate'/exp or 'fluticasone propionate plus salmeterol xinafoate'/exp OR 'muscarinic receptor blocking agent'/exp)	
Overall	6	#1 AND (#2 OR #3 OR #4 OR #5)	47,873
Study type	7	#6 NOT (editorial[ptyp] OR case reports[ptyp] OR comment[ptyp] OR news[ptyp] OR review[ptyp])	39,705
Total yield	8	#7 NOT ('animal'/exp OR 'nonhuman' NOT 'human') NOT (('Adolescent'/exp or "Child'/exp or "Infant'/exp) NOT ("Adult'/exp and ("Adolescent'/exp or "Child'/exp or "Infant'/exp)))	5,346

AQLQ, Asthma Quality of Life Questionnaire; HRQOL, health-related quality of life; HUI, health utility index;

LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; QOL, quality of life; SGRQ, St.

George's Respiratory Questionnaire.

**Supplementary Table 4: Embase Search Algorithm for Systematic Reviews on Asthma
Uncontrolled by GINA Step 4 or 5 Treatment**

Topic		Embase Search Algorithm	Hits
Severe asthma	1	'severe persistent asthma'/exp OR ('asthma'/exp OR 'asthmatic'/exp AND (severe OR refractory OR recurrent OR 'poorly controlled' OR 'inadequately controlled'))	56,607
Total yield	3	#1 AND ('systematic review'/exp 'meta analysis'/exp OR (('systematic review' or 'meta analysis' or 'metaanalysis'):ab,ti))	138

Supplementary Table 5. MedMeme Online Portal for Clinical Intelligence Database

Search Algorithm for Systematic Reviews on Asthma Uncontrolled by GINA Step 4 or 5 Treatment

Topic		MedMeme Search Algorithm	Hits
Severe asthma	1	(‘Asthma OR asthma* OR asthmatic) AND (severe OR persistent OR uncontrolled OR severity OR ‘poor control OR refractory OR recurrent OR ‘poorly controlled’ OR ‘inadequately controlled’)	59

Supplementary Table 6: Overview of All Studies Included in the Systematic Literature Review of Asthma Uncontrolled by GINA Step 4 or 5 Treatment (Severe, Uncontrolled Asthma [SUA])

Country	Title	Study Characteristics (study design/ definition of asthma control/definition of exacerbation)	Study Population/Treatment	Key Results (SUA incidence/EX rates [pre- and post-treatment]/percentage of patients with EX)/other clinical outcomes
International (France, Germany, Italy, Spain, United Kingdom, United States) ¹	Profile and perspective of patients with severe allergic asthma and those receiving omalizumab: Findings from the national health and wellness survey 2010	Cross-sectional study 2010 National Health and Wellness Survey (n=9,734) Asthma control assessed by ACT <20	Self-reported data from 2010 based on patient perception of asthma were analyzed	Incidence of SUA in asthma patient population: 10.0% (971 with severe allergic asthma inadequately controlled/9,734 with asthma) Incidence of SUA in SA patient population: 79.0% (951/1,204)
International (France, Germany, Spain, Switzerland, United Kingdom) ²	Effectiveness of omalizumab in patients with inadequately controlled severe persistent allergic asthma: An open-label study	RCT EX: Asthma worsening requiring treatment with systemic corticosteroids	Omalizumab (n=115) Control (n=49)	<u>EX rate post-tx:</u> Omalizumab: 1.26 per year Control: 3.06 per year <u>Mini AQLQ response (≥ 0.5 pts in overall score):</u> Omalizumab: 76.5% Control: 41.7% ($p < 0.001$) <u>Change from baseline in mini AQLQ scores (baseline NR):</u> Symptoms: <i>Omalizumab:</i> 3 months: 1.05 6 months: 1.20 9 months: 1.10 12 months: 1.31 <i>P-value for omalizumab vs. control:</i> 3 months: $p < 0.05$ 6 months: $p < 0.01$ 9 months: $p < 0.01$ 12 months: $p < 0.001$ Activities: <i>Omalizumab:</i> 3 months: 1.16 6 months: 1.11 9 months: 1.09 12 months: 1.38 <i>Control:</i> 3 months: 0.66

				6 months: 0.45 9 months: 0.49 12 months: 0.29 <i>P-value for omalizumab vs. control:</i> 3 months: $p < 0.05$ 6 months: $p < 0.01$ 9 months: $p < 0.05$ 12 months: $p < 0.001$ Environmental stimuli: <i>Omalizumab:</i> 3 months: 0.80 6 months: 0.99 9 months: 1.03 12 months: 1.19 <i>Control:</i> 3 months: 0.42 6 months: 0.44 9 months: 0.11 12 months: -0.03 <i>P-value for omalizumab vs. control:</i> 3 months: NS, p -value NR 6 months: $p < 0.05$ 9 months: $p < 0.001$ 12 months: $p < 0.001$ Emotions: <i>Omalizumab:</i> 3 months: 1.02 6 months: 1.24 9 months: 1.32 12 months: 1.37 <i>Control:</i> 3 months: 0.36 6 months: 0.50 9 months: 0.29 12 months: 0.09 <i>P-value for omalizumab vs. control:</i> 3 months: NS, p -value NR 6 months: $p < 0.05$ 9 months: $p < 0.01$ 12 months: $p < 0.001$ Overall: <i>Omalizumab:</i>
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				3 months: 1.03 6 months: 1.14 9 months: 1.14 12 months: 1.32 <i>Control:</i> 3 months: 0.50 6 months: 0.48 9 months: 0.36 12 months: 0.17 <i>P-value for omalizumab vs. control:</i> 3 months: $p<0.05$ 6 months: $p<0.01$ 9 months: $p<0.001$ 12 months: $p<0.001$ <u>Change from baseline in mini AQLQ scores among omalizumab responders (R) compared with control group:</u> Symptoms: <i>Omalizumab:</i> 3 months: 1.5 6 months: 1.79 9 months: 1.59 12 months: 1.73 <i>Control:</i> 3 months: 0.48 6 months: 0.47 9 months: 0.39 12 months: 0.19 Activities: <i>Omalizumab:</i> 3 months: 1.53 6 months: 1.65 9 months: 1.54 12 months: 1.84 <i>Control:</i> 3 months: 0.66 6 months: 0.45 9 months: 0.49 12 months: 0.29 Environmental stimuli: <i>Omalizumab:</i> 3 months: 1.21
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				6 months: 1.64 9 months: 1.65 12 months: 1.65 <i>Control:</i> 3 months: 0.42 6 months: 0.44 9 months: 0.11 12 months: -0.03 Emotions: <i>Omalizumab:</i> 3 months: 1.69 6 months: 1.95 9 months: 1.97 12 months: 1.99 <i>Control:</i> 3 months: 0.36 6 months: 0.50 9 months: 0.29 12 months: 0.09 Overall: <i>Omalizumab:</i> 3 months: 1.49 6 months: 1.76 9 months: 1.67 12 months: 1.81 <i>Control:</i> 3 months: 0.50 6 months: 0.48 9 months: 0.36 12 months: 0.17 <u>Other HRQOL:</u> Asthma symptom score: <i>Omalizumab:</i> Baseline: 19.1 ± 10.2 1 year: 12.0 <i>Control:</i> Baseline: 17.5 ± 9.44 1 year: 17.1 Significant improvement with omalizumab, $p < 0.05$
International ³	Efficacy and safety of benralizumab for patients with severe asthma uncontrolled	RCT EX: Worsening of asthma that led to	Benralizumab (n=797) Benralizumab 30 mg Q4W	<u>EX rates:</u> Pre-tx: Previous year: PBO: 3.0 ± 1.8

	with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): A randomised, multicentre, placebo-controlled phase 3 trial	one of the following: (1) use of systemic corticosteroids, or temporary increase in a stable OCS background dosage, for ≥ 3 days or a single injectable dose of corticosteroids; (2) visit to an ED or urgent care center (< 24 h) because of asthma that needed OCS; or (3) inpatient hospital stay (≥ 24 h) because of asthma	(n=399) Benralizumab 30 mg Q8W (n=398) PBO (n=407)	Benralizumab 30 mg Q4W: 2.9 ± 1.8 Benralizumab 30 mg Q8W: 2.8 ± 1.5 Post-tx: Annual EX rate over 48 weeks: <i>Eosinophils</i> ≥ 300 cells/μL: PBO: 1.33 (1.12–1.58) Benralizumab 30 mg Q4W: 0.73 (0.60–0.89)* Benralizumab 30 mg Q8W: 0.65 (0.53–0.80)* <i>Eosinophils</i> < 300 cells/μL: PBO: 1.21 (0.96–1.52) Benralizumab 30 mg Q4W: 0.85 (0.65–1.11)* Benralizumab 30 mg Q8W: 1.00 (0.78–1.28) Annual asthma EX rate ratio vs. PBO: <i>Eosinophils</i> ≥ 300 cells/μL: Benralizumab 30 mg Q4W: 0.55 (0.42–0.71)* Benralizumab 30 mg Q8W: 0.49 (0.37–0.64)* <i>Eosinophils</i> < 300 cells/μL: Benralizumab 30 mg Q4W: 0.70 (0.50–1.00)* Benralizumab 30 mg Q8W: 0.83 (0.59–1.16) <u>AQLQ(S)+12 score:</u> LSM change: <i>Eosinophils</i> ≥ 300 cells/μL: PBO: 1.26 (180) Benralizumab 30 mg Q4W: 1.44 (192) Benralizumab 30 mg Q8W: 1.56 (187) LSM difference vs. PBO: <i>Eosinophils</i> ≥ 300 cells/μL: Benralizumab 30 mg Q4W: 0.18 (–0.02–0.37; $p=0.0811$) Benralizumab 30 mg Q8W: 0.30 (0.10–0.50; $p=0.0036$) <u>ACQ-6 score at Week 48:</u> LSM change: <i>Eosinophils</i> ≥ 300 cells/μL: PBO: –1.17 (186) Benralizumab 30 mg Q4W: –1.32 (198) benralizumab 30 mg Q8W: –1.46 (191) <i>Eosinophils</i> < 300 cells/μL: PPBO: –0.89 (97) Benralizumab 30 mg Q4W: –0.89 (89) Benralizumab 30 mg Q8W: –1.11 (94) LSM difference vs. PBO: <i>Eosinophils</i> ≥ 300 cells/μL:
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				Benralizumab 30 mg Q4W: -0.15 (-0.34–0.04; $p=0.1107$) Benralizumab 30 mg Q8W: -0.29 (-0.48–-0.10; $p=0.0028$) <i>Eosinophils</i> <300 cells/μL: Benralizumab 30 mg Q4W: 0.00 (-0.27–0.27; $p=0.9903$) Benralizumab 30 mg Q8W: -0.22 (-0.48–0.05; $p=0.1066$)
International ⁴	Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): A randomized, double-blind, placebo-controlled phase 3 trial	RCT EX: Worsening of asthma that led to one of the following: (1) use of OCS for 3 days or more or a temporary increase in a stable, background dosage of oral corticosteroids; (2) an ED or urgent care visit (<24 h) due to asthma that required OCS; or (3) an inpatient admission to the hospital (≥ 24 h) due to asthma	<u>Study population for EX:</u> Benralizumab (n=866) Benralizumab 30 mg Q4W (n=425) Benralizumab 30 mg Q8W (n=441) PBO (n=407) <u>Study population for AQLQ and ACQ:</u> Benralizumab 30 mg Q4W (n=241) Benralizumab 30 mg Q8W (n=239) PBO (n=248)	<u>EX rates:</u> Pre-tx: Number of EX in the past 12 months: PBO: 2.7 ± 1.6 Benralizumab 30 mg Q4W: 2.7 ± 1.9 Benralizumab 30 mg Q8W: 2.7 ± 1.4 Post-tx: Annual EX rate over 56 weeks: <i>Eosinophils</i> ≥ 300 cells/μL: PPBO: 0.93 (0.77–1.12) Benralizumab 30 mg Q4W: 0.60 (0.45–0.74)* Benralizumab 30 mg Q8W: 0.66 (0.54–0.82)* <i>Eosinophils</i> <300 cells/μL: PBO: 1.21 (0.96–1.52) Benralizumab 30 mg Q4W: 0.78 (0.59–1.02)* Benralizumab 30 mg Q8W: 0.73 (0.55–0.95)* Annual asthma EX rate ratio vs. PBO: <i>Eosinophils</i> ≥ 300 cells/μL: Benralizumab 30 mg Q4W: 0.64 (0.49–0.85)* Benralizumab 30 mg Q8W: 0.72 (0.54–0.95) <i>Eosinophils</i> <300 cells/μL: Benralizumab 30 mg Q4W: 0.64 (0.45–0.92)* Benralizumab 30 mg Q8W: 0.60 (0.42–0.86)* <u>AQLQ(S)+12 score:</u> LSM change: <i>Eosinophils</i> ≥ 300 cells/μL: PBO: 1.31 (191) Benralizumab 30 mg Q4W: 1.47 (186) Benralizumab 30 mg Q8W: 1.56 (180) LSM difference vs. PBO: <i>Eosinophils</i> ≥ 300 cells/μL: Benralizumab 30 mg Q4W: 0.18 (-0.04–0.37; $p=0.1194$) Benralizumab 30 mg Q8W: 0.24 (0.04–0.45; $p=0.0194$)

				<u>ACQ (mean, SD) score at Week 48:</u> LSM change: <i>Eosinophils</i> ≥ 300 cells/μL: PBO: -1.19 (197) Benralizumab 30 mg Q4W: -1.38 (192) Benralizumab 30 mg Q8W: -1.44 (185) <i>Eosinophils</i> < 300 cells/μL: PBO: -0.89 (92) Benralizumab 30 mg Q4W: -1.14 (88) Benralizumab 30 mg Q8W: -1.00 (83) LSM difference vs. PBO: <i>Eosinophils</i> ≥ 300 cells/μL: Benralizumab 30 mg Q4W: -0.19 (-0.38--0.01; $p=0.0425$) Benralizumab 30 mg Q8W: -0.25 (-0.44--0.07; $p=0.0082$) <i>Eosinophils</i> < 300 cells/μL: Benralizumab 30 mg Q4W: -0.24 (-0.51--0.03; $p=0.0776$) Benralizumab 30 mg Q8W: -0.10 (-0.37--0.16; $p=0.4488$)
International ⁵	Efficacy and safety of a CXCR2 antagonist, AZD5069, in patients with uncontrolled persistent asthma: A randomized, double-blind, placebo-controlled trial	RCT Severe EX: Worsening of asthma symptoms leading to 3 days or more of OCS treatment, a visit to the ED, or admission to the hospital for an asthma episode leading to treatment with systemic corticosteroids	AZD5069 5 mg (n=160) 15 mg (n=156) 45 mg (162) PBO (n=162)	<u>EX rates:</u> Pre-tx: Number of EX in previous year: Total: 2.15 ± 1.04 AZD5069 5 mg: 2.09 ± 1.11 AZD5069 15 mg: 2.13 ± 1.10 AZD5069 45 mg: 2.19 ± 0.96 PPBO: 2.16 ± 1.00 Post-tx: Number of mild to moderate EX: Total: 25 AZD5069 5 mg: 5 AZD5069 15 mg: 5 AZD5069 45 mg: 7 PPBO: 8 <u>Rate of severe EX (90% CI):</u> AZD5069 5 mg: 0.26 (0.16--0.42) AZD5069 15 mg: 0.31 (0.19--0.49) AZD5069 45 mg: 0.31 (0.20--0.50) PBO: 0.20 (0.12--0.33) % with EX: 3.9% (25/640) <u>AQLQ and ACQ-5:</u> There was no evidence of benefits with AZD5069

				compared with PBO for any HRQOL endpoints, including ACQ-5 score or AQLQ(S) score after 6 months of treatment
International ⁶	Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: A multi-center, open-label, phase IIIb study	Open-label extension	<u>Study population for EX:</u> All patients (n=651) Previous PBO group (n=237) Previous mepolizumab group (n=414) <u>Study population for ACQ:</u> All patients (n=338) Previous PBO group (n=142) Previous mepolizumab group (n=196)	<u>EX rates:</u> Pre-tx: NR Post-tx: Annual EX rate (95% CI): Total: 0.93 (0.83–1.04) Previous PBO group: 0.99 (0.83–1.18) Previous mepolizumab group: 0.90 (0.78–1.04) <u>ACQ-5 Week 60, mean (SD):</u> Total: 0.20 (1.13) Previous PBO group: 0.05 (1.19) Previous mepolizumab group: 0.31 (1.08)
International ⁷	Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting $\beta(2)$ agonist: A randomized double-blind placebo-controlled pivotal phase 2b dose-ranging trial	RCT Severe EX: Deterioration of asthma that required use of systemic corticosteroids for at least 3 days, hospital admission, or ED visit because of asthma treated with OCS	<u>Treatment group for EX:</u> Overall population (n=776) ≥ 300 eosinophils/ μ L (n=325) < 300 eosinophils/ μ L (n=451) <u>Treatment groups for AQLQ and ACQ:</u> PBO Dupilumab 200 mg/4 weeks Dupilumab 300 mg/4 weeks Dupilumab 200 mg/2 weeks Dupilumab 300 mg/2 weeks	Pre-tx: Mean number of asthma EX in past year, (SD) <u>EX rates:</u> Overall population (n=776): 2.17 (2.14)300 eosinophils/ μ L (n=325): 2.37 (2.34) < 300 eosinophils/ μ L: 2.02 (1.98) Adjusted annualized severe EX rate, estimate (95% CI) (percentage reduction relative to PBO): <i>Overall population (n=776): PBO (n=158): 0.897 90.619–1.3000:</i> 200 mg/4 weeks (n=91): 0.415 (0.260–0.664) (–54%) 300 mg/4 weeks (n=91): 0.599 (0.396–0.907) (–33%) 200 mg/2 weeks (n=84): 0.269 (0.157–0.461) (–70%) 300 mg/2 weeks (n=92): 0.265 (0.157–0.445) (–71%) ≥ 300 eosinophils/ μ L: <i>PBO (n=158): 1.044 (0.572–1.904):</i> 200 mg/4 weeks (n=91): 0.358 (0.158–0.809) (–66%) 300 mg/4 weeks (n=91): 0.678 (0.356–1.290) (–35%) 200 mg/2 weeks (n=84): 0.300 (0.133–0.678) (–71%)

				300 mg/2 weeks (n=92): 0.201 (0.078–0.517) (–81%) <300 eosinophils/μL: PBO (n=158): 0.779 (0.493–1.231): 200 mg/4 weeks (n=91): 0.445 (0.252–0.786) (–43%) 300 mg/4 weeks (n=91): 0.489 (0.286–0.837) (–37%) 200 mg/2 weeks (n=84): 0.253 (0.124–0.516) (–68%) 300 mg/2 weeks (n=92): 0.313 (0.170–0.576) (–60%) <u>LSM change in AQLQ global score from baseline to Week 24, (SD): PBO (n=127): 0.88 (0.09):</u> 200 mg/4 weeks (n=127): 1.12 (0.09) 300 mg/4 weeks (n=132): 1.18 (0.08) 200 mg/2 weeks (n=132): 1.20 (0.09) 300 mg/2 weeks (n=141): 1.24 (0.08) <u>P-value vs. PBO:</u> 200 mg/4 weeks: 0.0530 300 mg/4 weeks: 0.0120 200 mg/2 weeks: 0.0090 300 mg/2 weeks: 0.0027 ≥300 eosinophils/μL: <u>LSM change in AQLQ global score from baseline to Week 24, (SD): PBO (n=53): 0.79 (0.13):</u> 200 mg/4 weeks (n=50): 1.32 (0.14) 300 mg/4 weeks (n=57): 1.22 (0.13) 200 mg/2 weeks (n=58): 1.46 (0.13) 300 mg/2 weeks (n=56): 1.57 (0.13) <u>P-value vs. PBO:</u> 200 mg/4 weeks: 0.0054 300 mg/4 weeks: 0.0184 200 mg/2 weeks: 0.0003 300 mg/2 weeks: <0.0001 <300 eosinophils/μL: <u>LSM change in AQLQ global score from baseline to Week 24, (SD): PBO (n=74): 1.01 (0.11):</u> 200 mg/4 weeks (n=77): 1.05 (0.11) 300 mg/4 weeks (n=75): 1.20 (0.11) 200 mg/2 weeks (n=74): 1.06 (0.11) 300 mg/2 weeks (n=85): 1.07 (0.11)
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				<u>P-value vs. PBO:</u> 200 mg/4 weeks: 0.7703 300 mg/4 weeks: 0.2176 200 mg/2 weeks: 0.7400 300 mg/2 weeks: 0.6899 <i>LSM change in ACQ-5 score from baseline to Week 24, (SD): PBO (n=127): -1.14 (0.08):</i> 200 mg/4 weeks (n=126): -1.32 (0.08) 300 mg/4 weeks (n=132): -1.34 (0.08) 200 mg/2 weeks (n=134): -1.49 (0.08) 300 mg/2 weeks (n=145): -1.45 (0.08) <u>P-value vs. PBO:</u> 200 mg/4 weeks: 0.0992 300 mg/4 weeks: 0.0724 200 mg/2 weeks: 0.0015 300 mg/2 weeks: 0.0049 ≥300 eosinophils/μL (n=325): <i>LSM change in ACQ-5 score from baseline to Week 24. PBO (n=52): -1.17 (0.13):</i> 200 mg/4 weeks (n=50): -1.48 (0.13) 300 mg/4 weeks (n=57): -1.38 (0.12) 200 mg/2 weeks (n=59): -1.59 (0.12) 300 mg/2 weeks (n=58): -1.72 (0.13) <u>P-value vs. PBO:</u> 200 mg/4 weeks: 0.0878 300 mg/4 weeks: 0.2371 200 mg/2 weeks: 0.0171 300 mg/2 weeks: 0.0021 <300 eosinophils/μL (n=451): <i>LSM change in ACQ-5 score from baseline to Week 24. PBO (n=75): -1.13 (0.10):</i> 200 mg/4 weeks (n=76): -1.26 (0.10) 300 mg/4 weeks (n=75): -1.34 (0.10) 200 mg/2 weeks (n=75): -1.46 (0.10) 300 mg/2 weeks (n=87): -1.29 (0.10) <u>P-value vs. PBO:</u> 200 mg/4 weeks: 0.3505 300 mg/4 weeks: 0.1328 200 mg/2 weeks: 0.0201 300 mg/2 weeks: 0.2259
International ^g	Reslizumab for inadequately controlled asthma with elevated	2 RCTs	<u>Study 1:</u>	<u>EX rates:</u> Pre-tx: Mean number of CAEs in past 12 months

	blood eosinophil counts: Results from two multicentre, parallel, double-blind, randomized, placebo-controlled, phase 3 trials	Clinical asthma EX: Worsening of asthma that resulted in the use of OCS in patients not already receiving treatment, or fold twice the dosage of either ICS or OCS for ≥ 3 days, or the need for asthma-related emergency treatment (ED visit, hospital admission, or unscheduled physician's office visit for nebulizer or other urgent treatment). To be analyzed as an asthma EX, these medical interventions must have been associated with a decrease in FEV₁ of 20% or more from baseline, a reduction in PEF rate by 30% or more from baseline on 2 consecutive days, or a worsening of signs or symptoms (as identified by physician assessment)	PBO (n=243) Reslizumab (n=245) <u>Study 2:</u> PBO (n=232) Reslizumab (n=232)	(number per patient [SD]): <i>Study 1:</i> PBO: 2.1 (2.3); Reslizumab: 1.9 (1.6) <i>Study 2:</i> PBO: 2.0 (1.8); Reslizumab: 1.9 (1.6) Post-tx: Frequency of CAEs: <i>Patients with ≥ 1 CAE, n (%)</i>: <i>Study 1:</i> PBO: 132 (54%); Reslizumab: 92 (38%) <i>Study 2:</i> PBO: 105 (45%); Reslizumab: 59 (25%) <i>Pooled Data:</i> PBO: 237 (50%); Reslizumab: 151 (32%) Adjusted CAE rate (events per patient per year): <i>All episodes:</i> <i>Study 1:</i> PBO (n=244): 1.80; Reslizumab (n=245): 0.90* <i>Study 2:</i> PBO: 2.11; Reslizumab: 0.86* <i>Pooled data:</i> PBO: 1.81; Reslizumab: 0.84* <u>Change in AQLQ total score:</u> Week 16: <i>Study 1:</i> PBO (n=244): 0.87, Reslizumab (n=245): 1.03; $p=0.0143$ <i>Study 2:</i> PBO (n=232): 0.79, Reslizumab (n=232): 0.95; $p=0.0259$ <i>Pooled data:</i> PBO: 0.83, Reslizumab: 0.99, $p=0.0008$ Week 52: <i>Study 1:</i> PBO (n=244): 0.79, Reslizumab (n=245): 1.09, $p=0.0004$ <i>Study 2:</i> PBO (n=232): 0.89, Reslizumab (n=232): 1.12, $p=0.0052$ <i>Pooled data:</i> PBO: 0.81, Reslizumab: 1.08, $p<0.0001$ <u>ACQ: Change in ACQ-7 score:</u> Week 16: <i>Study 1:</i> PBO (n=244): -0.68; Reslizumab (n=245): -0.94; $p=0.0001$ <i>Study 2:</i> PBO (n=232): -0.66; Reslizumab (n=232): -0.86; $p=0.0032$ <i>Pooled data:</i> PBO: -0.67; Reslizumab: -0.91; $p<0.0001$ Week 52: <i>Study 1:</i> PBO (n=244): -0.76; Reslizumab (n=245): -1.02; $p=0.0002$ <i>Study 2:</i> PBO (n=232): -0.80; Reslizumab (n=232):
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				-1.04; $p=0.0003$ <i>Pooled data:</i> PBO: -0.77; Reslizumab: -1.02; $p<0.0001$ <u>Other outcomes:</u> ASUI: Week 16: Study 1: PBO (n=244): 0.11; Reslizumab (n=245): 0.17; $p<0.0001$ Study 2: PBO (n=232): 0.08; Reslizumab (n=232): 0.12; $p=0.0037$ <i>Pooled data:</i> PBO: 0.10; Reslizumab: 0.15; $p<0.0001$ Week 52: Study 1: PBO (n=244): 0.13; Reslizumab (n=245): 0.19; $p<0.0001$ Study 2: PBO (n=232): 0.11; Reslizumab (n=232): 0.15; $p=0.0011$ <i>Pooled data:</i> PBO: 0.12; Reslizumab: 0.17; $p<0.0001$
International ⁹	Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: A secondary analysis of the DREAM and MENSA studies	2 RCTs EX: Worsening of asthma that required the use of OCS, admission to the hospital, or an ED visit (or a combination of these occurrences)	DREAM (n=616) MENSA (n=569) Combined (n=1,185) DREAM: 75 mg, 250 mg, or 750 mg of intravenous mepolizumab or matched PBO at 4-week intervals MENSA: 75 mg intravenous mepolizumab, 100 mg subcutaneous dose, or matched PBO	<u>EX rates:</u> Pre-tx: NR Post-tx: EX rate/person/year ITT total: 1.91 PBO vs. 1.01 mepolizumab (47% reduction; RR 0.53, 95% CI 0.44–0.62, $p<0.0001$) Baseline blood eosinophil ≥ 150 cells/μL: 1.94 PBO vs. 0.92 mepolizumab (52% reduction, RR 0.48, 95% CI 0.39–0.58) Baseline blood eosinophil ≥ 300 cells/μL: 2.19 PBO vs. 0.89 mepolizumab (RR 0.41, 95% CI 0.33–0.51) Baseline blood eosinophil ≥ 400 cells/μL: 2.36 PBO vs. 0.81 mepolizumab (RR 0.34, 95% CI 0.27–0.44) ACQ-5 change in score (95% CI), n (%): ≥ 150 cells/μL: ITT: -0.35 (-0.49–-0.20); 803 (68%) DREAM: -0.14 (-0.36–0.08); 401 (65%) MENSA: -0.52 (-0.70–-0.34); 402 (71%) ≥ 300 cells/μL: ITT: -0.49 (-0.67–-0.31); 536 (45%) DREAM: -0.24 (-0.51–0.03); 262 (43%)

				MENSA: -0.73 (-0.95--0.50); 274 (48%) ≥ 500 cells/μL: ITT: -0.61 (-0.85--0.37); 315 (27%) DREAM: -0.44 (-0.83--0.06); 144 (23%) MENSA: -0.76 (-1.07--0.46); 171 (30%) <u>Other outcomes:</u> SGRQ SGRQ change in score (95% CI), n (%): ≥ 150 cells/μL: MENSA: -8.1 (-11.2--5.1); 420 (74%) ≥ 300 cells/μL: MENSA: -10.4 (-14.2--6.7); 288 (51%) ≥ 500 cells/μL: MENSA: -11.3 (-16.3--6.4); 179 (31%)
International ¹⁰	Phase 2, randomized placebo-controlled trial to evaluate the efficacy and safety of an anti-GM-CSF antibody (KB003) in patients with inadequately controlled asthma	RCT EX: One or more of the following criteria: (1) use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days to treat worsening of asthma symptoms; (2) hospitalization or ED, urgent care, or physician visit for asthma worsening, requiring systemic corticosteroids; or (3) in those participants taking OCS at study entry, at least twice the OCS dose for at least 3 consecutive days. Courses of OCS separated by 7 days or more were treated as separate EX	KB003 400 mg PBO	<u>EX rates:</u> Pre-tx: NR Post-tx: There were no differences in mean cumulative asthma EX by visit over 24 weeks in the KB003 and PBO groups in the full analysis set and evaluable set. No differences with PBO in asthma EX rates over 24 weeks (KB003=0.398 vs. PBO=0.349) <u>ACQ:</u> No drug effect was observed for ACQ-5 scores
International ¹¹	Effect of anti-IL-13 treatment on airway dimensions in severe asthma	RCT EX: An increase in asthma symptoms resulting in use or increased dosage of OCS for 3 or more consecutive days	Tralokinumab (every 2 weeks) (n=150) Tralokinumab (every 4 weeks) (n=151) PBO (n=151)	<u>EX rates:</u> Pre-tx: EX in the past year, n (%): Year 1: PBO: 0; tralokinumab every 2 weeks: 1 (1%); tralokinumab every 4 weeks: 0 Year 2: PBO: 46 (61%); tralokinumab every 2 weeks: 96 (64%); tralokinumab every 4 weeks: 51 (68%) Year 3: PBO: 22 (29%); tralokinumab every 2 weeks: 32 (21%); tralokinumab every 4 weeks: 14 (19%) Year 4: PBO: 3 (4%); tralokinumab every 2 weeks: 11 (7%); tralokinumab every 4 weeks: 5 (7%)

				Year 5: PBO: 1 (1%); tralokinumab every 2 weeks: 5 (3%); tralokinumab every 4 weeks: 4 (5%) Year 6: PBO: 4 (5%); tralokinumab every 2 weeks: 5 (3%); tralokinumab every 4 weeks: 1 (1%) Post-tx annual asthma EX rates at Week 52, per patient per year (95% CI): PBO: 0.90 (0.75–1.08) Tralokinumab every 2 weeks: 0.91 (0.76–1.08) Tralokinumab every 4 weeks: 0.97, (0.81–1.14) % changes in annual asthma EX rate at 52 weeks: Tralokinumab every 2 weeks vs. PBO 6% [95% CI –31–33; $p=0.709$] Tralokinumab every 4 weeks vs. –PBO 2% [–46–29; $p=0.904$] EX rate at 52 weeks in patients who were reversible at baseline and not receiving long-term OCS, % reduction vs. PBO (95% CI; p-value): All: 44% (–22–74; 0.147) DPP-4-high group: 57% (–30–86; 0.134) DPP-4-low group: –7% (–88–88; 0.950) Periostin-high group: 67% (2–89; 0.046) Periostin-low group: –32% (–273–53; 0.597) <u>AQLQ(S):</u> Mean change from baseline (95% CI): PBO: 0.70 (0.50–0.91) Tralokinumab every 2 weeks: 0.91 (0.70–1.12) Tralokinumab every 4 weeks: 0.90 (0.69–1.11) Difference from PBO (95% CI; p-value): Tralokinumab every 2 weeks vs. PBO: 0.21 (–0.05–0.46; 0.110) Tralokinumab every 4 weeks vs. PBO: 0.20 (–0.06–0.46; 0.132) AQLQ(S) at 52 weeks in patients who were reversible at baseline and not receiving long-term oral corticosteroids, mean change from baseline (95% CI; p-value) All: 0.70 (0.12–1.28; 0.019) DPP-4-high group: 1.26 (0.48–2.04; 0.002) DPP-4-low group: 0.24 (–0.87–1.35; 0.663) Periostin-high group: 0.64 (–0.11–1.39; 0.095) Periostin-low group: 0.71 (–0.23–1.65; 0.138) <u>ACQ:</u>
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				Mean change from baseline (95% CI): P: -BO: 0.65 (-0.84--0.47) Tralokinumab every 2 weeks: -0.84 (-1.03--0.65) Tralokinumab every 4 weeks: -0.78 (-0.97--0.59) Difference from PBO (95% CI; <i>p</i>-value): Tralokinumab every 2 weeks vs. : -PBO: 0.19 (-0.43-0.06; 0.131) Tralokinumab every 4 weeks vs. : -PBO: 0.13 (-0.37-0.12; 0.306) ACQ-6 at 52 weeks in patients who were reversible at baseline and not receiving long-term oral corticosteroids, mean change from baseline (95% CI; <i>p</i>-value): All: 0.55 (-1.07--0.04; 0.036) DPP-4-high group: -0.89 (-1.63--0.14; 0.020) DPP-4-low group: -0.43 (-1.41-0.56; 0.390) Periostin-high group: -0.68 (-1.31--0.06; 0.033) Periostin-low group: -0.23 (-1.10-0.64; 0.596)
International ¹²	Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, vs. placebo for uncontrolled eosinophilic asthma: A phase 2b randomized dose-ranging study	RCT EX: An increase in asthma symptoms that did not resolve after rescue medication and needed treatment with OCS for ≥ 3 days	<u>Eosinophilic phenotype:</u> PBO (n=80) Benralizumab 2 mg (n=81) Benralizumab 20 mg (n=81) Benralizumab 100 mg (n=82) <u>Noneosinophilic phenotype:</u> PBO (n=142) Benralizumab 100 mg (n=140)	Pre-tx EX rates in past year, mean (SD): <u>Eosinophilic phenotype:</u> PBO (n=80): 2.2 (0.5) Benralizumab 2 mg (n=81): 2.3 (0.7) Benralizumab 20 mg (n=81): 2.5 (0.7) Benralizumab 100 mg (n=82): 2.3 (0.6) <u>Noneosinophilic phenotype:</u> PBO (n=142): 2.2 (0.5) Benralizumab 100 mg (n=140): 2.3 (0.7) <u>Post annual EX rate (SD):</u> <u>Eosinophilic phenotype:</u> PBO (n=80): 0.57 (0.75) Benralizumab 2 mg (n=81): 0.65 (0.81) Rate reduction compared with PBO (80% CI): -9% (-59-26) <i>P</i>-value for comparison with PBO: 0.781 Benralizumab 20 mg (n=81): 0.37 (0.61) Rate reduction compared with PBO (80% CI): 36% (3-58) <i>P</i>-value for comparison with PBO: 0.173 Benralizumab 100 mg (n=82): 0.34 (0.58) Rate reduction compared with PBO (80% CI): 41% (11-60) <i>P</i>-value for comparison with PBO: 0.096

				Noneosinophilic phenotype: PBO (n=142): 0.56 (0.75) Benralizumab 100 mg (n=140): 0.43 (0.66) Rate reduction compared with PBO (80% CI): 22% (-5–42) P-value for comparison with PBO: 0.284 <u>ACQ-6:</u> Eosinophilic phenotype: PBO (n=34), (SD): Change from baseline: -0.89 (1.20) Treatment difference (80% CI): -- P-value for comparison with compliance: -- <i>Benralizumab 2 mg (n=42):</i> Change from baseline: -1.10 (1.12) Treatment difference (80% CI): -0.36 (-0.65–-0.06) P-value for comparison with compliance: 0.125 <i>Benralizumab 20 mg (n=40):</i> Change from baseline: -1.25 (1.22) Treatment difference (80% CI): -0.45 (-0.77–-0.13) P-value for comparison with compliance: 0.074 <i>Benralizumab 100 mg (n=39):</i> Change from baseline: -1.12 (1.29) Treatment difference (80% CI): -0.47 (-0.79–-0.16) P-value for comparison with compliance: 0.057 Noneosinophilic phenotype: PBO (n=64): Change from baseline: -0.82 (1.11) Treatment difference (80% CI): -- P-value for comparison with compliance: -- <i>Benralizumab 100 mg (n=73):</i> Change from baseline: -1.13 (1.05) Treatment difference (80% CI): -0.34 (-0.57–-0.12) P-value for comparison with compliance: 0.053
International ¹³	Efficacy and safety of an anti-IL-13 mAb in patients with severe asthma: A randomized trial	RCT EX: Worsening of asthma symptoms requiring an ED visit, hospitalization, and/or an increased OCS dose	GSK679586 (humanized IgG1-type mAb that specifically binds and neutralizes IL-13) (n=99) PBO (n=99)	Asthma EX reported with similar frequency by patients receiving GSK679586 (14 events in 11 patients) and PBO (16 events in 13 patients) ACQ: Both treatment groups demonstrated a decrease

				(improvement) in ACQ-7 scores over 12 weeks of treatment (adjusted LSM values of 20.31 and 20.17 for GSK679586 and PBO, respectively). The estimated treatment difference of 20.14 (95% CI, 20.28–0.00) was not statistically significant ($p=5.058$) or clinically meaningful
International ¹⁴	Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma	RCT EX: Worsening of asthma requiring treatment with rescue OCS Severe EX: Clinically significant EX with one or more of the following: (a) hospital admission and/or intubation; (b) an ED visit; (c) breathlessness at rest or PEF or FEV ₁ <60% of predicted/personal best; or (d) a >30% fall from personal best PEF on 2 successive days	Omalizumab (n=272)	Omalizumab <u>EX rates, mean (SD)</u> Previous year: $2.7 \pm 1.55^*$ Post-tx: 0.55, * 0.24 (severe);* 5.5% (EX reported as an AE) Severe: NR <u>ACQ, mean (SD):</u> Baseline: NR LSM change at 16 weeks: -0.78 ± 0.074 LSM change at 32 weeks: -0.91 ± 0.081 Significant improvement omalizumab vs. OAT, $p<0.001$
			OAT	<u>EX rates, man (SD):</u> Previous year: 3.3 ± 1.82 (n=128) Post-tx: 0.98, 0.42 (severe); 10.9% (EX reported as an AE) Severe: NR <u>ACQ (n=128, mean (SD):</u> Baseline: NR LSM change at 16 weeks: -0.11 ± 0.104 LSM change at 32 weeks: -0.04 ± 0.110 <u>OCS maintained/increased:</u> $+0.16 \pm 0.95$ (n=16)
			Omalizumab/OAT	Change from baseline to 32 weeks (n=37): OCS stopped/reduced: -0.96 ± 1.11 OCS maintained/increased (n=22): 0.65 ± 1.24
			OAT (n=7)	Change from baseline to 32 weeks: OCS stopped/reduced: $+0.54 \pm 0.59$

International ¹⁵	Omalizumab in severe allergic (IgE-mediated) asthma patients	RCT EX: Worsening of asthma requiring treatment with rescue OCS Severe EX: Clinically significant EX with one or more of the following: (a) hospital admission and/or intubation; (b) an ED visit; (c) breathlessness at rest or PEF or FEV ₁ <60% of predicted/ personal best; or (d) a >30% fall from personal best PEF on 2 successive days	Omalizumab (n=272)	Omalizumab <u>EX rates, mean (SD):</u> Previous year: 2.7 ± 1.55* Post: 0.55,* 0.24 (severe);* 5.5% (EX reported as an AE) Severe: NR
			OAT (n=128)	Omalizumab <u>EX rates, mean (SD):</u> Previous year: 3.3 ± 1.82 Post-tx: 0.98, 0.42 (severe); 10.9% (EX reported as an AE) Severe: NR
International ¹⁶	Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE	RCT EX (clinically significant): Worsening of asthma symptoms requiring treatment with OCS Severe EX: PEF or FEV ₁ <60% of personal best, requiring treatment with OCS	Omalizumab (n=209) PBO (n=210)	<u>EX rates, mean (SD):</u> Omalizumab: Previous 14 months: 2.41 ± 1.09 Post-tx: 0.68*, severe: 0.24* % with severe EX: 16.8% PBO, mean (SD): Previous 14 months: 2.64 ± 1.56 Post-tx: 0.91, severe: 0.48 % with severe EX: 26.2% <u>AQLQ (mean, SD):</u> Omalizumab: Baseline: 3.9 ± 1.05 <i>Change from baseline to Week 28 or discontinuation:</i> Activities domain: 0.91 Emotional domain: 0.95 Symptoms domain: 0.90 Exposure domain: 0.89 Overall HRQOL:0.91 <i>Proportion of patients with improvement from baseline:</i> ≥0.5: 60.8% ≥1.0: 45.1% ≥1.5: 27.5% <i>P-value for AQLQ (vs. PBO):</i> Activities: p<0.001 Emotional: p=0.002 Symptoms: p<0.001 Exposure: p<0.001 Overall: p<0.001 vs. ≥0.5; p=0.008 vs. ≥1.0; p<0.001 vs. ≥1.15; p=0.011 vs. PBO: Baseline: 3.9 ± 1.12

				<i>Change from baseline to Week 28 or discontinuation:</i> Activities domain: 0.46 Emotional domain: 0.57 Symptoms domain: 0.40 Exposure domain: 0.44 Overall HRQOL: 0.46 <i>Percentage of patients with improvement from baseline:</i> ≥ 0.5: 47.8% ≥ 1.0: 24.9% ≥ 1.5: 17.1% Patient-evaluated GETE: <i>Omalizumab proportion of patients:</i> Excellent/good: 64.3% Moderate: 24.5% Worse/poor: 11.2% <i>PBO percentage of patients:</i> Excellent/good: 43.3% Moderate: 30.8% Worse/poor: 25.9% $p < 0.001$ overall for omalizumab vs. PBO
International ¹⁷	Characterization of a severe asthma patient population with and without eosinophilic inflammation and frequent exacerbations by multiple PROs (IDEAL)	Post-hoc analysis of a cross-sectional, noninterventional study (IDEAL: patients ≥ 12 years old with SA treated with high-dosage ICS plus additional controller[s] for ≥ 12 months)	Mepolizumab	<u>AQLQ (mean, SD):</u> Mepolizumab eligible: 4.1 (1.2) Non-mepolizumab eligible: 4.7 (1.3) <u>Other outcomes</u> SGRQ: Mepolizumab eligible: 53.2 (19.4) Non-mepolizumab eligible: 39.7 (19.4) ASUI: Mepolizumab eligible: 0.55 (0.25) Non-mepolizumab eligible: 0.71 (0.21)
International ¹⁸	Add-on omalizumab improves day-to-day symptoms in inadequately controlled severe persistent allergic asthma	RCT EX (clinically significant): Worsening of asthma symptoms requiring treatment with OCS	Omalizumab (n=209) PBO (n=210)	<u>EX rates:</u> Omalizumab: Previous 14 months: 2.41 ± 1.09 Post-tx: 0.68,* severe: 0.24* % with severe EX: 16.8% PBO: Previous 14 months: 2.64 ± 1.56 Post-tx: 0.91, severe: 0.48 % with severe EX: 26.2%
International ¹⁹	Relationship between pretreatment specific IgE and the response to omalizumab therapy	Severe EX: PEF or FEV ₁ <60% of personal best, requiring treatment with OCS		
International ²⁰	The beneficial effects of Xolair (omalizumab) as add-on			

	therapy in patients with severe persistent asthma who are inadequately controlled despite best available treatment (GINA 2002 step IV)—the Israeli arm of the INNOVATE study			
International ²¹ PrimoTinA-asthma 1 and PrimoTinA-asthma 2	Tiotropium in asthma poorly controlled with standard combination therapy	RCT Severe EX: A deterioration of asthma necessitating initiation or at least twice the dosage of OCS for ≥3 days	Tiotropium trial 1 (n=237) Tiotropium trial 2 (n=219) PBO trial 1 (n=222) PBO trial 2 (n=234)	<u>EX rates:</u> Tiotropium trial 1: Previous year: <3: 84.8% 3–5: 11.4% >5: 3.8% <i>Post-tx: Trial 1 and trial 2 pooled per patient year</i> Severe: 0.53 Tiotropium trial 2: Previous year: <3: 81.7% 3–5: 13.7% >5: 4.6% <i>Post-tx: Trial 1 and trial 2 pooled per patient year</i> Severe: 0.53 PBO trial 1: Previous year: <3: 83.3% 3–5: 12.2% >5: 4.5% <i>Post-tx: Trial 1 and trial 2 pooled per patient year</i> Severe: 0.66 <i>% with EX: Trial 1 and trial 2 pooled</i> Severe: 26.9%* PBO trial 2: Previous year: <3: 73.9% 3–5: 18.8% >5: 7.3% <i>Post-tx: Trial 1 and trial 2 pooled per patient year</i> Severe: 0.66 <i>% with EX: Trial 1 and trial 2 pooled</i> Severe: 32.8%* <u>AQLQ (mean ± SD):</u> Baseline tiotropium: Trial 1: 4.6 ± 1.1 Trial 2: 4.6 ± 1.0 Baseline pPBO: Trial 1: 4.6 ± 1.1

				Trial 2: 4.7 ± 1.1 Difference between tiotropium and PBO at 24 weeks: Trial 1: 0.04 units Trial 2: 0.18 units <u>P-value</u> Trial 1: NS, $p=NR$ Trial 2: $p=0.02$ <u>ACQ:</u> Baseline tiotropium: Trial 1: 2.7 ± 0.7 Trial 2: 2.6 ± 0.7 PBO: Trial 1: 2.7 ± 0.7 Trial 2: 2.6 ± 0.7 Difference between tiotropium and PBO at 24 weeks: Trial 1: -0.13 Trial 2: -0.2 Trial 1: $p=0.06$ Trial 2: $p=0.003$
International ²²	Tiotropium as add-on therapy to ICS plus LABA in patients with symptomatic severe asthma	Severe EX: A deterioration of asthma necessitating initiation or at least twice the dosage of OCS for ≥ 3 days	Tiotropium trial 1 (n=237) Tiotropium trial 2 (n=219) PBO trial 1 (n=222) PBO trial 2 (n=234)	<u>EX rates:</u> Tiotropium trial 1: Previous year: <3: 84.8% 3–5: 11.4% >5: 3.8% Tiotropium trial 2: Previous year: <3: 81.7% 3–5: 13.7% >5: 4.6% <i>Post-tx: Trial 1 and trial 2 pooled per patient year</i> Severe: 0.53 PBO trial 1: Previous year: <3: 83.3% 3–5: 12.2% >5: 4.5% <i>% with EX: Trial 1 and trial 2 pooled</i> Severe: 26.9%* PBO trial 2: Previous year: <3: 73.9% 3–5: 18.8% >5: 7.3%
International ²³	Once-daily tiotropium respimat [®] improves lung function in patients with severe symptomatic asthma independent of leukotriene modifier use			
International ²⁴	Improvements in lung function with tiotropium as add-on controller therapy to ICS+LABA for patients with symptomatic severe asthma			
International ²⁵	Tiotropium is effective in patients with severe asthma without evidence of chronic obstructive pulmonary disease			

International ²⁶	Once-daily tiotropium as add-on to ICS + LABA for patients with severe symptomatic asthma: Baseline characteristics in Japanese patients			<i>Post-tx: Trial 1 and Trial 2 pooled per patient year</i> Severe: 0.66 <i>% with EX: Trial 1 and trial 2 pooled</i> Severe: 32.8%*
International ²⁷	Mepolizumab for severe eosinophilic asthma (DREAM): A multicentre, double-blind, placebo-controlled trial	RCT EX (clinically significant): Worsening of asthma requiring use of OCS or at least double the existing maintenance dose for ≥3 days, hospital admission, or a visit to the ED. EX were corroborated by decreased PEF, 50% increase in rescue medication on at least 2 of 3 successive days, increased frequency of night-time awakening because of asthma for at least 2 of 3 successive nights, or overall asthma symptom score of 5 (on a scale of 1 to 5) for at least 2 of 3 successive days	Mepolizumab 75 mg (n=153) Mepolizumab 250 mg (n=152) Mepolizumab 750 mg (n=156) PBO (n=155)	<u>EX rates:</u> <i>Mepolizumab 75 mg:</i> Previous year, severe: 3.7 ± 3.1; Post-tx: clinically significant: 1.24 (0.12),* requiring admission or ED: 0.17 (0.30), requiring admission: 0.11 (0.35) [^] <i>Mepolizumab 250 mg:</i> Previous year, severe: 3.4 ± 2.4; Post-tx: clinically significant: 1.46 (0.11),* requiring admission or ED: 0.25 (0.26), requiring admission: 0.12 (0.32) <i>Mepolizumab 750 mg:</i> Previous year, severe: 3.5 ± 2.8; Post-tx: clinically significant: 1.15 (0.12),* requiring admission or ED: 0.22 (0.26), requiring admission: 0.07 (0.39) <i>PBO:</i> Previous year, severe: 3.7 ± 3.8; Post-tx: clinically significant: 2.40 (0.11), requiring admission or ED: 0.43 (0.24), requiring admission: 0.18 (0.29) <u>AQLQ (mean ± SD):</u> <i>Mepolizumab 75 mg:</i> Baseline: 4.2 ± 1.2; Change at 52 weeks: 0.80 ± 0.09; Difference from PBO: 0.08 (−0.16–0.32) <i>Mepolizumab 250 mg:</i> Baseline: 4.2 ± 1.2; Change at 52 weeks: 0.77 ± 0.09; Difference from PBO: 0.05 (−0.19–0.29) <i>Mepolizumab 750 mg:</i> Baseline: 4.2 ± 1.2; 52 weeks: 0.93 ± 0.09; Difference from PBO: 0.22 (−0.02–0.46) <i>PBO:</i> Baseline: 4.1 ± 1.2; 52 weeks: 0.71 ± 0.09 <u>CQ (mean, SD):</u> <i>MMepolizumab 75 mg</i> Baseline: 2.2 ± 1.1; 52 weeks: −0.75 ± 0.09 Difference from PBO: −0.16 (−0.39–0.07) <i>Mepolizumab 250 mg</i> Baseline: 2.4 ± 1.1; 52 weeks: −0.87 ± 0.09 Difference from PBO: −0.27 (−0.51–0.04) <i>Mepolizumab 750 mg</i> Baseline: 2.3 ± 1.2; 52 weeks: −0.80 ± 0.09 Difference

				from PBO: -20 (-0.42-0.03) PBO Baseline: 2.5 ± 1.1; 52 weeks: -0.59 ± 0.09
International ²⁸	The correlation between asthma control and health status: The GOAL study	RCT	SFC (n=359) FP (n=360)	<u>AQLQ (mean ± SD):</u> Baseline: Overall: SFC: 4.5 ± 1.05, FP: 4.5 ± 1.05 Activity limitation: SFC: 4.5 ± 1.11, FP: 4.5 ± 1.13 Symptom: SFC: 4.5 ± 1.09, FP: 4.5 ± 1.09 Emotional function: SFC: 4.6 ± 1.44, FP: 4.7 ± 1.45 Environmental stimuli: SFC: 4.4 ± 1.41, FP: 4.4 ± 1.45 Change in AQLQ at 52 weeks: ≤1.5: SFC: 42%, FP: 32% ≤1.0-<1.5: SFC: 18%, FP: 17% ≤0.5-<1.0: SFC: 18%, FP: 23% >0-<0.5: SFC: 12%, FP: 17% ≤0: SFC: 11%, FP: 12%
International ²⁹	Blood eosinophil count is a useful biomarker to identify patients with severe eosinophilic asthma	RCT EX (clinically significant): Worsening of asthma requiring use of OCS or at least double the existing maintenance dose for ≥3 days, hospital admission, or a visit to the ED. EX were corroborated by decreased PEF, 50% increase in rescue medication on at least 2 of 3 successive days, increased frequency of night-time awakening because of asthma for at least 2 of 3 successive nights, or overall asthma symptom score of 5 (on a scale of 1 to 5) for at least 2 of 3 successive days	Mepolizumab 75 mg (n=153) Mepolizumab 250 mg (n=152) Mepolizumab 750 mg (n=156) PBO (n=155)	<u>EX rates:</u> <i>Mepolizumab 75 mg:</i> Previous year, severe: 3.7 ± 3.1; Post-tx: clinically significant: 1.24 (0.12),* requiring admission or ED: 0.17 (0.30)^, requiring admission: 0.11 (0.35)^ <i>Mepolizumab 250 mg:</i> Previous year, severe: 3.4 ± 2.4 Post-tx: clinically significant: 1.46 (0.11),* requiring admission or ED: 0.25 (0.26), requiring admission: 0.12 (0.32)^ <i>Mepolizumab 750 mg:</i> Previous year, severe: 3.5 ± 2.8 Post-tx: clinically significant: 1.15 (0.12),* requiring admission or ED: 0.22 (0.26), requiring admission: 0.07 (0.39) <i>PBO:</i> Previous year, severe: 3.7 ± 3.8; Post-tx: clinically significant: 2.40 (0.11), requiring admission or ED: 0.43 (0.24), requiring admission: 0.18 (0.29)
International ³⁰	A randomized, double-blind, placebo-controlled study of tumor necrosis factor-alpha blockade in severe persistent asthma	RCT Mild EX: A >20% decrease in morning PEF, >3 additional inhalations of rescue medication/24 hours on 2 consecutive days compared with baseline, or an increase in night-time awakenings because of asthma on 2 consecutive	Golimumab 50 mg (n=77) Golimumab 100 mg (n=76) Golimumab 200 mg (n=78) PBO (n=78)	<u>Post-tx EX rates:</u> Golimumab combined 100 and 200 mg: 0.5 ± 0.97 PBO: 0.5 ± 1.07 <u>% with EX:</u> Golimumab 50 mg: severe: 31.2% Golimumab combined 100 and 200 mg: severe: 19.7% Golimumab 200 mg: severe: 24.4% PBO: severe: 32.1%

		nights compared with baseline Severe EX: An episode of worsening asthma requiring treatment with IV or oral steroids		<u>AQLQ (mean ±SD):</u> Baseline: Golimumab 50 mg: 4.0 ± 1.1 Golimumab 100 mg: 4.0 ± 1.2 Golimumab 200 mg: 4.4 ± 1.0 Baseline: 4.3 ± 1.2 76 weeks: Golimumab 100 mg & 200 mg: 0.71 ± 1.02 PBO: 0.54 ± 0.91 p-value: NR <u>ACQ (mean, SD):</u> Baseline: Golimumab 50 mg: 3.0± 0.8 Golimumab 100 mg: 3.1± 0.8 Golimumab 200 mg: 2.9 ± 0.7 24 weeks for the combined 100 mg & 200 mg group: -0.83 ± 0.94 PBO: Baseline: 3.0 ± 0.8 24 weeks: -0.76 ± 0.89 <u>Other outcomes:</u> Baseline data: NR Change in SF-36 component summary scores: Physical: 100 mg and 200 mg: 4.14 ± 8.19 PBO: 3.16 ± 8.13 Mental: 100 mg and 200 mg: 1.18 ± 9.19 PBO: 0.31 ± 8.76
International ³¹	Tiotropium improves lung function, exacerbation rate, and asthma control, independent of baseline characteristics including age, degree of airway obstruction, and allergic status	2 RCTs	Tiotropium 5 g (n=456) PBO (n=456) Total (N=912)	<u>AQLQ:</u> An analysis of AQLQ responder rate data showed numerically greater but nonsignificant improvements with tiotropium 5 mg vs. PBO, with a numerically greater improvement also observed at Week 48 (OR: 1.20; 95% CI: 0.92–1.57; p=0.19) compared with Week 24 (OR: 1.12; 95% CI: 0.85–1.47; p=0.44) <u>ACQ (mean, SD):</u> At Week 24, 53.9% of patients who received tiotropium 5 mg were responders compared with 46.9% of patients who received PBO (OR: 1.32; 95% CI: 1.01–1.73; p=0.04). The difference in responder rate

				between tiotropium 5 mg and PBO increased at Week 48 (OR: 1.68; 95% CI: 1.28–2.21; $p<0.001$). The improvements in ACQ-7 responder rate with tiotropium 5 mg compared with PBO were not significantly influenced by patients' baseline characteristics, except for smoking status and FEV ₁ % predicted at Week 24 screening and blood eosinophils at Week 48
International ³²	Ciclesonide reduces the need for oral steroid use in adult patients with severe, persistent asthma	RCT Compliance rate was calculated from the daily diary recordings at the end of the trial	Ciclesonide 320 µg (n=47) Ciclesonide 640 µg (n=49) PBO (n=45)	FEV ₁ : Trend toward increase, no statistically significant changes from baseline to 12 weeks, specific values NR; NS vs. baseline, specific value NR $p=0.0237$ vs. PBO More than 93% of patients in each treatment group had a compliance rate of 90% with the trial medication
International ³³ Meeting abstract	Reduction in oral corticosteroid use in patients with severe allergic (IgE-mediated) asthma receiving omalizumab in a real-world setting	Prospective cohort study Time point for follow up: 12 months, 24 months	Omalizumab (n=916) (n=734 at 12 months) (n=643 at 24 months)	Mean baseline OCS use (mg/day): 15.49 (SD: 14.01) Follow-up OCS use (mg/day): 12 months: 7.68 (SD: 10.94) 24 months: 5.77 (SD: 8.89)
International ³⁴ Meeting abstract	Efficacy and safety of lebrikizumab in severe uncontrolled asthma: Results from the lute and verse phase II randomized, double-blind, placebo-controlled trials	RCT	Lebrikizumab 37.5 mg (n=117) Lebrikizumab 125 mg (n=112) Lebrikizumab 250 mg (n=118) PBO (n=116)	Reduction in EX rate compared with PBO: Lebrikizumab 37.5 mg: 62% Lebrikizumab 125 mg: 35% Lebrikizumab 250 mg: 11%
International ³⁵	Healthcare Resource utilization in patients receiving omalizumab for allergic asthma in a real-world setting	Observational registry (24 months)	Omalizumab	Prior hospitalizations in previous year: Pre-treatment (n=882): 34% Prior ED visits reported at baseline: At least one pretreatment (n=867): 50.7%
United States ³⁶	Estimated prevalence and economic burden of severe, uncontrolled asthma in the United States	Peer-reviewed publications, U.S. National Center for Health Statistics and Centers for Disease Control and Prevention, American Thoracic Society, and World Health Organization		5–10% of Americans experience SA, and about half of those have uncontrolled asthma Annual direct costs of asthma are \$56 billion; half of these costs (\$28 billion) are incurred by patients with SA and 37.5% (\$21 billion) by patients with SUA
United States ³⁷	Omalizumab for the treatment of severe persistent allergic asthma: A systematic review and economic evaluation	Systematic review of the literature	Omalizumab	Omalizumab significantly reduced the incidence of EX in both adults and children (adults: INvestigationN of Omalizumab in seVere Asthma Trial [INNOVATE]; RR 0.74; 95% CI 0.55–1.00; children IA-05 EUP [the

				priori subgroup of patients who met the European Medicines Agency license criteria]], RR 0.66; 95% CI 0.44–1.00) Omalizumab: the ICER for adults and adolescents is £83,822 per QALY gained, whereas the ICER for children is £78,009 per QALY gained
United Kingdom ³⁸	Real-life effectiveness of omalizumab in reducing healthcare utilization in patients with severe allergic (IE-mediated) asthma at a single UK hospital	Prospective cohort study	Severe allergic patients receiving omalizumab therapy at Bradford Royal Infirmary (n=25)	24.15 (96.0%) patients responded to omalizumab therapy at 16 weeks. Prior to omalizumab therapy, 29.2% of patients were admitted to an ICU a total of 12-times; this reduced to 4.2% of patients admitted to an ICU on one occasion post-treatment, a 91.7% reduction in ICU admissions with omalizumab
United States ³⁹	Prevalence of obstructive sleep apnea-hypopnea in severe vs. moderate asthma	Observational	Complete overnight polysomnography performed in: Severe asthma (n=26) Moderate asthma (n=26) Control (n=26) Flow rates and Juniper asthma control and quality of life questionnaires also obtained	Obstructive sleep apnea-hypopnea, defined as ≥ 1 event/hour using Chicago apnea-hypopnea criteria, was present in 88% of patients with SA, 58% of patients with moderate asthma, and 31% of control patients ($p < 0.001$) Of patients with asthma, no significant correlations were identified between the severity of sleep-disordered breathing and asthma severity of control measures (FEV₁, Juniper scores)
United States ⁴⁰	Insurance status and asthma-related health care utilization in patients with severe asthma	Subset analysis of the prospective cohort study TENOR study (n=1,315 of 4,755) Control assessed by patient self-assessment of asthma control in the previous 4 weeks	Subset of adult patients from the TENOR study cohort with physician-evaluated severe asthma (patients with severe or difficult to treat asthma recruited from diverse health care settings including pulmonary and allergy practices)	<u>Incidence of SUA in SA patient population:</u> Medicaid: 47.7% (62/130) Non-Medicaid: 34.9% (414/1,185) <u>Other outcomes:</u> Higher ATAQ scores (OR 95% CI; range) Medicaid vs. non-Medicaid: 1.67 (1.17–2.40) Age, per 10-year increase: 0.73 (0.68–0.80) Female vs. male: 2.01 (1.61–2.50) Race other than white vs. white: 1.20 (0.94–1.53) BMI >30 vs. ≤ 30: 1.47 (1.21–1.80) Lower vs. higher education level: 1.10 (0.87–1.38) Current smoker vs. nonsmoker: 1.85 (1.12–3.06)
United States ⁴¹	Care of asthma patients in relation to guidelines	Database analysis Ingenix i3 LabRx database claims of 8–10 million covered lives Control assessed by EPR-3	Patients 12–64 years old with evidence of uncontrolled asthma identified between April 1, 2005, and March 31, 2006, based on ICD-9 code 493 in any setting (n=580,955 patients with asthma)	Incidence of SUA in asthma patient population: 1.06% (5,478/580,955) <u>Incidence of SUA in uncontrolled asthma patient population:</u> Defined using asthma steps based on Expert Panel

		definition: defined as the presence of either risk or impairment	claims; 514,492 with no exclusion criteria and 12–64 years of age; 79,428 with evidence of uncontrolled asthma; 18,343 with uncontrolled disease having 2 consecutive years of enrollment, within age limit, and no other exclusion criteria [COPD, emphysema, cystic fibrosis, pregnancy, or bronchopulmonary dysplasia])	Report 3 NHLBI guidelines ⁴² :29.9% (5,478/18,343) Step 4: 20.2% (3,697/18,343) Step 5: 9.1% (1,676/18,343) Step 6: 0.6% (105/18,343)
United States ⁴³	Omalizumab adherence in an observational study of patients with moderate to severe allergic asthma	Prospective cohort study EXCELS study (n=520 patients on omalizumab) Controlled defined as ACT <20 at baseline and 6 months	Multicenter study	Incidence of SUA in asthma patient population: 49.2% (255/520) Incidence of SUA in SA patient population (ACT score 15.2 ± 5.2): 49.2% (255/520)
United States ⁴⁴	The few who use the most: costs of severe and persistent asthma in a US managed care plan	Retrospective observational study from a large U.S. health care claims database (12.6 million individuals with medical and pharmacy benefit coverage) 63,597 with or severe PA or SA Control assessed by previous EX history	Patients aged ≥12 years who had at least one medical claim with an asthma diagnosis in 2012 and had continuous medical and pharmacy coverage under a commercial or Medicare Advantage plan from January 1, 2012, to December 31, 2013	Incidence of SUA in asthma patient population: 2.7% (1,762/63,597) Incidence of SUA in SA patient population: 19.9% (5,170/25,961) Incidence of SUA in general population: 0.03% (5,170/14,409,880)
United States ⁴⁵	Utilization and costs of severe uncontrolled asthma in a managed-care setting	Observational study SUCAS study (n=585 SUA; n=25,530 non-SUA) Patients with SUA were identified from the PA cohort if they met all of the following three criteria in 2012 (baseline period): (a) 2 or more asthma EX (see below for definition), (b) 6 or more medium- or high-dosage ICS canisters dispensed as monotherapy or in combination with LABA, and (c) 3 or more non-ICS controller canisters dispensed	Observational study Patients with persistent asthma in a real-world setting Treatment: treatments for persistent asthma	Incidence of SUA in asthma patient population: 25.2% Incidence of SUA in SA patient population: 100% (all patients controlled) <u>EX rates:</u> Pre-tx: 100% with 2 or more; Count: mean 2.7 (1.3), post-tx: 1.1 ± 1.6; Unadjusted rate or risk ratio (95% CI): 3.97 (3.52–4.48); Adjusted* rate or risk ratio (95% CI): 2.80 (2.46–3.18) % with EX: Any: 52.8%; 2 or more: 26.2%; Any: Unadjusted rate or risk ratio (95% CI): 2.72 (2.51–2.94); Adjusted* rate or risk ratio (95% CI): 2.12 (1.94–2.32);

		Asthma EX: defined as any of the following service utilizations with an asthma diagnosis in the primary or secondary position: hospitalization, ER visit, or physician office or outpatient visit coupled with a pharmacy claim for oral corticosteroids (OCS) within 7 days before or after the visit.	2 or more: Unadjusted rate or risk ratio (95% CI): 5.06 (4.37–5.86); Adjusted* rate or risk ratio (95% CI): 3.22 (2.73–3.81) <u>Costs:</u> Total costs/all-cause/total all-cause SUA: \$4,800 ± 185 Total asthma-related: SUA: \$2,325 ± 75 Non-SUA: \$1,269 ± 9 $p < 0.001$ Direct costs: All-cause: Hospitalization including laboratory and radiology: SUA: \$1,043 ± 141 Non-SUA: \$844 ± 5 $p = 0.17$ ED including laboratory and radiology: SUA: \$105 ± 12 Non-SUA: \$75 ± 1 $p = 0.010$ Outpatient visits including laboratory and radiology: SUA: \$1,235 ± 41 Non-SUA: \$1,107 ± 7 $p = 0.002$ Laboratory not accounted by above visit encounters: SUA: \$93 ± 7 Non-SUA: \$64 ± 1 $p < 0.001$ Other: radiology, skilled nursing, hospital outpatient, and home health: SUA: \$191 ± 36 Non-SUA: \$183 ± 7 $p = 0.82$ Asthma-related: Asthma hospitalization including laboratory and radiology: SUA: \$179 ± 51 Non-SUA: \$52 ± 4 $p = 0.014$ Asthma ED including laboratory and radiology: SUA: \$21 ± 4
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				Non-SUA: \$6 ± 0.3 $p < 0.001$ <i>Asthma outpatient visits including laboratory and radiology:</i> SUA: \$133 ± 8 Non-SUA: \$51 ± 1 $p < 0.001$ <i>Asthma drug:</i> SUA: \$2,007 ± 56 Non-SUA: \$1,159 ± 7 $p < 0.001$
United States ⁴⁶	Changes in asthma control, work productivity, and impairment with omalizumab: 5-year EXCELS study results	Prospective cohort analysis (5 years of data from patients ≥12 years old with moderate to severe persistent allergic asthma who were enrolled in the EXCELS observational study Control assessed by ACT <20 at baseline and every 6 to 24 months	N=7,709 4,930 patients on omalizumab 2,279 on non-omalizumab	<u>Incidence of SUA in all patients with asthma at baseline:</u> 49.9% severe (2,456/4,930) 31.6% poorly controlled (1,552/4,906) <u>Incidence of SUA in SA omalizumab cohort:</u> Baseline: 54.8% 60 months: 38.8% <u>Incidence of SUA in SA non-omalizumab cohort:</u> Baseline: 51.4% 60 months: 33.3% <u>ACT (mean, SD):</u> Baseline: 16.6 60 months: 18.7
United States ⁴⁷	Inflammatory and co-morbid features of patients with severe asthma and frequent exacerbations	Retrospective patient recall (n=709) Control assessed by EX frequency ≥3 EX: Number of OCS courses lasting 3 or more days	NHLBI Severe Asthma Research Program-3	Incidence of SUA in asthma patient population: 21.4% (152/709) Incidence of SUA in uncontrolled asthma patient population: 88.0% (152/173) Incidence of SUA in SA patient population: 36.2% (152/419) <u>EX rates:</u> Pre-tx: None: 41.4% (294/709) 1–2 EX: 34.1% (242/709) (65% severe) 3+ EX: 24.4% (173/709) (88% severe) Post-tx: NR; % with EX: 1–2 EX: 34.1% (242/709) (65% severe) *severe 3+ EX: 24.4% (173/709) (88% severe) *severe

United States ⁴⁸	Factors affecting ability to achieve asthma control in adult patients with moderate to severe persistent asthma	Prospective (n=320) adult patients Control defined as well controlled, not well controlled, or very poorly controlled (2007 NAEPP guidelines)	Tertiary medical center–based asthma outpatient specialty clinic patients with uncontrolled asthma, July 1, 2003, through June 30, 2011	Incidence of SUA in uncontrolled asthma patient population: 49.0% (129/263) Incidence in general population: 3.6% (95% CI, 3.0–4.1) of adult Dutch asthma patients have severe refractory asthma
United States ⁴⁹	Persistence of community-acquired respiratory distress syndrome toxin-producing <i>Mycoplasma pneumoniae</i> in refractory asthma	Prospective observational study	64 patients with refractory asthma	52% of patients tested positive for <i>Mycoplasma pneumoniae</i> . 10 patients followed for up to 633 days tested persistently positive
United States ⁵⁰	Distinguishing severe asthma phenotypes: Role of age at onset and eosinophilic inflammation	Cross-sectional study	80 patients with SA: onset before age 12 years (n=50) onset after age 12 years (n=30)	Patients with early onset SA had significantly greater allergen sensitivity (skin test positivity, 98% vs. 76%, $p<0.007$) and more allergic symptoms (p -values all ≤ 0.02) than patients with late onset asthma. Presence of eosinophils in either age at onset group was associated with the lowest lung function ($p\leq 0.02$)
United States ⁵¹	Outcomes before and after treatment escalation to Global Initiative for Asthma steps 4 and 5 in severe asthma	Retrospective study (n=19,227) A β -agonist was used as a surrogate of asthma control	Patients (GINA steps 4 and 5) with uncontrolled asthma newly initiated treatment 2002 to 2011 MarketScan data	Incidence of SUA in SA patient population: 62–70% LABA usage during follow up <u>Costs:</u> Total costs: Same as Sullivan 2015 + oOATS Health care total expenditures: Mean: \$6,146 Median: \$2,909 Direct costs: OATS (mean/median) Rx cost: \$1,091/\$310 Medical cost: \$5,056/\$1,986 Outpatient cost: \$3,740/\$1,704 Inpatient cost: \$1,036/\$0 ED cost: \$280/\$0 Specialty care cost: \$237/\$0 Asthma-related health care cost: \$857/\$193 Asthma-related Rx cost: \$55/\$0 Asthma-related medical cost: \$802/\$152 Asthma-related outpatient cost: \$338/\$130 Asthma-related inpatient cost: \$405/\$0 Asthma-related ED cost: \$59/\$0 Asthma-related specialty care cost: \$76/0
United States ⁵²	Characterizing the severe	Retrospective cohort study	Patients (GINA steps 4 and 5) with	Incidence of SUA in SA patient population: 62–70%

Meeting abstract	asthma population in the United States: Claims-based analysis of three treatment cohorts in the year prior to treatment escalation	(n=25,297) A β -agonist was used as a surrogate of asthma control	uncontrolled asthma newly initiated treatment 2002 to 2011 MarketScan data <u>Incidence study:</u> N=25,297 <u>Cost study:</u> Multiple interventions (n=70,343) Omalizumab (n=1,046) High-intensity corticosteroids (n=24,319) High-dosage ICS (n=44,978)	LABA usage during follow up Incidence of SUA in SA patient population: Couple rated: 85.2% (144/169) Overall: 87.4% (429/491) <u>Costs:</u> Total costs (HDICS/HICS/omalizumab): Health care cost: \$9,826/\$15,557/\$34,887 Direct costs (HDICS/HICS/omalizumab): Rx cost: \$4,275/\$5,494/\$24,507 Medical cost: \$5,551/\$10,063/\$10,380 Outpatient cost: \$4,284/\$7,343/\$7,708 Inpatient cost: \$1,058/\$2,381/\$2,305 ED cost: \$208/\$339/\$366 Specialty care cost: \$312/\$557/\$1,993 Asthma-related health care cost: \$2,851/\$3,872/\$24,399 Asthma-related Rx cost: \$2,003/\$2,407/\$21,561 Asthma-related medical cost: \$848/\$1,465/\$2,838 Asthma-related outpatient cost: \$428/\$640/\$2,039 Asthma-related inpatient cost: \$381/\$750/\$698 Asthma-related ED cost: \$39/\$74/\$101 Asthma-related specialty care cost: \$94/\$172/\$1,148
United States ⁵³	Clinical burden and predictors of asthma exacerbations in patients on guideline-based steps 4-6 asthma therapy in the TENOR cohort	Prospective cohort study	Treatment: Steps 4/5/6 therapy	55.1% considered difficult to treat because of frequent EX
United States ⁵⁴	Inhaled mometasone furoate reduces oral prednisone usage and improves lung function in severe persistent asthma	RCT	MF-MDI 400 μ g (n=42) MF-MDI 800 μ g (n=43) PBO (n=38)	<u>% with EX:</u> MF-MDI (400 μ g n=42): 17.0% MF-MDI (800 μ g n=43): 19.0% PBO (n=38): 47.0% <u>Other outcomes:</u> SF-36 data NR. No significant differences between groups in the change from baseline for any of the SF-36 HRQOL domain scores Mean $\pm$ SEM: <u>AM wheezing score:</u> MF-MDI 400 μ g bid:

				Baseline: 0.84 ± 0.12 Change at 3 months: -0.29 ± 0.15 <u>MF-MDI 800 µg bid:</u> Baseline: 0.8 ± 0.11 Change at 3 months: -0.37 ± 0.14 <u>PBO:</u> Baseline: 0.69 ± 0.13 Change at 3 months: 0.22 ± 0.16 Significant improvement with both dosages of MF-MDI, $p < 0.01$ <i>AM difficulty breathing score:</i> <u>MF-MDI 400 µg bid:</u> Baseline: 1.07 ± 0.13 Change at 3 months: -0.16 ± 0.16 <u>MF-MDI 800 µg bid:</u> Baseline: 0.55 ± 0.10 Change at 3 months: -0.24 ± 0.15 <u>PBO:</u> Baseline: 0.85 ± 0.13 Change at 3 months: 0.22 ± 0.17 Significant improvement with MF-MDI 800 µg, $p < 0.05$ <i>AM cough score:</i> <u>MF-MDI 400 µg bid:</u> Baseline: 0.32 ± 0.11 Change at 3 months: $+0.13 \pm 0.14$ <u>MF-MDI 800 µg bid:</u> Baseline: 0.77 ± 0.12 Change at 3 months: -0.10 ± 0.13 <u>PBO:</u> Baseline: 0.48 ± 0.11 Change at 3 months: $+0.21 \pm 0.15$ <i>Number of awakenings for albuterol (per night):</i> <u>MF-MDI 400 µg bid:</u> Baseline: 0.52 ± 0.11 Change at 3 months: -0.13 ± 0.12 <u>MF-MDI 800 µg bid:</u> Baseline: 0.48 ± 0.11 Change at 3 months: -0.13 ± 0.11 <u>PBO:</u> Baseline: 0.28 ± 0.12 Change at 3 months: $+0.40 \pm 0.13$
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				Significant improvement with both dosages of MF-MDI, $p<0.01$ <i>Number of awakenings for albuterol use (inhalations/day):</i> <u>MF-MDI 400 µg bid:</u> Baseline: 5.45 ± 0.58 Change at 3 months: -0.61 ± 0.57 <u>MF-MDI 800 µg bid:</u> Baseline: 5.17 ± 0.54 Change at 3 months: -0.85 ± 0.54 <u>PBO:</u> Baseline: 3.90 ± 0.61 Change at 3 months: $+1.93 \pm 0.61$, not significant Significant improvement with both dosages of MF-MDI, $p<0.01$
United States ⁵⁵	Economic burden of illness among patients with severe asthma in a managed care setting	Retrospective cohort study EX: Consistent with the ATS and ATS/ERS definition of EX,²⁰ an asthma EX was operationalized as any of the following service utilizations with an asthma diagnosis in the primary or secondary position: hospitalization, ED visit, or physician office or outpatient visit coupled with a pharmacy claim for OCS within 7 days before or after the visit	Most used (Year 1): Persistent asthma: 3.14 (count) leukotriene modifiers Severe asthma: 6.79 inhaled corticosteroids and long-acting β-agonists N=1,762 SA patients	In the first year of the study, the majority of PA patients (53.3%) experienced no asthma EX; 32.5% had 1 EX; and 14.2% had 2 or more EX. Per inclusion criteria, all patients in the SA cohort had at least 2 EX, and 42.5% had 3 or more <u>Severe asthma yYear 1, EX, n (%):</u> 0: 0 1: 0 2: 1,013 (57.5%) 3: 749 (42.5%) <u>Direct costs:</u> <i>Asthma-related unit cost (SD):</i> <u>SA:</u> ED visit (n=542): \$795 (1,511) Hospitalization (any length) (n=196): \$14,479 (17,672) ED visit + hospitalization (any length) (n=738): \$4,429 (10,994) <u>SEA:</u> ED visit (n=43): \$750 (605) Hospitalization (any length) (n=21): \$15,563 (20,787) ED visit + hospitalization (any length) (n=738): \$5,610 (13,659) <i>EX unit cost (SD):</i>

				<u>SA:</u> AMB visit coupled with OCS (n=5,698) \$637 (2,950) Any type: ED, hospitalization, and AMB visits coupled with OCS (n=7,610): \$2,333 (8,570) <u>SEA:</u> AMB visit coupled with OCS (n=629): \$772 (3,954) Any type: ED, hospitalization, and AMB visits coupled with OCS (n=798): \$2,820 (11,265)
United States ⁵⁶	Dupilumab in persistent asthma with elevated eosinophil levels	RCT EX: Occurrence of any one of the following: a reduction of 30% or more in morning PEF from baseline on 2 consecutive days, at least six additional reliever inhalations of albuterol or levalbuterol in a 24-hour period relative to baseline on 2 consecutive days, or an EX requiring OCS, an increase in ICS of at least 4-times the most recent dose, or hospitalization for asthma, as determined by the investigator	Dupilumab (n=52) PBO (n=52)	<u>EX rates:</u> Dupilumab: Previous 2 years: 1.4 ± 1.3 % with EX: 6.0%* PBO: Previous 2 years: 1.4 ± 1.0 % with EX: 44.0%* <u>ACQ-5 (mean, SD):</u> Dupilumab: Baseline: 2.1 ± 0.5 12 weeks: -1.00 ± 0.16 Significant improvement with dupilumab, <i>p</i> =0.001 PBO: Baseline: 2.1 ± 0.5 12 weeks: -0.27 ± 0.16 Difference, dupilumab vs. PBO: -0.73 (95% CI: -1.15, -0.30) <u>Other outcomes:</u> Morning asthma symptom score: Dupilumab: Baseline: 0.8 ± 0.8 Change at 12 weeks: -0.4 ± 0.1 PBO: Baseline: 0.7 ± 0.6 Change at 12 weeks: 0.3 ± 0.1 Evening asthma symptom score: Dupilumab: Baseline: 0.9 ± 0.7 Change at 12 weeks: -0.6 ± 0.1 PBO: Baseline: 1.1 ± 0.7 Change at 12 weeks: 0.1 ± 0.1

				Number of night-time awakenings: <i>Dupilumab:</i> Baseline: 0.4 ± 0.8 Change at 12 weeks: -0.2 ± 0.1 <i>PBO:</i> Baseline: 0.2 ± 0.5 Change at 12 weeks: 0.1 ± 0.1 SNOT-22 score: <i>Dupilumab:</i> Baseline: 30.9 ± 14.8 Change at 12 weeks: -8.26 ± 2.20 <i>PBO:</i> Baseline: 26.2 ± 15.6 Change at 12 weeks: 0.23 ± 2.15 Change in morning asthma symptom score, $p < 0.001$ Change in evening asthma symptom score, $p < 0.001$ Change in number of night-time awakenings, $p = 0.05$ Change in SNOT-22 score, $p = 0.003$
United States ⁵⁷	Effect of roflumilast on asthma control in moderate and severe asthma patients	Retrospective cohort study	Roflumilast (n=12) SoC (n=68)	<u>Other outcomes:</u> Standard therapy + roflumilast: Controlled disease course achieved in 2 patients (17.0%; 0.39 points) Partially controlled course achieved in 4 patients (33.0%; 1.35 points) No changes: 2 patients (16.6%) SoC: Controlled disease course achieved in 2 patients (2.94%) Partially controlled course achieved in 12 patients (17.64%) Uncontrolled disease course: 54 patients (79.4%)
United States ⁵⁸	A 26-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the effect of omalizumab on asthma control in patients with persistent allergic asthma	RCT	Omalizumab (n=136) n NR for subgroups PBO (N=135)	<u>Other outcomes:</u> ACT (mean, SD): <i>Omalizumab:</i> Baseline: 13.9 ± 3.3 LSM change at 24 weeks: 5.01 <i>PBO:</i> Baseline: 13.7 ± 3.5 LSM change at 24 weeks: 4.36 LSM treatment differences increased over the course of the study: Week 8: 0.35

				Week 16: 0.58 Week 24: 0.64 (95% CI: -0.30, 1.5) <i>Post-hoc</i> analysis (subgroup analysis of patients with very poorly controlled asthma (ACT ≤ 15 at baseline): Treatment with omalizumab resulted in significantly greater improvement in ACT total score at Week 24 compared with PBO Statistical significance: NS improvement with omalizumab at Week 24, $p=0.178$ Significant improvement with omalizumab only in subgroup with baseline ACT ≤ 15, $p=0.033$ LSM change from baseline to Week 24: Omalizumab: 6.66 PBO: 5.27 LSM treatment difference: 1.39 (95% CI: 0.11, 2.66) No significant differences at Week 24 between omalizumab and PBO subgroups of patients with baseline FEV₁ $\leq 80\%$ predicted $p=0.337$ Average number of days per week with any daytime asthma symptoms: <i>Omalizumab:</i> Baseline: NR LSM change at Week 24: -2.16 <i>PBO:</i> Baseline: NR LSM change at Week 24: -1.77 Average number of night-time awakenings per week due to asthma: <i>Omalizumab:</i> Baseline: NR LSM change at Week 24: -1.45 <i>PBO:</i> Baseline: NR LSM change at Week 24: -1.06
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				Average number of days per week with any daytime asthma symptoms: $p=0.202$ Average number of night-time awakenings per week because of asthma: $p=0.019$
United States ⁵⁹	Asthma exacerbation rates in adults are unchanged over a 5-year period despite high-intensity therapy	Retrospective market scan database (n=2,543); 5 years EX: OCS prescription within 7 days of a hospitalization, ED visit, outpatient encounter or physician office visit with a diagnosis of asthma (primary ICD-9 code of 493 or secondary ICD-9 code of 493 with other respiratory primary diagnosis)	Treatment: at least 120 days of high-dosage ICS and LABA medication (defined as HI asthma treatment)	<u>EX rates:</u> 0.70 to 0.63 declining Year 1 through 5, post: NR % with EX: All patients: 28% to 25% declining Year 1 through 5 (OR: 0.96, 95% CI: 0.94–0.99) High-intensity patients: 29% to 31% during the 5-year follow up
United States ⁶⁰	Omalizumab in severe allergic asthma inadequately controlled with standard therapy: A randomized trial	RCT Protocol-defined EX: Worsening asthma symptoms requiring treatment with systemic corticosteroids for 3 or more days; for patients receiving long-term OCS, an EX was a 20-mg or more increase in the average daily dosage of oral prednisone (or a comparable dosage of another systemic corticosteroid)	Omalizumab (n=427) PBO (n=421) <u>Subgroup low FENO* (n=193)</u> Omalizumab (n=102) PBO (n=91) <u>Subgroup high FENO* (n=201)</u> Omalizumab (n=101) PBO (n=100) <u>Subgroup low eosinophil* (n=383)</u> Omalizumab (n=186) PBO (n=197) <u>Subgroup high eosinophil* (n=414)</u> Omalizumab (n=214) PBO (n=200) <u>Subgroup low periostin* (n=255)</u> Omalizumab (n=142) PlaceboPBO (n=137) <u>Subgroup high periostin* (n=255)</u> Omalizumab (n=128) PlaceboPBO (n=127)	<u>EX rates:</u> Omalizumab: Previous year: 2.0 ± 2.2 Post-tx: 0.66* (omalizumab vs. PBO) PBO: Previous year: 1.9 ± 1.5 Post-tx: 0.48 Subgroup low FENO: <u>Omalizumab:</u> Previous year: 2 ± 1 Post-tx: 0.60* (omalizumab vs. PBO) <u>PBO:</u> Previous year: 2 ± 1 Post-tx: 0.71 Subgroup high FENO: <u>Omalizumab:</u> Previous year: 2 ± 3 Post-tx: 0.50 <u>PBO:</u> Previous year: 2 ± 3 Post-tx: 1.07 Subgroup low eosinophil: <u>Omalizumab:</u> Previous year: 2 ± 1 Post-tx: 0.65 <u>PBO:</u> Previous year: 2 ± 1 Post-tx: 0.72

				Subgroup high eosinophil: <i>Omalizumab:</i> Previous year: 2 ± 2 Post-tx: 0.70* (omalizumab vs. PBO) <i>PBO:</i> Previous year: 2 ± 2 Post-tx: 1.03 Subgroup low periostin: <i>Omalizumab:</i> Previous year: 2 ± 2 Post-tx: 0.73 <i>PBO:</i> Previous year: 2 ± 2 Post-tx: 0.72 Subgroup high periostin: <i>Omalizumab:</i> Previous year: 2 ± 3 Post-tx: 0.66 <i>PBO:</i> Previous year: 2 ± 3 Post-tx: 0.93 <u>AQLQ (mean, SD):</u> Improvement of 0.29 points, comparing omalizumab with PBO; significant, CI: 0.15, 0.43, no <i>p</i>-value reported Low FEno (<19.5 ppb) (n=193): Baseline (omalizumab and PBO combined): 4 ± 1; <i>p</i>=0.16 LSM at 48 weeks omalizumab: 1.00 LSM at 48 weeks PBO: 0.76 High FENO (≥ 19.5 ppb) (n=201): Baseline (omalizumab and PBO combined): 4 ± 1 LSM at 48 weeks omalizumab: 1.28 LSM at 48 weeks PBO: 0.89; <i>p</i>=0.02 Low eosinophil (<260/μL) (n=383): Baseline (omalizumab and PBO combined): 4 ± 1 LSM at 48 weeks: 1.13 LSM at 48 weeks: 0.84; <i>p</i>=0.01 High eosinophil (≥ 260/μL) (n=414): Baseline (omalizumab and PBO combined): 4 ± 1
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				LSM at 48 weeks: 1.14 LSM at 48 weeks: 1.01; $p=0.29$ Low periostin (<50 ng/mL) (n=279): Baseline (omalizumab and PBO combined): 4 ± 1 LSM at 48 weeks: 1.32 LSM at 48 weeks: 0.82; $p=0.0005$ High periostin (≥ 50 ng/mL) (n=255): Baseline (omalizumab and PBO combined): 4 ± 1 LSM at 48 weeks: 1.17 LSM at 48 weeks: 1.07; $p=0.51$ <u>Other outcomes:</u> TASS: Mean difference for omalizumab (n=427) compared with PBO (n=421) over 48 weeks: -0.26 (mixed effects analysis; significant improvement comparing omalizumab with PBO, 95% CI -0.42, -0.10, no p-value reported) Low FEno (<19.5 ppb) (n=193): Baseline (omalizumab and PBO combined): 4 ± 2 LSM at 48 weeks: -1.32 LSM at 48 weeks: -1.11; $p=0.37$ High FEno (≥ 19.5 ppb) (n=201): Baseline (omalizumab and PBO combined): 4 ± 2 LSM at 48 weeks: -1.80 LSM at 48 weeks: -1.51; $p=0.23$ Low eosinophil (<260/μL) (n=383): Baseline (omalizumab and PBO combined): 4 ± 2 LSM at 48 weeks: -1.41 LSM at 48 weeks: -1.06 High eosinophil (≥ 260/μL) (n=414): Baseline (omalizumab and PBO combined): 4 ± 2 LSM at 48 weeks: -1.63 LSM at 48 weeks: -1.47; $p=0.37$ Low periostin (<50 ng/mL) (n=279): Baseline (omalizumab and PBO combined): 4 ± 2 LSM at 48 weeks: -1.69 LSM at 48 weeks: -1.07; $p=0.0017$ High periostin (≥ 50 ng/mL) (n=255): Baseline (omalizumab and PBO combined): 4 ± 2 LSM at 48 weeks: -1.46 LSM at 48 weeks: -1.50; $p=0.86$
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United States ⁶¹	Exploring the effects of omalizumab in allergic asthma: An analysis of biomarkers in the EXTRA study		Omalizumab (n=427) PBO (n=421) <u>Subgroup low FENO* (n=193)</u> Omalizumab (n=102) PBO (n=91) <u>Subgroup high FENO* (n=201)</u> Omalizumab (n=101) PBO (n=100) <u>Subgroup low eosinophil* (n=383)</u> Omalizumab (n=186) PBO (n=197) <u>Subgroup high eosinophil* (n=414)</u> Omalizumab (n=214) PBO (n=200) <u>Subgroup low periostin* (n=255)</u> Omalizumab (n=142) PBO (n=137) <u>Subgroup high periostin* (n=255)</u> Omalizumab (n=128) PBO (n=127)	<u>EX rates:</u> Omalizumab: Previous year: 2.0 ± 2.2 Post-tx: 0.66* (omalizumab vs. PBO) PBO: Previous year: 1.9 ± 1.5 Post-tx: 0.48 Subgroup low FENO: Omalizumab: Previous year: 2 ± 1 Post-tx: 0.60* (omalizumab vs. PBO) PBO: Previous year: 2 ± 1 Post-tx: 0.71 Subgroup high FENO: Omalizumab: Previous year: 2 ± 3 Post-tx: 0.50 PBO: Previous year: 2 ± 3 Post-tx: 1.07 Subgroup low eosinophil: Omalizumab: Previous year: 2 ± 1 Post-tx: 0.65 PBO: Previous year: 2 ± 1 Post-tx: 0.72 Subgroup high eosinophil: Omalizumab: Previous year: 2 ± 2 Post-tx: 0.70* (omalizumab vs. PBO) PBO: Previous year: 2 ± 2 Post-tx: 1.03 Subgroup low periostin: Omalizumab: Previous year: 2 ± 2 Post-tx: 0.73 PBO: Previous year: 2 ± 2 Post-tx: 0.72
United States ⁶²	Population-based efficacy modeling of omalizumab in patients with severe allergic asthma inadequately controlled with standard therapy			

				Subgroup high periostin: <i>Omalizumab:</i> Previous year: 2 ± 3 Post-tx: 0.66 <i>PBO:</i> Previous year: 2 ± 3 Post-tx: 0.93
United States ⁶³	Impact of omalizumab on emergency-department visits, hospitalizations, and corticosteroid use among patients with uncontrolled asthma	Retrospective cohort study	Omalizumab (n=644)	<u>Baseline OCS use:</u> Mean ± SD number of OCS claims: 5.0 ± 3.7 Mean ± SD days of supply: 91.0 ± 101.5 Mean ± SD nonoverlapping days of supply: 78.7 ± 78.2 <u>12-month follow-up OCS use:</u> Mean ± SD number of OCS claims: 3.6 ± 4.0 Mean ± SD days of supply: 77.9 ± 114.5 Mean ± SD nonoverlapping days of supply: 68.2 ± 85.8 % reduction OCS claims: 28% % reduction days of supply: 14.4% % reduction nonoverlapping days of supply: 13.3% The number of dispensings ($p<0.0001$), days of supply ($p=0.0002$), nonoverlapping days of supply ($p<0.0001$), and proportion of days covered ($p<0.0001$) were all significantly lowered post-omalizumab
United States ⁶⁴	Concomitant asthma medication use in patients receiving omalizumab: Results from three large insurance claims databases	Claims database analysis 12-month follow up	Omalizumab (n=644, overall; n=439, OCS subgroup)	<u>Baseline hospitalization:</u> Overall: Due to all-cause events: 197/644 (30.6%) Due to asthma-related events: 161/644 (25.0%) <i>Number of hospitalizations (mean ± SD):</i> Due to all-cause events: 0.48 ± 0.92 Due to asthma-related events: 0.36 ± 0.77 Subgroup of patients on high-dosage ICS+LABA and OCS: <i>Patients with ≥1 hospitalization:</i> Due to all-cause events: 132/439 (30.1%) Due to asthma-related events: 116/439 (26.4%) <i>Number of hospitalizations (mean ± SD):</i> Due to all-cause events: 0.48 ± 0.92 Due to asthma-related events: 0.36 ± 0.77 <u>Follow-up hospitalizations:</u>

				Overall: Due to all-cause events: 0.33 ± 0.79; 31.3% reduction, $p=0.0001$ vs. baseline Due to asthma-related events: 0.21 ± 0.59; 41.7% reduction, $p<0.0001$ vs. baseline Subgroup of patients on high-dosage ICS+LABA and OCS: Due to all-cause events: 0.33 ± 0.79; 31.3% reduction, $p=0.0001$ vs. baseline Due to asthma-related events: 0.21 ± 0.59; 41.7% reduction, $p<0.0001$ vs. baseline
United States ⁶⁵	Impact of omalizumab on all-cause and asthma-related health care resource utilisation in patients with moderate or severe persistent asthma	Retrospective market scan January 1, 2007, to September 30, 2012	Omalizumab (n=429)	<u>Asthma related:</u> 80.0% reduction in asthma-related ED visits ($p=0.0449$) 90.6% reduction in length of stay ($p=0.0442$) <u>All-cause:</u> 64.7% reduction in ED visit count (all $p \leq 0.0155$)
Mexico ⁶⁶	Clinical experience with omalizumab in patients with severe asthma. Real-world data	Open, analytical, cross-sectional, retrospective, observational study		a) 68.75% of uncontrolled patients (GINA 2006 classification), despite medication and adherence to treatment, will achieve asthma control when omalizumab is added to their treatment in the stepwise regimen b) 18.75% of patients will achieve partial control (improvement in SA) when omalizumab is added to their treatment in the stepwise regimen c) 77% of patients will have an improvement in SA when omalizumab is added to their treatment in the stepwise regimen (patients who achieved controlled asthma plus those who achieved partially controlled asthma) d) At least 7 months should be awaited to determine that the product will not be beneficial for a certain patient e) Adverse events are unlikely in the short- or medium-term of treatment with omalizumab f) About 14% of patients who receive omalizumab are likely not to respond to the medication
United States and Canada ⁶⁷	Reslizumab for poorly controlled, eosinophilic asthma: A randomized, placebo-controlled study	RCT Clinical asthma EX: (1) a 20% or more decrease from baseline in FEV_1 or (2) worsening of asthma requiring	Reslizumab (n=53) PBO (n=53)	<u>% with EX:</u> Reslizumab: 8.0%* PBO: 19.0%* <u>Other outcomes:</u>

		emergency treatment, hospital admission, or 3 or more days of OCS treatment		ACQ (mean, SD): <i>Reslizumab</i> (n=53): Baseline: 2.8 ± 0.79 Change at 15 weeks: -0.7 ± 1.02 p=0.054 <i>PBO</i> (n=53): Baseline: 2.5 ± 0.73 Change at 15 weeks: -0.3 ± 1.01 Baseline sputum eosinophil <10% <i>Reslizumab</i> Baseline: 3.0 ± 0.80 Change at 15 weeks: -0.7 ± 1.24 p=0.379 <i>PBO</i> Baseline: 2.6 ± 0.80 Change at 15 weeks: -0.3 ± 1.01 Baseline sputum eosinophil $\geq 10\%$: <i>Reslizumab</i> (n=28): Baseline: 2.6 ± 0.74 Change at 15 weeks: -0.8 ± 0.79 p=0.093 <i>PBO</i> (n=25): Baseline: 2.5 ± 0.63 Change at 15 weeks: -0.3 ± 1.04 p=0.0933 Baseline blood eosinophil $<0.5 \times 10^9$ cells/L: <i>Reslizumab</i> (n=25): Baseline: 2.7 ± 0.61 Change at 15 weeks: -0.6 ± 0.87 p=0.80 <i>PBO</i> (n=26): Baseline: 2.6 ± 0.84 Change at 15 weeks: -0.4 ± 0.88 p-value: NS Baseline blood eosinophil $\geq 0.5 \times 10^9$ cells/L: <i>Reslizumab</i> (n=28): Baseline: 2.9 ± 0.92 Change at 15 weeks: -0.9 ± 1.13 p-value: NS <i>PBO</i> (n=27): Baseline: 2.5 ± 0.61 Change at 15 weeks: -0.1 ± 1.12
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Canada ⁶⁸	Direct health care costs associated with asthma in British Columbia	Database analysis	158,516 asthma patients from British Columbia Linked Health Database and PharmaNet database from 1996 to 2000	$p=0.072$ <u>Costs:</u> Total costs, calculated: \$25,115,166 (\$33,668,744 based on a broader definition of asthma related utilization) Direct costs: SUA patients accounted for 60% of the total direct costs, and controlled SA patients accounted for 1% Asthma (any disease severity and level of control) resulted in \$41,858,610 in annual health care-related costs during the study period (\$331 per patient-year) When broader definitions of asthma-related hospitalizations and physician visits were used, total costs increased to \$56,114,574 annually (\$444 per patient-year)
United Kingdom ⁶⁹	A study of a multi-level intervention to improve non-adherence in difficult to control asthma	RCT	Nurse-led menu-driven intervention to improve adherence to ICT (n=9) No intervention (n=11)	<u>AQLQ (mean, SD):</u> Intervention (adherence): Baseline: 3.4 ± 1.0 6 months: 3.9 ± 1.2 12 months: 4.3 ± 1.4 No intervention: Baseline: 3.4 ± 1.1 6 months: 3.4 ± 1.4 12 months: 3.8 ± 1.6 $p=0.75$ for adherence intervention vs. no intervention <u>ACQ (mean, SD):</u> Intervention: Baseline: 3.7 ± 0.7 6 months: 2.9 ± 1.1 12 months: 2.9 ± 1.4 No intervention: Baseline: 4.0 ± 0.9 6 months: 3.5 ± 1.2 12 months: 3.1 ± 1.6 $p=0.74$, intervention vs. no intervention
United Kingdom ⁷⁰	The prevalence of nonadherence in difficult	Cross-sectional study (audit of outcome for patients of the Northern Ireland Regional Difficult Asthma	All patients (n=182) Nonadherent to ICT* (n=63)	<u>AQLQ:</u> Baseline symptom score: All patients: 3.29 ± 1.45

	asthma	Service)	Adherent to ICT* (n=119)	Nonadherent: 2.83 ± 1.04 Adherent: 3.52 ± 1.58 Adherent vs. nonadherent, $p=0.001$ Baseline activity score: All patients: 3.55 ± 1.31 Nonadherent: 3.20 ± 1.13 Adherent: 3.72 ± 1.36 Adherent vs. nonadherent, $p=0.02$ Baseline emotional score: All patients: 3.23 ± 1.58 Nonadherent: 3.01 ± 1.51 Adherent: 3.33 ± 1.61 Adherent vs. nonadherent, $p=0.23$ Baseline environment score: All patients: 3.89 ± 1.49 Nonadherent: 3.70 ± 1.36 Adherent: 3.99 ± 1.54 Adherent vs. nonadherent, $p=0.25$ Baseline total score: All patients: 3.42 ± 1.30 Nonadherent: 3.07 ± 1.03 Adherent: 3.59 ± 1.39 Adherent vs. nonadherent, $p=0.007$ <u>EQ-5D (mean, SD):</u> HRQOL thermometer: All patients: 0.59 ± 0.20 Nonadherent: 0.54 ± 0.20 Adherent: 0.62 ± 0.20 Improved score with adherence, $p=0.02$ HRQOL score: All patients: 0.54 ± 0.35 Nonadherent: 0.48 ± 0.36 Adherent: 0.57 ± 0.34 Adherent vs. nonadherent, $p=0.12$
United Kingdom ⁷¹	Airway impedance entropy and exacerbations in severe asthma	Cross-sectional study	Treatment group NR (n=66)	<u>AQLQ (mean, SD):</u> Patients with infrequent EX: 5.2 ± 0.2 Patients with frequent EX: 4.6 ± 0.2 No significant difference between groups, p-value NR <u>ACQ (mean, SD):</u> In patients with infrequent EX: 1.7 ± 0.2 In patients with frequent EX: 2.3 ± 0.2

				Significantly greater than infrequent EX group, <i>p</i> -value NR
United Kingdom ⁷² Meeting abstract	Long-term effectiveness of omalizumab in patients with severe persistent allergic (IgE-mediated) asthma: UK centre real-life experience	Retrospective cohort study (patient database of the Birmingham Heartlands Hospital)	Omalizumab (n=45) n=NR for patients with and without OCS	<u>ACQ (mean, SD):</u> Total: Baseline: 4.1 (range 3.7–4.7) Post-tx: 2.27 (range 0.5– 4.1) Patients on OCS: Baseline: 4.1 Post-tx: 1.6 Patients not on OCS: Baseline: 4.0 Post-tx: 2.7
United Kingdom ⁷³ Meeting abstract	Real life effectiveness of omalizumab in severe allergic asthma, does the IgE level matter? A Bradford experience	Retrospective cohort study	Omalizumab (n=41) n unclear for licensed and unlicensed	<u>AQLQ (mean, SD):</u> Licensed use: Baseline: 2.6 Post-tx: 3.95 % change: 34.2% Unlicensed use: Baseline: 2.87 Post-tx: 4.97 % change: 35.0% <u>ACT (mean, SD):</u> Licensed use: Baseline: 8.3 Post-tx: 14.2 % change: 41.6% Unlicensed use: Baseline: 9.0 Post-tx: 17.2 % change: 47.8%
United Kingdom ⁷⁴	Prevalence of gastroesophageal reflux in difficult asthma: Relationship to asthma outcome	Prospective cohort study (patients with difficult-to-control asthma referred to the Difficult Asthma Service in the Regional Respiratory Centre, Belfast City Hospital)	NR (n=68) Treatment responsive (n=34) Treatment resistant (n=34) Related publication (n=65)	<u>AQLQ (mean, SD):</u> Treatment responsive: Baseline: 3.3 ± 0.22 Mean change at 12–18 months: 0.87 (95% CI 0.42, 1.33) Treatment resistant: Baseline: 3.2 ± 0.17 Mean change at 12–18 months: 0.32 (95% CI –0.03, 0.66)
United Kingdom (Scotland) ⁷⁵	Symptoms, spirometry, exhaled nitric oxide, and asthma exacerbations in clinical	Prospective cohort study (n=267) Control assessed by BTS guideline	Adults with a physician diagnosis of asthma visiting five primary care	Incidence of SUA in asthma patient population: 16.9% (45/267)

	practice		asthma clinics in Tayside, Scotland	
United Kingdom ⁷⁶	Mepolizumab and exacerbations of refractory eosinophilic asthma	RCT Severe EX: Periods of deterioration in asthma control in patients who had been treated with high-dosage oral prednisolone for ≥ 5 days	Mepolizumab (n=29) PBO (n=329)	<u>EX rates:</u> Mepolizumab: Pre-tx: previous year, severe: 5.5 Post-tx: 2.0* (mepolizumab vs. PBO) % with EX: 69.0% PBO: Pre-tx: previous year, severe: 5 Post-tx: 3.4 % with EX: 84.0% <u>AQLQ (mean, SD):</u> Mepolizumab: Baseline: 4.72 ± 1.26 Change at 50 weeks: 0.55 PBO: Baseline: 4.84 ± 1.13 Change at 50 weeks: 0.19 Significant improvement with mepolizumab, $p=0.02$ <u>ACQ (mean, SD):</u> Mepolizumab: Baseline: 1.98 ± 1.07 Change at 50 weeks: -0.17 PBO: Baseline: 2.38 ± 1.35 Change at 50 weeks: -0.21; $p=0.65$
United Kingdom ⁷⁷	The role of a soluble TNFalpha receptor fusion protein (etanercept) in corticosteroid refractory asthma: A double blind, randomised, placebo controlled trial	RCT	Etanercept (n=19) PBO (n=20)	Equal number of EX in both groups (data NR in text), page 424 <u>AQLQ (mean, SD):</u> Etanercept: Baseline: 3.72 ± 1.05 12 weeks: 4.76 PBO: Baseline: 3.56 ± 1.15 12 weeks: 4.26 $p=0.084$ for etanercept vs. PBO <u>ACQ (mean, SD):</u> Etanercept: Baseline: 3.34 ± 1.16 12 weeks: 2.24 PBO: Baseline: 3.07 ± 0.74

				12 weeks: 2.56 $p=0.037$ for etanercept vs. PBO
United Kingdom ⁷⁸	Mycophenolate mofetil improves lung function and symptoms in severe treatment resistant asthma	Prospective cohort study	Mycophenolate mofetil Overall (n=22) Evaluated (n=16)	<u>EX rates:</u> Previous 6 months: 4 (3–6) Post-tx: 1 (0–3)* (for baseline vs. follow up) <u>ACQ (mean, SD):</u> Median ACQ-6 (IQR): Baseline: 3.4 (2.5–4.1) 6 months: 2.5 (1.0–3.6) Significant improvement post-MMF, $p=0.01$
United Kingdom ⁷⁹	Impact of omalizumab on treatment of severe allergic asthma in UK clinical practice: A UK multicentre observational study (the APEX II study)	Retrospective and prospective cohort study (APEX II: data on patients from UK NHS secondary care centers using omalizumab as part of normal clinical practice, including specialist centers and district general hospitals, from across the UK) EX: Defined as hospital EX when patients attended ED or were admitted, and defined as dose EX when OCS dose increased by ≥ 10 mg at any point for at least 3 days	<u>Treatment groups for EX:</u> Omalizumab (n=258) ITT (n=218) Responders: (n=184) CCS (n=76) <u>Treatment group for AQLQ:</u> Omalizumab 16 weeks (n=192) 8 months (n=149) 12 months (n=161)	<u>EX rates:</u> Pre-tx: <u>Hospital EX:</u> ITT: 1.66 Responders: 1.71 CCS: 1.20 <u>Dose EX:</u> ITT: 4.58 Responders: 4.62 CCS: 3.64 Post-tx: <u>Hospital EX:</u> ITT: 0.69 Responders: 0.66 CCS: 0.46* <u>Dose EX:</u> ITT: 2.53 Responders: 2.36 CCS: 2.40* % with EX: 52.0% <u>AQLQ (mean, SD):</u> Baseline: 16 weeks: 3.27 ± 1.29 8 months: 3.14 ± 1.28 12 months: 3.20 ± 1.27 $p<0.001$ At visit: 16 weeks: 4.65 ± 1.55 8 months: 4.61 ± 1.54 12 months: 4.39 ± 1.48 <u>ACT (mean, SD):</u> Baseline:

				16 weeks: 9.76 (4.29) 8 months: 9.77 (4.38) 12 months: 9.84 (4.34) $p < 0.001$ At visit: 16 weeks: 15.01 (5.71) 8 months: 14.99 (5.78) 12 months: 14.41 (5.69) <u>EQ-5D (mean, SD):</u> Baseline (index): 16 weeks: 0.59 (0.25) 8 months: 0.58 (0.26) 12 months: 0.58 (0.25) At visit (index): 16 weeks: 0.71 (0.25) 8 months: 0.68 (0.26) 12 months: 0.69 (0.26) $p < 0.001$
United Kingdom ⁸⁰	PTU-107 NAFLD in patients with severe asthma	Retrospective cohort study	209 patients with SA	41 (20%) patients with SA had abnormal liver function tests, but only 14 (34%) were further investigated with liver imaging. Of those with deranged liver function who were imaged, 11 (79%) had radiological evidence of NAFLD
United Kingdom ⁸¹	Comorbidity in severe asthma requiring systemic corticosteroid therapy: Cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry	Cross-sectional observational study (data from the OPCR and BTS Difficult Asthma Registry)	Severe noncorticosteroid dependent asthma (n=328) Severe corticosteroid dependent asthma (n=442)	<u>AQLQ (mean, SD):</u> Severe noncorticosteroid dependent asthma (n=328): 3.86 ± 1.26 ; $p < 0.001$ Severe corticosteroid dependent asthma (n=442): 3.30 ± 1.18 <u>EQ-VAS:</u> Severe noncorticosteroid dependent asthma: 58 ± 21.9 Severe corticosteroid dependent asthma: 53 ± 20.9 ; $p = 0.013$ <u>HADS anxiety:</u> Severe noncorticosteroid dependent asthma: 8.18 ± 4.95 Severe corticosteroid dependent asthma: 8.61 ± 4.72 ; $p = 0.32$ <u>HADS depression:</u> Severe noncorticosteroid dependent asthma: 5.83 ± 4.41 Severe corticosteroid dependent asthma: 7.15 ± 4.26 ; $p = 0.001$

United Kingdom ⁸²	Effects of older age and age of asthma onset on clinical and inflammatory variables in severe refractory asthma	Retrospective cohort study (BTS Severe Asthma Registry)	<65 years of age (n=896) >65 years of age (n=146)	<u>AQLQ median (IQR):</u> <65 years of age (n=533): 3.32 (2.54–4.31) >65 years of age (n=70): 3.79 (2.93–4.85) $p=0.005$ <u>ACQ median (IQR):</u> <65 years of age (n=411): 3.4 (2.3–4.3) >65 years of age (n=51): 2.9 (2.0–3.60) $p=0.006$ <u>Other HRQOL:</u> EQ-VAS median (IQR): <65 years of age (n=464): 50 (35–70) >65 years of age (n=58): 57 (39–71) HADS anxiety median (IQR): <65 years of age (n=610): 9.0 (4.7–13.0) >65 years of age (n=85): 8.0 (4.0–12.0) HADS depression median (IQR): <65 years of age (n=608): 7.0 (3.0–10.0) >65 years of age (n=85): 6.0 (3.0–9.0) All comparisons between <65 and >65 are nonsignificant
United Kingdom ⁸³ Meeting abstract	Long-term effectiveness of omalizumab in patients with severe persistent allergic (IgE-mediated) asthma: Real-life data from 3 UK centres	Retrospective cohort study (pooled analysis of data from three UK health centers)	Omalizumab (n=50) n=NR for patients with and without OCS	<u>AQLQ (mean, SD):</u> Baseline: NR Change at 16 weeks: Total: 1.6 ± 1.5 No OCS: 2.2 ± 1.1 OCS: 1.5 ± 1.5 <u>ACT (mean, SD):</u> Baseline: NR Change at 16 weeks: Total: $+3.9 \pm 10.3$ Follow-up score at 16 weeks*: No OCS: 8.8 ± 4.9 OCS: 7.0 ± 6.5 NR
United Kingdom ⁸⁴	Health experiences of adolescents with uncontrolled severe asthma	Cross-sectional study (patient interviews)	n=22 adolescents (11–18 years) with uncontrolled SA	
United Kingdom ⁸⁵	The APEX Study: A retrospective review of outcomes in patients with severe allergic asthma who were or were not hospitalised in	Retrospective cohort study (review of medical records from 10 National Health Service secondary and primary care centers)	Omalizumab (n=136) Hospitalized in prior year (n=81) Not hospitalized in prior year (n=55)	<u>AQLQ :</u> All patients: Pre-omalizumab: 3.03 Post-omalizumab at 16 weeks: 4.99; OR 1.96 (95% CI: 1.7, 2.3); $p<0.001$

	the year prior to omalizumab initiation in UK clinical practice			Patients hospitalized in prior year: Pre-omalizumab: 3.11 Post-omalizumab at 16 weeks: 5.13; $pp=0.001$ Patients not hospitalized in prior year: Pre-omalizumab: 2.91 Post-omalizumab at 16 weeks: 4.78; $p<0.001$
United Kingdom ⁸⁶	The APEX Study: A retrospective review of the effects of omalizumab treatment on patient-reported outcomes in severe allergic asthma patients in UK clinical practice	Retrospective cohort study (review of medical records from 10 NHS secondary and primary care centers)	Omalizumab (n=54)	ACQ (mean, SD): Pre-omalizumab: 5.45 Post-omalizumab (16 weeks): 3.90; OR -1.55 (95% CI: -2.1--1.0) Significant improvement post-omalizumab, $p<0.001$ ACT (mean, SD): Pre-omalizumab: 11.85 Post-omalizumab (16 weeks): 16.22; OR 4.37 (95% CI: 2.6--6.2) Significant improvement post-omalizumab, $p<0.001$
United Kingdom ⁸⁷	Parameters associated with persistent airflow obstruction in chronic severe asthma	Cross-sectional study (patients referred to the Royal Brompton Hospital, London, with a presumed diagnosis of SA) S: Severe persistent airflow limitation ($FEV_1 < 50\%$ predicted, n=37) N: No obstruction ($FEV_1 > 80\%$ predicted, n=29) In multiple logistic regression analyses, peripheral blood eosinophils were considered with a threshold of >450 vs. $\leq 450 \times 10^6/L$	N=66 Group 1: $FEV_1 < 50\%$ predicted (n=37) Group 2: $FEV_1 > 80\%$ predicted (n=29)	<u>SGRQ (mean $\pm$ SD):</u> Overall score: S: 59.57 ± 3.20; N: 51.70 ± 3.39 Symptom: S: 79.03 ± 2.26; N: 75.65 ± 3.22 Activity: S: 67.66 ± 4.30; N: 60.63 ± 5.31 Impact: S: 49.37 ± 3.55; N: 40.07 ± 3.28 <u>Hospital admissions for asthma (median, range):</u> Group 1: $FEV_1 < 50\%$ predicted: 2 (1–3.5) Group 2: $FEV_1 > 80\%$ predicted: 3 (1–4) <u>Peripheral blood eosinophils ($\times 10^9$ cells/L; mean $\pm$ SEM):</u> Group S; patients with PAO: 0.41 ± 0.06 Group N; patients without PAO: 0.15 ± 0.03 ($p<0.0001$)
United Kingdom ⁸⁸ Meeting abstract	Fungal sensitisation and bronchiectasis in a severe asthma clinic	Retrospective cohort study	Total (n=141) ABPA (n=12) ABPM (n=5) FS (n=18) No FS (n=106)	<u>Blood eosinophil $\times 10^9/L$:</u> Patients with ABPA: 0.93 Patients with ABPM: 0.68 Patients with FS: 1.03 Patients without FS: 0.8
United Kingdom ⁸⁹	The cost of treating severe refractory asthma in the UK: An economic analysis from the British Thoracic Society Difficult Asthma Registry	Retrospective cohort study	SRA (n=516) Non-SRA (n=80)	<u>Hospital admission median (IQR):</u> SRA: 0 (0–1) Non-SRA: 0 (0–1) <u>Unscheduled GP/ED (1-year prereferral) median (IQR):</u> SRA: 4 (2–6) Non-SRA: 3 (0–6)

United Kingdom ⁹⁰	Continuous terbutaline infusion in severe asthma in adults: A retrospective study of long-term efficacy and safety	Retrospective case note review	Terbutaline treatment Continuous infusion of terbutaline administered subcutaneously or intravenously (n=42) Patients with suitable hospitalization records (n=16)	Mean FEV ₁ pretreatment (SD): 2.251 (0.80) Mean FEV ₁ 12 months after start of treatment (SD): 2.131 (1.08) Mean pretreatment admissions (95% CI): 6.7 (0.96–12.4) Pretreatment mean blood eosinophil count (n=20): 0.32x10 ⁹ /L 12 months after treatment, mean blood eosinophil count (n=20): 0.28x10 ⁹ /L; <i>p</i> =0.65
United Kingdom ⁹¹	Prevalence of psychiatric morbidity in a difficult asthma population: Relationship to asthma outcome	Prospective cohort study	N=65	Hospital admission in the previous year (mean ± SD): 0.82 ± 0.2 Mean hospital admissions ± SD: 0.82 ± 0.2 Mean number of unscheduled visits** ± SD: 5.3 ± 1.4
France ⁹²	Insights into severe asthma control as assessed by guidelines, pulmonologist, patient, and partner	Cross-sectional study (n=491 overall study population, n=169 couple data) Control assessed by ANAES	Epidemiological survey administered to asthma patients treated in general practice in 2003	<u>Incidence of SUA in SA patient population:</u> ANAES (French adaptation of GINA guidelines) Couple rated: 85.2% (144/169) Overall: 87.4% (429/491) Pulmonologist Couple rated: 35.5% (60/169) Overall: 42.6% (209/491) Patient rated 26.6% (45/169) Partner rated 23.3% (39/169)
France ⁹³	Omalizumab-induced decrease of FcεRI expression in patients with severe allergic asthma	RCT EX definition NR. Prior EX were those who required corticosteroids	Omalizumab (n=20) PBO (n=11)	<u>EX rates:</u> Omalizumab: Previous year: 4.7 ± 3.33 Post-tx: NR % with EX: 55% PBO: Previous year: 4.0 ± 2.90 Post-tx: NR % with EX: 36.7% <u>Other HRQOL:</u> Omalizumab: Baseline: 3.4 ± 1.2 Change at 16 weeks: -0.43 NS improvement, <i>p</i> -value not reported PBO: Baseline: No control of asthma 16 weeks: 9.1% had acceptable/optimal control of

				asthma at the end of the study (ANAES score of 0)
France ⁹⁴	A proof-of-concept, randomized, controlled trial of omalizumab in patients with severe, difficult-to-control, nonatopic asthma	RCT	Omalizumab (n=20) PBO (n=21)	<u>EX rates:</u> Omalizumab: Previous year: 5.05 ± 3.10 Post-tx: 1.43 ± 1.94 (4.29) % with EX: 40.0% PBO: Previous year: 5.05 ± 3.10 Post-tx: 1.43 ± 1.94 % with EX: 52.4% <u>ACQ (mean, SD) – for Garcia 2013 only:</u> Omalizumab: Baseline: 2.2 ± 0.98 Change at 16 weeks: -0.5 ± 0.98 PBO: Baseline: 2.2 ± 1.2 Change at 16 weeks: -0.5 ± 1.43
France ⁹⁵	A randomized-controlled trial of omalizumab in patients with severe difficult to control nonatopic asthma			
France ⁹⁶	Omalizumab therapy: Patients who achieve greatest benefit for their asthma experience greatest benefit for rhinitis	RCT EX: Deterioration of asthma symptoms requiring an ED visit, hospitalization, or increase in OCS treatment	Masitinib Total (n=33) 3 mg (n=12) 4.5 mg (n=11) 6 mg (n=10) PBO (n=11)	<u>EX rates:</u> Masitinib: <i>Previous year:</i> Per month: 0.37 ± 0.53 Per patient: 0.9 ± 1.0 for combined doses <i>Post-tx:</i> Per month: 0.22 ± 0.59 Per patient: 0.5 ± 0.7 for combined doses % with EX: 42.4% PBO: % with EX: 54.5% <u>ACQ (mean, SD):</u> Masitinib: Baseline: 3.2 ± 1.1 Change at 16 weeks: -0.99 Significant improvement, $p < 0.001$ PBO: Baseline: 3.4 ± 1.2 Change at 16 weeks: -0.43 NS improvement, p --value not reported
France ⁹⁷	Does omalizumab make a difference to the real-life treatment of asthma exacerbations?: Results from a	Prospective cohort study Severe EX: Requiring ED visit or hospitalization	Omalizumab (n=374, 564.9 person-years) Never prescribed omalizumab	<u>EX rates (severe):</u> Omalizumab: Pre-tx: 32.3 per 100-person-years Post-tx: 20.8 per 100-person-years X

	large cohort of patients with severe uncontrolled asthma		(n=393) Allergic patients (n=486, 750-person-years)	Adjusted hazard rate: 0.40 (95% CI: 0.28, 0.58) Allergic patients: Pre-tx: 31.9 per 100-person-years Post-tx: 20.2 per 100-person-years Adjusted hazard ratio (95% CI): 0.53 (0.39—0.75) % with EX: 20.2 per 100-person-years
France ⁹⁸	Effectiveness of omalizumab (Xolair®) in the first patients treated in real-life practice in France	Prospective cohort study	Omalizumab Overall (n=147) Baseline (n=75) Follow up (n=74)	EX rate: Previous year: 6.0 Post-tx: 2.3
France ⁹⁹	Observational study in severe asthmatic patients after discontinuation of omalizumab for good asthma control	Cross-sectional, retrospective study	Omalizumab (n=61)	Time free of EX, months (mean, SD): 8.7 ± 7.7
France ¹⁰⁰	Phenotypic determinants of uncontrolled asthma	Multicenter cross-sectional study Outcome – compliance to ICS (assessed by asking patients four questions about their attitude toward compliance)	Total (n=501) ICS+ (n=246) ICS+ with uncontrolled asthma (n=92) ICS- (n=255)	Compliance was not related to level of asthma control For combined treatment groups: Uncontrolled: 38.4% Partially controlled: 29.3% Controlled: 37.3%
France ¹⁰¹	[Phenotype of asthmatic patients according to a score derived from the Asthma Control Test]	Cross-sectional study Epidemiological survey administered to asthma patients treated in general practice in 2003	ER asthma study (n=15,534)	SUA among asthma population: 3.2% (499/15,534) ACT score <15 (very poorly controlled): 242/15,534 ACT score 15–20 (poorly controlled): 257/15,534
France ¹⁰²	Masitinib, a c-kit/PDGF receptor tyrosine kinase inhibitor, improves disease control in severe corticosteroid-dependent asthmatics	RCT EX: Deterioration of asthma symptoms requiring an ED visit, hospitalization, or increase in OCS treatment	Masitinib Total (n=33) 3 mg (n=12) 4.5 mg (n=11) 6 mg (n=10)	<u>Prior EX rate (mean ± SD):</u> Per month: 0.37 ± 0.53 Per patient: 0.9 ± 1.0 for combined doses <u>Post-tx EX rate (mean ± SD):</u> Per month: 0.22 ± 0.59 Per patient: 0.5 ± 0.7 for combined doses $p=0.275$ for masitinib per patient EX rate vs. baseline
France ¹⁰³	Effectiveness of omalizumab on asthma exacerbations following its introduction in a large cohort of patients with severe uncontrolled asthma	Longitudinal Study	Omalizumab (n=374)	Omalizumab use was associated with an adjusted RR of hospitalisation and/ or ED visits for asthma of 0.57 (95% CI: 0.43–0.78). In omalizumab users, the adjusted RR of hospitalisation and/or ED for asthma during omalizumab treatment vs. non-treatment periods was 0.40 ((95% CI: 0.28–0.58).

Germany ¹⁰⁴	Prospective evaluation of current asthma control using ACQ and ACT compared with GINA criteria	Prospective cohort study (n=150) Control assessed by GINA 2009 criteria	Consecutive adult patients with a previous physician diagnosis of asthma who were routinely followed up in an outpatient clinic	Incidence of SUA in asthma patient population: 30.0% (45/150) Incidence of SUA in uncontrolled asthma patient population: 66.2% (45/68) Incidence of SUA in SA patient population: 31.8% (45/118)
Germany ¹⁰⁵	Omalizumab in patients with severe persistent allergic asthma in a real-life setting in Germany	Prospective cohort study EX: FEV ₁ <60% of personal best, intermittent treatment with OCS, unscheduled healthcare visits, emergency treatments, hospitalizations due to asthma	Omalizumab Baseline (n=280) Follow up (n=241)	<u>EX rates:</u> Pre-tx: 4.5 ± 7.5 per year in 90% of patients Post-tx: 0.3 ± 0.8 per year* % with EX: 18.3% <u>AQLQ (mean, SD):</u> Mini AQLQ: Baseline: 2.9 ± 0.9 6 months: 4.5 ± 1 p<0.001 Mean ± SD (mini AQLQ) Baseline: 3.6 ± 1.3 (range: 1.8–6.5) <u>Other HRQOL:</u> 85.9% and 93.7% of patients rated the efficacy and tolerability as “excellent” and “good,” respectively
Germany ¹⁰⁶	Effectiveness of omalizumab in patients 50 years and older with severe persistent allergic asthma	Prospective cohort study EX: FEV ₁ <60% of personal best, intermittent treatment with OCS, unscheduled healthcare visits, emergency treatments, hospitalizations due to asthma	Omalizumab (n=195)	<u>EX rates:</u> Pre-tx: per 4 months: 0.9 ± 1.7 in 92.5% of patients Post-tx: 0.7 ± 1.6 % with EX: 34.2%*
Germany ¹⁰⁷	Monitoring free serum IgE in severe asthma patients treated with omalizumab	Prospective cohort study	Omalizumab (n=22)	<u>AQLQ (mean, SD):</u> Mean ± SD (mini AQLQ): Baseline: 3.6 ± 1.3 (range: 1.8–6.5) Change at 16 weeks mean ± SEM (range): Responders (n=17): 1.9 ± 0.4 (–1.8–3.7) Nonresponders (n=5): 0.1 ± 0.2 (–0.5–0.9) Significant improvement among responders compared with nonresponders, p=0.001 <u>ACQ-5 (mean, SD):</u> Baseline: 3.0 ± 1.2 (range: 0.2–4.8) Change at 16 weeks, mean ± SEM (range): Responders: –1.7 ± 0.4 (–3.6–2.8) Nonresponders: 0.1 ± 0.1 (–0.2–0.6)

				Significant improvement among responders compared with nonresponders, $p<0.001$
Germany ¹⁰⁸	Omalizumab in patients with severe asthma: The XCLUSIVE study	Prospective cohort study Severe EX: Worsening of 85 health centers in Germany) requiring systemic corticosteroids, an ED visit, hospitalization, or reduction of FEV ₁ <60% of personal best	Omalizumab (n=195)	EX rate: Pre-tx (time period NR): 3.99 ± 6.49 Post-tx: $1.0 \pm 1.87^*$ <u>ACQ (mean, SD):</u> Baseline: 3.58 ± 1.28 16 weeks: 2.01 ± 1.05 6 months: 1.92 ± 1.13 Significant improvement, $p<0.0001$
Germany ¹⁰⁹	Improvement of quality of life in patients with concomitant allergic asthma and atopic dermatitis: One year follow-up of omalizumab therapy	Prospective cohort study	Omalizumab Asthma (n=13) Asthma+ atopic dermatitis (n=9)	<u>AQLQ (mean, SD):</u> Omalizumab: asthma: Baseline: $102 \pm 40^*$ 6 months: $148 \pm 48^*$ 12 months: $152 \pm 45^*$ Comparison between groups: Baseline: $p=0.041$ 6 months: $p=0.041$ 12 months: $p=0.04$ Asthma + atopic dermatitis: Baseline: $143 \pm 44^*$ 6 months: $175 \pm 40^*$ 12 months: $170 \pm 42^*$ Comparison vs. baseline at 6 months: All patients: $p=0.01$ Asthma: $p=0.01$ Asthma + atopic dermatitis: $p=0.12$ *The range of AQLQ scores reported in this study suggest that the authors did not use the mean score on each of the 32 AQLQ items (the standard approach), which would result in an overall score between 1 and 7; it is possible that the authors instead used the sum of the scores, rendering the results not directly comparable to those reported in other studies <u>Other HRQOL:</u> DLQI (mean $\pm$ SD): Baseline: 19 ± 10 6 months: 7 ± 8 12 months: 6 ± 6 Significant improvement, $p=0.01$

Germany ¹¹⁰	X-Tab: Non-interventional study to assess patient-related mid-term outcomes of omalizumab therapy in severe allergic asthmatic patients	Ongoing multicenter study with a follow up of 3 years	Omalizumab (n=161)	ACQ: Baseline: mean (SD) ACQ score: 1.95 ± 1.17
Italy ¹¹¹	Real-life prospective study on asthma control in Italy: Cross-sectional phase results	Cross-sectional phase of the PRISMA study (n=2,835 overall asthma patients; n=1,380 patients on medium- to high-dosage ICS+LABA) Control assessed by ACT	PBO (n=11)	Pre-tx: -4.0 ± 2.90 Post-tx: NR
Italy ¹¹²	Changes in total IgE plasma concentration measured at the third month during anti-IgE treatment predict future exacerbation rates in difficult-to-treat atopic asthma: A pilot study	Prospective cohort study EX: Events of asthma impairment requiring a substantial implementation of regular daily treatment (mainly with OCS) or leading to hospitalization	Omalizumab (n=23)	<u>EX rates:</u> Pre-tx (time period NR): 2.1 ± 1.1 Post-tx: 0.5 ± 0.7* <u>ACT (mean, SD):</u> Baseline: 11.9 ± 3.1 3 months: 19.1 ± 4.3 12 months: 20.3 ± 4.3 Significant change, $p < 0.001$, at 3 months. No additional improvement over remaining months ($p = 0.16$)
Italy ¹¹³	Omalizumab management beyond clinical trials: The added value of a network model	Retrospective cohort study Major EX: Need for ED visits or hospitalization Minor E: Need for OCS	Omalizumab (n=59)	<u>% with major EX:</u> Pre-tx: 41.9% Post-tx start: 88.6% <u>% with minor EX:</u> Pre-tx: 16.3% Post-tx start: 79.6%*
Italy ¹¹⁴	Italian real-life experience of omalizumab	Prospective cohort study	Omalizumab Baseline (n=139) Follow up (n=93)	<u>EX rate:</u> Pre-tx: 4.87 ± 4.00 EX rate: 88.5% Post-tx: per year: 1 ± 1.29 % with EX: 18.3%
Italy ¹¹⁵	Asthma control in severe asthmatics under treatment with omalizumab: A cross-sectional observational study in Italy	Cross-sectional national observational study (patients in 26 Italian health centers)	Omalizumab (n=296)	<u>ACT (mean, SD):</u> ACT score, mean (range): 21 (6—25) ACT score ≥20, n (%): 202 (66%) Poorly controlled asthma (n=75): ACT score, mean (range): 17 (6–22) Partially controlled asthma (n=144): ACT score, mean (range): 21 (14–25) Well controlled asthma (n=77): ACT score, mean

				(range): 24 (16–25) No EX in last year of omalizumab treatment (n=167): ACT score, mean (range): 22 (10–25) ≥1 EX in last year of omalizumab treatment (n=125): ACT score, mean (range): 20 (6–25)
Italy ¹¹⁶	Profiles of proinflammatory cytokines in sputum from different groups of severe asthmatic patients	Prospective cohort study (36 months) Patients with SA were recruited from the Pneumology Section of the Cardiothoracic Department, University of Pisa, during a 3-year period Eosinophilia: >2% of sputum cells	ICS+LABA (n=64)	<u>Group 1</u> (patients with frequent EX, ≥3 per year): 6.0 ± 4.3 <u>Group 2</u> (patients with persistent bronchoconstriction (postbronchodilator: FEV₁ ≤70% of predicted, without frequent EX): 0.9 ± 0.9 <u>Group 3</u> (both frequent EX and bronchoconstriction): 4.9 ± 3.9 <u>Hospitalizations per year (mean ±, SD):</u> Group 1: 0.4 ± 0.6 Group 2: N/A Group 3: 0.1 ± 0.3 <u>Mean hospitalizations per year:</u> Group 1: 0.4 ± 0.6 Group 2: N/A Group 3: 0.1 ± 0.3 <u>Sputum eosinophil characteristics, median (range), %:</u> Group 1: Patients with frequent EX of asthma (≥3/year): 1.3 (0–68.1) Group 2: Persistent bronchoconstriction (postbronchodilator FEV₁ ≤70% of predicted) without frequent EX: 0.6 (0–46.1) Group 3: Patients with features of both groups: 1.8 (0–34.9)
Italy ¹¹⁷ Meeting abstract	Relationship between clinical-functional findings and biomarkers in patients with severe asthma	Prospective cohort study Eosinophilia: >2% of sputum cells	Overall (n=56) Uncontrolled (n=27) Partially controlled (n=25) Controlled= (n=4)	<u>In uncontrolled patients:</u> Sputum eosinophils >2%: 14/27 (63.6%) Sputum eosinophils (%) median (range): 20.1 (0–84.1)
Italy ¹¹⁸	Effects of oral prednisone on sputum eosinophils and cytokines in patients with severe refractory asthma	RCT	Prednisone (n=39) PBO (n=20) Subgroup analysis: Eosinophilic (n=20)	<u>Prednisone:</u> FEV₁ (L) baseline: 1.86 ± 0.67 2 weeks: 2.04 ± 0.64 % predicted FEV₁ baseline: 67.6 ± 16.3 Baseline vs. second visit (p=0.03) <u>PBO:</u> FEV₁ (L) baseline: 1.84 ± 0.57 2 weeks: 1.78 ± 0.55

				% predicted FEV₁ baseline: 69.6 ± 18.1 Baseline vs. second visit NS, <i>p</i>-value NR <u>Subgroup analysis:</u> FEV₁ (L) baseline: 1.85 ± 0.69 % predicted FEV₁ baseline: 68.4 ± 17.8 Before prednisone: 68.2 ± 16.9 After prednisone: 80.8 ± 12.5 % predicted FEV₁, after prednisone vs. before prednisone (<i>p</i><0.001)
Italy ¹¹⁹	Drop-out rate among patients treated with omalizumab for severe asthma: Literature review and real-life experience	Literature review and comparative analysis Outcome: Dropout/discontinuation	Omalizumab treatment RCTs (n=1,719) Real-life studies (n=13,466) NEONet database (Italian North East Omalizumab Network database) (n=221)	<u>Dropout rate:</u> RCTs: 7.1%—19.4% Real-life studies: 0–45.5% NEONet database: 32% Comparison of dropout rate mean values and reasons between NEONet database and published real-life studies Dropout: NEONet: 31.67% Real life: 17.50% <i>p</i>-value: 0.0000 Patient decision: NEONet: 48.57% Real life: 35.01% <i>p</i>-value: 0.0160 Lack of efficacy: NEONet: 25.71% Real life: 23.53% <i>p</i>-value: 0.3475 Adverse events: NEONet: 7.14% Real life: 12.04% <i>p</i>-value: 0.1176 Other causes: NEONet: 18.57% Real life: 29.41% <i>p</i>-value: 0.0318
Italy ¹²⁰	Burden of disease and health care costs of adult patients with severe refractory asthma in a	Retrospective cohort study 9 months	Various treatments	Patients hospitalized from all causes during follow up was 12%

	big real-world database (Arco)			
Italy ¹²¹	RItA: The Italian severe/uncontrolled asthma registry		493 adult patients from 27 Italian centers	About 30% of patients showed late onset asthma diagnosis/symptoms (>40 years old). The mean age for asthma symptoms onset was 30.2 years and asthma diagnosis onset was 34.4 years. 97.1% used ICS (dose 2,000 BDP), 93.6% LABA in association with ICS, 53.3% LTRAs, 64.1% anti-IgE, 10.7% theophylline, and 16.0% oral corticosteroids. Mean FEV ₁ % predicted of 75.1%, median values of 300/mm ³ of blood eosinophil count, 323 kU/L of serum total IgE, and 24 ppb of FENO were shown
Spain ¹²²	Factors associated with the control of severe asthma	Cross-sectional study (n=1,224) Control assessed by ACQ	Patients with SA attending respiratory medicine and allergology clinics throughout Spain	Incidence of SUA in SA patient population: 55.7% (377/677)
Spain ¹²³	Prevalence of uncontrolled severe persistent asthma in pneumology and allergy hospital units in Spain	Cross-sectional study (patients of 164 pneumology and allergology researchers at hospital units proportionally distributed throughout Spain) (n=36,649) for incidence study Control assessed by clinical judgement and GINA guidelines	All patients with asthma attending the pneumology or allergology units at the participating hospitals Treatment groups for AQLQ: NR (n=666)	<u>Incidence of SUA in asthma patient population:</u> Clinician judgment: 3.9% (1,423/36,649) GINA guidelines: 1.8% (666/36,649) AQLQ (mean, SD): 3.5 ± 1.1 ACQ (mean, SD): 3.8 ± 1.0
Spain ¹²⁴	Omalizumab therapy in severe asthma: Experience from the Spanish registry - Some new approaches	Retrospective cohort study	Omalizumab Baseline (n=263) 4 months (n=229) 1 year (n=225) 2 years (n=128)	<u>EX rates:</u> Omalizumab: Pre-tx: previous year, severe: 3.6 ± 3.6 Post-tx: 0.67 ± 1.2* Post-tx: Omalizumab baseline: 0.64 ± 1.2* Omalizumab 4 months: 0.71 ± 1.3* Omalizumab 2 years: 1.04 ± 1.8* EX rates of a subgroup with baseline IgE >700 IU/mL: Pre-tx: 3.58 ± 3.1 Post-tx: 0.72 ± 1.7* <u>ACT (mean, SD):</u> Baseline: 14.3 ± 4.7 4 months: 18.4 ± 4.4 (p<0.05) 12 months: 19.4 ± 4.5 24 months: 20.3 ± 4.0 (p<0.05) Significant improvement at all timepoints, p<0.05
Spain ¹²⁵	Factors associated with	Prospective observational and cross-	N=343	Only 10% of patients with SA evaluated in this study

	uncontrolled severe asthma and with control perception by physicians and patients	sectional study Control according to GEMA criteria		are controlled according to GEMA criteria. Patients and physicians overestimate control, and the overestimation by patients is greater. Physical inactivity and obesity are associated with a lack of control according to GEMA
Spain ¹²⁶	[Relationship between comorbidity and asthma control]	Prospective observational study		Compared with patients with ACT <20, those with ACT ≥20 had better lung function, less variation in PEF, less bronchial hyper-reactivity, and lower FENO values. 95% and 97% of patients with controlled and uncontrolled asthma had comorbidities, respectively. Only the presence of nasal polyps, GORD, and ABPA were more frequent in the uncontrolled group. The simultaneous presence of three or more comorbidities was significantly more frequent in patients with suboptimal control ($p=0.01$)
Spain ¹²⁷	Experience with omalizumab in the treatment of patients with severe allergic asthma: A first approach at 16 weeks	Retrospective cohort study (medical records of patients of the Asthma Unit of the Hospital Costa del Sol, Marbella, Málaga)	Omalizumab (n=25)	<u>ACT (mean, SD):</u> Baseline: 14 ± 3 16 weeks: 20 ± 3 NS improvement, $p=0.12$
Spain ¹²⁸	Profile of patients treated with omalizumab in routine clinical practice in Spain	Retrospective observational study	Omalizumab (pre vs. post) N=214	<u>ACQ (mean, SD):</u> Pre-omalizumab (n=55): 3.0 ± 1.3 Post-omalizumab (n=17): 2.5 ± 1.7 $p<0.0008$ vs. baseline
Spain ¹²⁹	Comparison of costs and clinical outcomes between hospital and outpatient administration of omalizumab in patients with severe uncontrolled asthma	Retrospective cohort study (patients of a day hospital and primary care center)	Omalizumab (pre vs. post) N=130	<u>ACQ (mean, SD):</u> Pre-omalizumab: 3 ± 1 Post-omalizumab: 2 ± 1 $p<0.001$ vs. baseline <u>ACT (mean, SD):</u> Pre-omalizumab: 12 ± 4 Post-omalizumab: 21 ± 4 $p<0.001$ vs. baseline
Spain ¹³⁰	Exhaled nitric oxide predicts control in patients with difficult-to-treat asthma	Prospective cohort study (pneumology and allergology units of the Hospital Xeral-Calde, Lugo)	ICS+LABA (n=102)	<u>ACT (mean, SD):</u> Baseline: 14 ± 1 1 month: 17 2 months: 16 1 month vs. baseline: $p<0.05$
Poland ¹³¹	Gender and presence of profound psychological traumas vs. the presence and intensity of panic disorder in difficult and severe asthma and	Prospective cohort study	Overall (n=206) SUA (n=106) Aspirin-induced asthma (n=100)	Trauma during adulthood was significantly more common ($p<0.001$) in SUA patients than among patients with aspirin-induced asthma

	aspirin-induced asthma of different severity			
Poland ¹³²	High-sensitivity C-reactive protein in the exhaled breath condensate and serum in stable and unstable asthma	Cross-sectional study	Overall (N=62) Severe, unstable asthma (n=23)	Blood eosinophil count, median (range) in SUA patients: 341 ± 102 cells/mm ³ (0.341×10^9 cells/L)
Ireland ¹³³	A study into efficacy of omalizumab therapy in patients with severe persistent allergic asthma at a tertiary referral centre for asthma in Ireland	Retrospective cohort study EX: Events of asthma impairment requiring a substantial implementation of regular daily treatment (mainly with OCS) or leading to hospitalization	Omalizumab responders after 4 months of treatment (n=30)	EX rates: Pre-tx: 3.48 ± 2.20 (time period NR) Post-tx: $0.93 \pm 0.83^*$
Belgium ¹³⁴	Azithromycin for prevention of exacerbations in severe asthma (AZISAST): A multicentre randomised double-blind placebo-controlled trial	RCT Severe EX: Deterioration in asthma leading to at least one of the following: 1) hospitalization 2) ED visit 3) need for systemic corticosteroids for at least 3 days	Azithromycin (n=55) PBO (n=54) <u>Noneosinophilic subgroup ($\leq 200/\mu\text{L}$):</u> Azithromycin: n=NR laceboPBO: n=NR <u>Eosinophilic subgroup ($> 200/\mu\text{L}$):</u> Azithromycin: n=NR laceboPBO: n=NR	EX rates: Post-tx: Azithromycin: 0.55 (severe) PBO: 0.52 (severe) Number of severe events: Azithromycin: 30 PBO: 27 Noneosinophilic subgroup: Post-tx azithromycin: 0.26 (severe)* PBO: 0.62 (severe) Eosinophilic subgroup: Post-tx azithromycin: 0.82 (severe)* PBO: 0.38 (severe) <u>AQLQ (mean, SD):</u> Azithromycin: Baseline: 5.5 ± 0.9 10 weeks: 0.24 ± 0.84 26 weeks: 0.32 ± 0.89 PBO: Baseline: 5.2 ± 1.1 10 weeks: 0.15 ± 0.63 26 weeks: 0.20 ± 0.73 NS improvement with azithromycin vs. PBO, $p=0.467$ <u>ACQ (mean, SD):</u> Azithromycin: Baseline ACQ-7: 1.4 ± 0.9 Change at 10 weeks: -0.05 ± 0.98

				Change at 26 weeks: -0.24 ± 0.93 10 weeks: $p=0.940$ vs. PBO 26 weeks: $p=0.485$ vs. PBO PBO: Baseline ACQ-7: 1.7 ± 1.0 Change at 10 weeks: -0.04 ± 0.76 Change at 26 weeks: -0.12 ± 0.70
Belgium ¹³⁵ Meeting abstract	Cross-sectional analysis of the Belgian severe asthma registry	Cross-sectional study (refractory asthmatics from seven centers enrolled in the Belgian Severe Asthma Registry)	Treatment group: NR (n=229)	AQLQ (mean, SD): 4.39 ACQ (mean, SD): >0.75: 87.0% ACT (mean, SD): <20: 85%
Switzerland ¹³⁶	Health status measurement in patients with severe asthma	Cross-sectional study (patients with SA who were referred to the Dutch Asthma Centre in Davos for high altitude treatment)		<u>AQLQ (mean, SD):</u> Symptoms: 3.9 ± 1.1 Activity limitation: 3.5 ± 1.2 Emotional function: 4.9 ± 1.3 Environmental stimuli: 4.2 ± 1.5 Total: 4.0 ± 1.0 95% CI: Symptoms: 3.7, 4.1 Activity limitation 3.3, 3.6 Emotional function: 4.7, 5.1 Environmental stimuli: 4.0, 4.5 Total: 3.8, 4.1 <i>p</i>-value NR <u>ACQ (mean, SD):</u> 3.2 ± 1.1 <u>Other HRQOL:</u> NSCI (mean $\pm$ SD): Symptoms Subjective symptoms: 14.1 ± 4.2 Dyspnea emotions: 12.0 ± 4.0 Fatigue: 47.1 ± 8.7 <i>p</i>-value NR 95% CI Subjective symptoms: 13.5, 14.8 Dyspnea emotions: 11.4, 12.6 Fatigue: 45.8, 48.5 Functional impairment: Behavioral impairment: 26.2 ± 20.5 Subjective impairment: 17.7 ± 5.4 QOL: General QOL: 28.0 ± 17.8 HRQOL: 6.1 ± 1.7

				Satisfaction relations: 4.1 ± 2.0
Sweden ¹³⁷	Phenotypic predictors of response to oral glucocorticosteroids in severe asthma	RCT	Prednisolone, pPBO (n=85, whole study population)	<u>FEV₁ % predicted, mean $\pm$ SD:</u> Baseline (whole study population): 73.2 ± 2.3 <u>FEV₁ (L), mean $\pm$ SD</u> Baseline (whole study population): 2.08 ± 0.08 <u>FEV₁ % predicted:</u> $p=0.002$ vs. PBO OCS use resulted in a mean 6.6% increase in FEV ₁ % predicted in SA: 58.3% of the SA
Belgium ¹³⁸	“Real-life” effectiveness of omalizumab in patients with severe persistent allergic asthma: The PERSIST study	Prospective cohort study (PERSIST: an open-label, observational, multicenter study in patients with severe persistent allergic asthma treated with omalizumab)	Omalizumab (n=158) PBO? (not listed on SUA final report Table 74)	<u>EX rates:</u> Omalizumab: 98.1% of patients had ≥ 1 severe EX in prior year % with severe EX: 9.1% PBO: % with severe EX: 34.4% <u>AQLQ (mean, SD):</u> Baseline: 3.24 ± 1.21 16 weeks: ≥ 0.5 patient improvement: 82.3% ≥ 1.0 patient improvement: 67.8 ≥ 1.5 patient improvement: 36.7% Mean improvement: 1.37 ± 1.09 16 weeks: significant improvement ≥ 0.5 pt with omalizumab, $p<0.001$ 52 weeks: ≥ 0.5 patient improvement: 84.4% ≥ 1.0 patient improvement: 68.9% ≥ 1.5 patient improvement: 53.3% Mean improvement: 1.79 ± 1.13 52 weeks: significant improvement ≥ 0.5 pt with omalizumab, $p<0.001$ <u>VAS (mean, SD):</u> Baseline: 52.29 ± 17.34 52 weeks: 14.22 ± 20.99 ; $p<0.001$ <u>Utility</u> Baseline: 0.54 ± 0.24 52 weeks: 0.14 ± 0.23 ; $p<0.001$ <u>Other HRQOL</u> Reduction in daytime symptoms: 16 weeks: 60.8%

				52 weeks: 63.8% 16 weeks: NS, <i>p</i> -value NR 52 weeks: <i>p</i> <0.001 Reduction in night-time symptoms: 16 weeks: 52.9% 52 weeks: 49.2% 16 weeks: <i>p</i> =0.034 52 weeks: NS, <i>p</i> -value NR
Denmark ¹³⁹	The prevalence of severe asthma and low asthma control among Danish adults	Register-based cross-sectional study (N=61,583) Control assessed by high SABA use (≥600 doses of SABA) and/or at least 1 EX in the 1-year period of observation	Asthma patients aged 18–44 years in 2010 who had redeemed ≥2 prescriptions for drugs with an ATC R03 during 365 days of observation or had a registered code in The Danish National Patient Register for omalizumab therapy	Incidence of SUA in asthma patient population: 3% (1,882/61,583) Incidence of SUA in uncontrolled asthma patient population: 11.7% (1,882/16,134) Incidence of SUA in SA patient population: 36.4% (1,822/5,001)
The Netherlands ¹⁴⁰	Severe adult-onset asthma: A distinct phenotype	Cross-sectional study (n=176) Control assessed: ACQ >1.5	Patients with adult onset asthma recruited from one academic and three nonacademic pulmonary outpatient clinics ACQ study population: NR (n=78)	Incidence of SUA in asthma patient population with adult onset asthma: 44.3% (78/176) AQLQ (mean, SD): 4.8 ± 1.15 ACQ (mean, SD): 1.91 ± 0.98
The Netherlands ¹⁴¹	The prevalence of severe refractory asthma	Descriptive observational study Questionnaires sent to patients with at least one prescription for an ICS in 2011 gathered from automated dispensing records from 65 community pharmacies in The Netherlands for ACQ Control assessed by IMI consensus statement 2011	Patients aged >18 years with ≥1 prescription for an ICS in 2011, selected from registration databases. Prescription for a high-dosage ICS (>1,000 mg/d fluticasone equivalent) plus a LABA or a medium- to high-dosage ICS (500–1,000 mg/d fluticasone equivalent) plus chronic OCS* and LABA Study population for ACQ: high-intensity treatment (high-dosage ICS/LABA) (N=929)	Incidence of SUA in asthma patient population: 3.6% (95% CI, 3.0–4.1) of adult Dutch asthma patients have severe refractory asthma 2.9% of adult Dutch asthma patients have difficult-to-control asthma ACQ (mean, SD): ACQ-6 median (range): 1.33 (0–5)
The Netherlands ¹⁴²	Airway inflammation in obese and non-obese patients with difficult-to-treat asthma	Observational	136 nonsmoking asthmatic adults with persistent symptoms despite high dosages of inhaled or oral corticosteroids and long-acting bronchodilators	Obese patients (n=29) had a higher FEV ₁ %pred (<i>p</i> =0.05) and a lower FRC/TLC%pred (<i>p</i> <0.01) compared with nonobese patients (n=107)
The Netherlands ¹⁴³	Extent of uncontrolled disease and associated medical costs in	Retrospective database analysis (N=32,163)	Patients aged 12–49 years who had redeemed ≥2 prescriptions for	Incidence of SUA in asthma patient population: 264 (0.8%) in database asthma population; 2,650 (0.7%)

	severe asthma--a PHARMO study	Control assessed by hospitalization for asthma or use of more than one short course (<30 days) of oral corticosteroids in 2004	asthma drugs (ATC code: R03) Study population for cost: Severe asthma patients (n=1,518) Uncontrolled with hospitalization (n=34) Uncontrolled with multiple courses of OCS (n=230)	[extrapolated] in The Netherlands Incidence of SUA in SA patient population: 17% <u>Costs:</u> Total costs: Uncontrolled with hospitalization (total): €376 Uncontrolled with multiple OCS courses (per patient): €11.1 Excess costs for uncontrolled asthma with hospitalization (per patient): €1.1 Excess costs for uncontrolled asthma with multiple OCS (total): €980 Direct costs: Medication and hospitalization costs in 2004 (1=€1,000) <i>Uncontrolled with hospitalization (total):</i> Total medication costs: 49 Controller medication: 36 Reliever medication: 13 Hospitalization costs: 327 <i>Uncontrolled with multiple OCS courses (per patient):</i> Total medication costs: 1.4 Controller medication: 1.0 Reliever medication: 0.4 Hospitalization costs: 9.6 <i>Excess costs for uncontrolled asthma with hospitalization (per patient):</i> Total medication costs: 1.1 Controller medication: 0.8 Reliever medication: 0.3 Hospitalization costs: 0
The Netherlands ¹⁴⁴	Cost-effectiveness of omalizumab for uncontrolled allergic asthma in the Netherlands	Retrospective cohort study Clinically significant EX: Worsening of asthma as judged clinically significant by the physician, requiring treatment with rescue oral or IV corticosteroids Clinically significant severe EX: A clinically significant EX also resulting in PEF <60% of personal best or predicted and requiring	Omalizumab Baseline (n=154) Follow up (n=114)	<u>EX rates:</u> Pre-tx: Clinically significant Prior year: 2.42 (SD NR) Severe: Prior year: 0.97 (SD NR) All: Prior year: 3.39 (SD NR) Post-tx: Clinically significant: 0.86 (SD NR) Severe: 0.22 (SD NR) All: 1.07 (SD NR)

		treatment with systemic corticosteroids		
The Netherlands ¹⁴⁵	Internet-based tapering of oral corticosteroids in severe asthma: A pragmatic randomized controlled trial	RCT Severe EX: Deterioration in asthma leading to at least one of the following: hospitalization, ED visit, need for systemic corticosteroids for at least 3 days	<u>Study population for EX:</u> Internet-based tapering of OCS (n=51) Conventional tapering of OCS (n=38) <u>Study population for AQLQ:</u> Internet-based tapering of OCS (n=52) Conventional tapering of OCS (n=43) <u>Study population for other HRQOL:</u> Internet (n=52) Conventional (n=43)	<u>EX rates:</u> Internet-based tapering of OCS: Pre-tx: Per patient: 1 (0–1) Per year: 1.68 (0–3.9) Conventional tapering of OCS (n=38): Pre-tx: Per patient: 1 (0–1) Per year: 1.68 (0–3.9) <u>AQLQ (mean, SD):</u> Internet-based tapering: Baseline: 5.0 ± 1.06 Change at 6 months: --0.03 ± 0.10 Conventional tapering: Baseline: 4.6 ± 1.18 Change at 6 months: 0.14 ± 0.13 <u>ACQ (mean, SD):</u> Internet-based tapering: Baseline: 2.2 ± 1.11 Change at 6 months: 0.26 ± 0.09 (SE) Conventional tapering: Baseline: 2.5 ± 0.95 Change at 6 months: 0.12 ± 0.12 (SE) NS difference between groups, $p=0.37$ <u>Other HRQOL:</u> Global satisfaction scale (mean ± SD): Internet-based tapering: 5.58 ± 0.2 Conventional tapering: 6.08 ± 0.18 NS improvement with internet intervention, $p=0.09$
The Netherlands ¹⁴⁶	Tiotropium improves lung function in patients with severe uncontrolled asthma: A randomized controlled trial	RCT	Tiotropium 5 µg (n=104) Tiotropium 10 µg (n=103) PBO (n=103)	<u>AQLQ (mean, SD):</u> Baseline (all patients): 4.8 ± 1.1 Change of 0.1 points for both active treatments compared with PBO NS, p -value NR
The Netherlands ¹⁴⁷	Risk factors of frequent exacerbations in difficult-to-treat asthma	Cross-sectional study Patients with difficult-to-treat bronchial asthma consecutively recruited from outpatient pulmonary departments of 10 hospitals to evaluate clinical factors EX: Periods of deteriorating	Overall (n=63) 1 prior EX (n=24) ≥3 prior EX (n=39)	<u>Median (range) number of EX in the previous year:</u> Group with 1 EX in the past year: 1 (1–1) Group with ≥3 EX in the past year: 4 (3–7) <u>In patients with a history of frequent EX (≥3 per year):</u> Hospitalizations in previous year (median, range): 0 (0–8) <u>In patients without frequent EX (1 per year):</u>

		symptoms or lung function requiring a course of oral corticosteroids, as judged by the patient's own chest physician		Hospitalizations in previous year (median, range): 0 (0–1) <u>In patients with a history of frequent EX (≥ 3 per year):</u> Emergency visits in previous year (median, range): 2 (0–10) <u>In patients without frequent EX (1 per year):</u> Emergency visits in previous year (median, range): 0 (0–5)
Portugal ¹⁴⁸	Real-life efficacy and safety of omalizumab in Portuguese patients with persistent uncontrolled asthma	Single-arm open-label observational study (the eXpeRience registry collected data from patients receiving omalizumab for uncontrolled persistent allergic asthma in Europe, Canada, and Asia)	Treatment group; Portuguese Experience patients (N=62)	<u>AQLQ (mean, SD):</u> Mini AQLQ: Baseline: 3.1 ± 1.1 Month 12: 5.1 ± 1.5 Month 24: 5.8 ± 1.3 <u>ACT (mean, SD) 12 months:</u> ≥ 2 -point improvement: 31 (88.6%) Transition from uncontrolled to controlled asthma: 22 (62.9%) 24 months ≥ 2 -point improvement: 23 (88.5%) Transition from uncontrolled to controlled asthma: 18 (69.2%)
Portugal ¹⁴⁹	Clinical experience with omalizumab in the severe asthma unit	Single-arm open-label observational study (records from the Severe Asthma Outpatient Clinic of Pulido Valente Hospital, Lisbon)	Omalizumab (N=26)	ACT scores Baseline: 12.08 6 months: 19.52 12 months 19.87 24 months: 19.92 Significant improvements at 6 months of follow up (Wilcoxon 0.00)
Portugal ¹⁵⁰	Asthma control and exacerbations in patients with severe asthma treated with omalizumab in Portugal	Observational prospective study The study was conducted in six hospitals in Portugal. In each unit, all asthma patients under treatment with omalizumab were included regardless of age, length of previous therapy with omalizumab, or actual treatment schedule	Omalizumab (N=48)	Sparing of prednisone in 6 months (mg, median): 6.2 Unscheduled health care utilization or increase in OCS intake because of asthma: 12-month rate: 1.7
Greece ¹⁵¹	Increased levels of osteopontin in sputum supernatant in severe refractory asthma	Cross-sectional study	N=33	Sputum eosinophils (%) median (IQR): 11% (4–19%)
Greece, Cyprus ¹⁵²	Long-term omalizumab treatment in severe allergic asthma: The South-Eastern	Retrospective cohort study Severe EX: Required systemic	Omalizumab (n=60)	<u>EX rates:</u> Prior year: 2.27 ± 2.82 17 weeks: $0.40 \pm 0.81^*$

	Mediterranean “real-life” experience	corticosteroid or ED visit or hospitalization		52 weeks: $0.77 \pm 0.94^*$ 209 weeks: $0.66 \pm 0.73^*$ <u>ACT (mean, SD):</u> Baseline: 17.28 ± 4.67 4 months: 19.73 ± 3.40 ; $p=0.001$ 1 year: 21.20 ± 2.44 ; $p<0.0001$ 4 years: 21.50 ± 1.83 ; $p<0.0001$
Azerbaijan ¹⁵³	Tiotropium in uncontrolled and severe bronchial asthma: Can we modify the treatment of severe disease?	Prospective cohort study	Tiotropium+ salmeterol/fluticasone compared with salmeterol/fluticasone (n=34)	<u>FEV₁ % predicted, mean $\pm$ variance measure not specified</u> Baseline: NR 3 months: 70.41 ± 6.23 $p=0.05$, not clear if comparison with baseline or between groups
11 EU Countries ¹⁵⁴	Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort	Multicenter prospective cohort study (16 clinical centers in 11 European countries; part of the U-BIOPRED project)	Treatment group: Nonsmoking SUA (n=276) Smoking/ex-smoking SUA (n=92) Total SUA population (N=421)	<u>AQLQ (mean, SD):</u> Nonsmoking SUA: Symptoms: 4.46 ± 0.08 Activity limitation: 4.35 ± 0.07 Emotional: 4.63 ± 0.1 Environmental stimuli: 4.69 ± 0.09 Total: 4.48 ± 0.07 $pp<0.001$ in all categories (severe asthma group vs. mild/moderate group) Smoking/ex-smoking SUA: Symptoms: 4.36 ± 0.14 Activity limitation: 4.45 ± 0.13 Emotional: 4.52 ± 0.16 Environmental stimuli: 4.57 ± 0.16 Total: 4.44 ± 0.13 <u>ACQ (mean, SD):</u> ACQ-5: Nonsmoking SUA: 2.28 ± 0.07 Smoking/ex-smoking SUA: 2.23 ± 0.12 ACQ-7: Nonsmoking SUA: 2.67 ± 0.08 Smoking/ex-smoking SUA: 2.62 ± 0.12 $p<0.001$ in all categories (severe asthma group vs. mild/moderate group) <u>Other HRQOL:</u> HADS (nonsmoking SUA): Total: 12.33 ± 0.54 Anxiety: 6.94 ± 0.3 Depression: 5.39 ± 0.28

				HADS (smoking/ex-smoking SUA): Total: 13.64 ± 1.01 Anxiety: 7.71 ± 0.54 Depression: 5.93 ± 0.56 SNOT-20 (total): Nonsmoking SUA: 31.76 ± 1.01 Smoking/ex-smoking SUA: 32.12 ± 1.92 ESS (total): Nonsmoking SUA: 7.48 ± 0.26 Smoking/ex-smoking SUA: 7.95 ± 0.47 MARS (total): Nonsmoking SUA: 22.44 ± 0.14 Smoking/ex-smoking SUA: 22.17 ± 0.29 $p < 0.001$ in all categories except MARS, where $p = 0.002$ (severe asthma group vs. mild/moderate group)
Multinational: Germany and United Kingdom ¹⁵⁵	Specific IgE against Staphylococcus aureus enterotoxins: An independent risk factor for asthma	Retrospective cohort study	N=166	Proportion of patients hospitalized in the previous year: 83/166 (50%)
Non-European Union-5 (EU countries other than Germany, France, Italy, Spain, the UK) ¹⁵⁶	Risk factors and characteristics associated with severe and difficult to treat asthma phenotype: An analysis of the ENFUMOSA group of patients based on the ECRHS questionnaire	Cross-sectional study	N=155 SUA	Work affecting breathing in SUA patients vs. patients with nonsevere, controlled disease: OR (95% CI): 2.7 (1.6–4.5) Having to change jobs in SUA patients vs. patients with nonsevere, controlled disease: OR (95% CI): 4.3 (2.1—7.8) Employment status at the time of the study in SUA patients vs. patients with nonsevere, controlled disease: OR (95% CI): 0.39 (0.24—0.7) The prevalence of self-reported allergy was lower in the severe/difficult-to-treat asthma group compared with the mild to moderate group (OR 0.45 [95% CI 0.28—0.70])
Turkey ¹⁵⁷	Comparison of allergic asthma patients treated with omalizumab and non-allergic patients treated with continuous oral corticosteroids: Results of five year follow-up therapies	Prospective cohort study EX: Requiring at least 3 days of steroid treatment	Omalizumab Allergic group (n=17) Nonallergic group (n=16)	<u>EX rates:</u> Pre-tx: Allergic: 2.57 Nonallergic: 2.38 Post-tx: * Year 1: Allergic: 0.29

				Nonallergic: 1.07 Year 2: Allergic: 0.24 Nonallergic: 1.5 Year 5: Allergic: 0.59 Nonallergic: 3.3 <u>ACT (mean, SD):</u> Allergic: Baseline: 17.7 ± 1.4 16 weeks: 21.4 ± 1.5 Year 1: 23.2 ± 1.5 Year 2: 23.2 ± 1.3 Year 5: 22.8 ± 2.7 Allergic: $p < 0.01$ for every follow-up time vs. allergic group baseline $p < 0.01$ for 16-week and 2-year follow-up points between the two groups $p < 0.05$ for 1-year follow-up points between the two groups Nonallergic: Baseline: 14.6 ± 3.9 16 weeks: 18.8 ± 3.1 Year 1: 21.0 ± 3.1 Year 2: 20.7 ± 2.9 Year 5: 22.1 ± 2.3 Nonallergic $p < 0.01$ for every follow-up time vs. nonallergic group baseline
Turkey ¹⁵⁸	A breath for health: An exploratory study in severe asthma patients in Turkey	Structured questionnaire	Patients with SA at 25 centers across Turkey: Uncontrolled asthma (n=274) Controlled asthma (n=177)	Nearly 70% of uncontrolled asthmatic patients defined asthma as disturbing with significant restrictions in daily life
Turkey ¹⁵⁹	Assessment of long-term omalizumab treatment in patients with severe allergic asthma long-term omalizumab treatment in severe asthma	Medical records review	Study population: 26 patients (female/male: 21/5) with severe allergic asthma, uncontrolled despite GINA 2006 step 4 therapy	FEV ₁ improved significantly at all control points vs. baseline ($p < 0.05$). The level of asthma control (ACT) improved significantly after treatment ($p < 0.05$). EX, ED visits, hospitalizations, SGCs, and SABA use significantly reduced by the end of 36 months ($p < 0.05$). The percentage of patients with improvements larger than 1.5 points in AQLQ(S) total score was 80.7% at

Turkey ¹⁶⁰ Conference abstract	Omalizumab in patients with severe persistent asthma in real life setting in Manisa, Turkey	Retrospective cohort study	Omalizumab (N=47)	Month 4 and 96.1% at Month 36 of treatment *Statistically significant decrease in EX in Years 1, 2, 3, 4 <u>ACT:</u> Significant improvement in ACT score (at 16 weeks, $p<0.002$; at 1 year, $p<0.001$; at 2 years, $p<0.001$; at 3 years, $p<0.001$; and 4 years, $p<0.003$) and in almost all of the five individual questions
Turkey ¹⁶¹	Tiotropium may improve asthma symptoms and lung function in asthmatic patients with irreversible airway obstruction: The real-life data	Retrospective database analysis 1 year of asthma follow up and ≥ 3 months of tiotropium bromide treatment and follow up	Tiotropium add-on therapy (n=64)	FEV1 12 months before add-on: 57.5 ± 1.9 12 months after add-on: 65.5 ± 1.9 $p=0.000$ vs. baseline Hospitalization rate: Pre-tx: 1.5 ± 0.3 Post-tx: 0.4 ± 0.1 $p=0.002$
Turkey ¹⁶²	Long term effect of anti-IgE (omalizumab) treatment on asthma control in patients with uncontrolled severe persistent asthma: Real Life study	Real-life cohort study	Omalizumab (n=29)	Adjusted RR risk of hospitalization or ED visits for asthma during omalizumab treatment vs. nontreatment periods was 0.35 (95% CI, 0.23–0.44). Mean duration of hospitalization was decreased (17.8 days vs. 3.3 days)
Brazil ¹⁶³	Comparison between two methods of asthma control evaluation based on individual perception	Cross-sectional study (n=423) Control assessed by patient self-assessment and ACQ	Patients with SA treated at the Bahia State Asthma and Allergic Rhinitis Control Program Central Referral Clinic between August 2008 and March 2010	Incidence of SUA in SA patient population (patient self-assessment): 8.0% (34/423) Incidence of SUA in SA patient population (ACQ ≥ 1.5): 38.8% (164/423)
Brazil ¹⁶⁴	Factors associated with uncontrolled asthma in Porto Alegre, Brazil	Cross-sectional study (n=275) GINA 2006 criteria	Patients were sequentially recruited from the outpatient Asthma Clinic of HCPA, Porto Alegre, State of Rio Grande do Sul, Brazil	Incidence of SUA in asthma patient population: 38.9% (107/275) Incidence of SUA in uncontrolled asthma patient population: 69.9% (107/153) Incidence of SUA in SA patient population: 74.3% (107/144)
Brazil ¹⁶⁵	Risk factors for death in patients with severe asthma	Nested case-control study	Patients with SA who died (n=58) Controls (n=232)	Most deaths were attributed to respiratory causes. Multivariate analysis showed that male gender, FEV ₁ prebronchodilator $<60\%$ of predicted, and the lack of control of asthma symptoms were significantly and independently associated with death among patients

				with SA
Brazil ¹⁶⁶	Estimating the budget impact of adding omalizumab to standard therapy in patients with uncontrolled severe allergic asthma from private health care system perspective in Brazil	Population survey (n=183 million)	Local epidemiological data using 2013 population estimate (age ≥6 years) in a population of 183 million	Estimated prevalence of asthma: 10.0% Proportion of asthma patients with SUA: 2.4%
Brazil ¹⁶⁷	Clinical characteristics and possible phenotypes of an adult severe asthma population	Cross-sectional study (asthma patients from several regions of Sao Paulo, who registered at the outpatient asthma clinic of a university hospital)	All patients (n=74) Atopic (n=44) Nonatopic (n=25) Eosinophil + (n=53) Eosinophil – (n=14)	<u>ACQ (mean, SD):</u> All patients: 3.2 ± 1.1 Atopic: 3.19 ± 1.5 Nonatopic: 3.21 ± 1.0 Eosinophil +: 3.22 ± 1.11 Eosinophil –: 3.04 ± 1.22 <u>ACT (mean, SD):</u> All patients: 11.7 ± 4.5 Atopic: 12 ± 4.5 Nonatopic: 11.5 ± 4.5 Eosinophil +: 11.8 ± 4.8 Eosinophil –: 12 ± 3.8 <u>SGRQ:</u> Symptoms: 63 ± 18 Activity: 80 ± 17 Impact: 64 ± 14 Total: 67 ± 14 <u>SF-36:</u> Physical function: 34.9 ± 22.9 Physical role: 25.4 ± 31.4 Body pain: 39.4 ± 22.5 General health: 40.5 ± 19.8 Vitality: 40.8 ± 20.2 Social function: 54.4 ± 26.8 Emotional aspects: 32.4 ± 42.2 Mental health: 50.1 ± 22.9 <u>STAI:</u> Score: 36.6 ± 9.2 Score ≥30: 81% Score ≥50: 8.5% <u>Beck Depression Index:</u> Score: 16.2 ± 11.7 Score ≥19: 31% Score ≥30: 11%

Brazil ¹⁶⁸	Effect of omalizumab as add-on therapy on asthma-related quality of life in severe allergic asthma: A Brazilian study (QUALITX)	RCT	Omalizumab+ LABA + ICS (n=78) LABA + ICS (n=38)	<u>EX rates:</u> Omalizumab + LABA + ICS: % of patients with EX: 43.6% LABA + ICS: % of patients with EX: 52.6% <u>AQLQ (mean, SD):</u> Omalizumab + LABA+ ICS total score: Baseline: 3.0 ± 1.0 Week 12: 4.2 ± 1.4 Week 20: 4.4 ± 1.4 Mean change from baseline at Week 20: Activity limitation: 1.3 ± 0.1 Symptoms: 1.2 ± 0.2 Emotional function: 1.3 ± 0.2 Environmental stimuli: 1.2 ± 0.2 $p < 0.001$ vs. baseline at both timepoints Domain scores $p < 0.001$ vs. baseline for all LABA + ICS total score: Baseline: 3.1 ± 1.1 Week 12: 3.2 ± 1.2 Week 20: 3.0 ± 1.1 Mean change from baseline at Week 20: Activity limitation: -0.2 ± 0.1 Symptoms: -0.2 ± 0.2 Emotional function: 0 ± 0.1 Environmental stimuli: 0 ± 0.2 $p < 0.001$ vs. omalizumab at all timepoints Symptoms domain vs. omalizumab at Week 12 ($p = 0.002$) and Week 20 ($p < 0.001$) Significance vs. baseline: Activity limitation: $p = 0.490$ Symptoms: $p = 0.469$ Emotional function: $p = 0.877$ Environmental stimuli: $p = 0.844$ Patient-evaluated GETE: <i>Excellent:</i> Omalizumab + LABA + ICS: 47.5% LABA + ICS: 10.3% <i>Good:</i> Omalizumab + LABA + ICS: 33.9% LABA + ICS: 37.9% <i>Moderate:</i> Omalizumab + LABA + ICS: 16.9%
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				LABA + ICS: 24.1% <i>Poor:</i> Omalizumab + LABA + ICS: 1.7% LABA + ICS: 24.1% $p < 0.001$ between groups for all measures
Latin America ¹⁶⁹	The burden of unscheduled health care for asthma in Latin America	Asthma Insights and Reality in Latin America survey	2,074 total asthma patients* 448 with severe PA* Number of adults with severe PA NR	<u>Costs</u> The cost of unscheduled asthma care in adults with severe symptoms was U.S. \$558 compared with U.S. \$204 for those with mild intermittent symptoms. An average of 73.2% of annual asthma-related health care costs were from unscheduled health care.
China ¹⁷⁰	Omalizumab improves quality of life and asthma control in Chinese patients with moderate to severe asthma: A randomized phase III study	RCT EX: Just refer to “protocol-defined asthma exacerbations”	Omalizumab (n=310) PBO (n=299)	<u>EX rates:</u> Omalizumab: Pre-tx: 2.3 (0.8) Post-tx: 0.72 PBO: Pre-tx: 2.2 Post-tx: 0.109 <u>AQLQ (mean, SD):</u> In the omalizumab group, LSM changes from baseline for the overall (0.51), emotions (0.64), and environmental (0.54) scores were clinically meaningful (≥ 0.5 -point change from baseline) Change from baseline to Week 24 in AQLQ(S) scores: <i>Overall score:</i> Omalizumab: 58.2% (106/182) PBO: 39.3% (2/178) $p = 0.40$ <i>Symptoms score:</i> Omalizumab (n=208) PBO (n=206) $p = 0.30$ <i>Activity score:</i> Omalizumab (n=203) PBO (n=198) $p = 0.30$ <i>Emotions score:</i> Omalizumab (n=217) PBO (n=213) $p = 0.28$

				<i>Environmental score:</i> Omalizumab (n=201) PBO (n=203) $p=0.37$ All comparisons are statistically significant <u>ACQ (mean, SD):</u> LSM changes from baseline of ACQ scores were clinically meaningful (reduction of ≥ 0.5 unit) in the omalizumab group (-0.51) at Week 24 Change from baseline in ACQ scores: <i>Week 16:</i> Omalizumab (n=225) PBO (n=223) LSM-TD=-: -0.20; $p<0.001$ <i>Week 24:</i> Omalizumab (n=210) PBO (n=211) LSM-TD=-: -0.17; $p=0.002$ The percentage of patients achieving clinically meaningful improvements in ACQ scores was 49.5% (104/210) for the omalizumab group vs. 35.5% (75/211) for the PBO group when considering the response rate based on number of patients with available ACQ data <u>Other HRQOL:</u> Asthma symptom scores at 24 weeks change from baseline: Total omalizumab (n=287) PBO (n=282) LSM-TD=-: -0.21; $p=0.048$ <i>Night-time:</i> Omalizumab (n=292) PBO (n=288) LSM-TD: -0.12; $p=0.011$ <i>Morning:</i> Omalizumab (n=292) PBO (n=288)
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				LSM-TD=-: -0.01; $p=0.845$ <i>Daytime:</i> Omalizumab (n=292) PBO (n=288) LSM-TD=-: -0.08; $p=0.173$
South Korea/Japan ¹⁷¹	A Phase 2a study of benralizumab for patients with eosinophilic asthma in South Korea and Japan	RCT EX: An increase in asthma symptoms that required treatment OCS for at least 3 days	PBO (n=26) Benralizumab 2 mg (n=26) Benralizumab 20 mg (n=25) Benralizumab 100 mg (n=26)	<u>EX rate:</u> Pre-tx: PBO: 2.6 ± 1.0 Benralizumab 2 mg: 2.9 ± 1.1 Benralizumab 20 mg: 2.6 ± 1.1 Benralizumab 100 mg: 2.7 ± 0.9 Post-tx: Annual EX rate, counts/year (rate reduction %): PBO (n=26): 3.5 (--) Benralizumab 2 mg: 2.4 (33%) Benralizumab 20 mg: 1.9 (45%) Benralizumab 100 mg: 2.2 (36%) <u>ACQ (mean, SD):</u> Week 0 (baseline) (SD) PBO (n=26): 1.6 (0.6) Benralizumab 2 mg (n=26): 1.8 (0.6) Benralizumab 20 mg (n=25): 1.9 (0.7) Benralizumab 100 mg (n=26): 1.9 (0.8) Week 52: PBO (n=26): 0.8 (1.0) Benralizumab 2 mg (n=26): 0.9 (0.8) Benralizumab 20 mg (n=25): 1.0 (0.8) Benralizumab 100 mg (n=26): 1.0 (0.9) Mean ACQ-6 score decreased more rapidly in the benralizumab groups than in the PBO group. Clinically significant changes in the mean ACQ-6 score, as indicated by a decrease of ≥ 0.5, were noted from Week 8 onward in the 2-mg group and from Week 4 onward in the 20- and 100-mg groups
Korea ¹⁷²	Economic costs for adult asthmatics according to severity and control status in Korean tertiary hospitals	Prospective cohort Cohort for Reality and Evolution of Adult Asthma study	92 SA patients The proportion of patients with severe, uncontrolled asthma was NR	<u>Costs:</u> Total costs (mean, SD): U.S. \$7,784.4 $\pm$ 35 per year in SUA patients <i>For comparison:</i> U.S. \$3,868.2 $\pm$ 25 per year in SA patients who are somewhat controlled U.S. \$3,245.1 $\pm$ 32 per year in SA patients who are well controlled

				Direct costs: U.S. \$2,874.8 per year in SUA patients <i>For comparison:</i> U.S. \$1,530.9 per year in SA patients who are somewhat controlled U.S. \$2,024.6 per year in SA patients who are well controlled Indirect costs: U.S. \$4,909.5 per year in SUA patients <i>For comparison:</i> U.S. \$2,337.3 per year in SA patients who are somewhat controlled U.S. \$1,217.8 per year in SA patients who are well controlled
Taiwan ¹⁷³	Efficacy of omalizumab (Xolair(R)) in patients with moderate to severe predominately chronic oral steroid dependent asthma in Taiwan: A retrospective, population-based database cohort study	Retrospective database cohort study	Omalizumab (n=282)	<u>Baseline:</u> Inpatient visit: 55 (34.8 %) ED visit: 69 (43.7 %) Inpatient visit: 55 (34.8 %)
Japan ¹⁷⁴	Effects of adding omalizumab, an anti-immunoglobulin E antibody, on airway wall thickening in asthma	RCT	Omalizumab (n=14) Maintenance therapy (n=16)	<u>AQLQ (mean, SD):</u> Omalizumab: <i>Baseline: NR</i> <i>Change at 16 weeks:</i> Symptoms: 1.35 Activities: 1.56 Emotions: 1.52 Environmental stimuli: 1.46 Overall: 1.47 Significant change overall at 16 weeks, $p < 0.01$ Maintenance therapy: <i>Baseline: NR</i> <i>Change at 16 weeks:</i> Symptoms: 0.38 Activities: 0.12 Emotions: 0.23 Environmental stimuli: 0.37 Overall: 0.28
Japan ¹⁷⁵	Efficacy of omalizumab in	Prospective cohort study	Omalizumab (n=29)	<u>AQLQ (mean, SD):</u>

Meeting abstract	patients with severe refractory asthma: A comprehensive study			59.0% of patients experienced a ≥ 0.5-point improvement in overall score; no other specific data reported. There was significant improvement with omalizumab at 16 weeks, $p=0.002$ <u>ACQ – specific data NR:</u> Week 16: $p=0.009$ Week 48: Improvement persisted, specific data NR <u>Other HRQOL:</u> SGRQ: no specific data reported. Significant improvement at Week 16, $p=0.04$. Persisted to Week 48, p-value NR
Japan ¹⁷⁶	Effects of salmeterol in patients with persistent asthma receiving inhaled corticosteroid plus theophylline	Randomized, PBO-controlled, crossover study	Inhaled salmeterol (n=20) PBO	Compared with PBO, salmeterol significantly increased FEV₁. In 9 patients treated with high-dosage ICS plus theophylline and a leukotriene receptor antagonist, FEV₁ increased significantly more with salmeterol than PBO
Japan ¹⁷⁷	Predictors for identifying the efficacy of systemic steroids on sustained exhaled nitric oxide elevation in severe asthma	Retrospective cohort study	Prednisolone (n=20)	<u>ACQ (mean, SD):</u> Baseline: 1.8 ± 0.6 2 weeks: 1.1 ± 0.6, $p<0.01$
Japan ¹⁷⁸	Comprehensive efficacy of omalizumab for severe refractory asthma: A time-series observational study	Prospective cohort study (adult patients of the asthma clinic of Kyoto University Hospital)		<u>AQLQ:</u> Symptoms: Baseline all omalizumab: 4.3 ± 1.6 Baseline vs. 16 weeks: 0.97, $p<0.001$ 16 vs. 48 weeks: 0.66, $p<0.01$ Baseline vs. 48 weeks: 1.74, $p<0.001$ Activities: Baseline all omalizumab: 4.1 ± 1.4 Baseline vs. 16 weeks: 0.59, $p<0.05$ 16 vs. 48 weeks: 0.48, $p<0.01$ Baseline vs. 48 weeks: 1.07, $p<0.001$ Emotions: Baseline all omalizumab: 4.4 ± 1.6 Baseline vs. 16 weeks: 0.86, $p<0.01$ 16 vs. 48 weeks 0.42, $p<0.05$ Baseline vs. 48 weeks: 1.29, $p<0.001$ Environmental: Baseline all omalizumab: 4.5 ± 1.7 Baseline vs. 16 weeks: 0.62, $p<0.05$ 16 vs. 48 weeks: 0.47, $p<0.05$ Baseline vs. 48 weeks: 1.09, $p<0.001$

				Overall: Baseline all omalizumab: 4.2 ± 1.4 Baseline vs. 16 weeks: $0.81, p < 0.01$ 16 vs. 48 weeks: $0.50, p < 0.05$ Baseline vs. 48 weeks: $1.36, p < 0.001$ <u>ACQ (mean, SD):</u> Baseline all omalizumab: 2.0 ± 1.0 Baseline vs. 16 weeks: $-0.62, p < 0.01$ 16 vs. 48 weeks: $-0.37, p < 0.05$ Baseline vs. 48 weeks: $-1.11, p < 0.001$ <u>Other HRQOL:</u> SGRQ: Symptoms: Baseline all omalizumab: 65.7 ± 24.1 Baseline vs. 16 weeks: $-10.08, p < 0.05$ 16 vs. 48 wk: $-12.45, p < 0.01$ Baseline vs. 48 weeks: $-22.49, p < 0.001$ Activities: Baseline all omalizumab: 51.6 ± 27.8 Baseline vs. 16 weeks: -4.31 16 vs. 48 weeks: $-12.04, p < 0.05$ Baseline vs. 48 weeks: $-14.41, p < 0.001$ Impact: Baseline all omalizumab: 40.6 ± 23.4 Baseline vs. 16 weeks: $-9.81, p < 0.01$ 16 vs. 48 weeks: $-9.70, p < 0.01$ Baseline vs. 48 weeks: $-19.08, p < 0.001$ Total: Baseline all omalizumab: 48.1 ± 23.1 Baseline vs. 16 weeks: $-4.88, p < 0.05$ 16 vs. 48 weeks: $-14.81, p < 0.01$ Baseline vs. 48 wk: $-18.24, p < 0.001$
Japan ¹⁷⁹	Budesonide/formoterol maintenance and reliever therapy in moderate-to-severe asthma: Effects on eosinophilic airway inflammation	Prospective cohort study	Treatment group: as-needed budesonide/formoterol with salbutamol (n=32)	<u>ACT (mean, SD):</u> Run-in: 15.3 ± 2.2 Week 48: $22.2 \pm 0.8, p = < 0.005$
Japan ¹⁸⁰	Effects of nebulized sodium cromoglycate on adult patients with severe refractory asthma	RCT	Treatment groups: SCG (n=114) PBO (n=114)	<u>HRQOL:</u> Baseline median asthmatic symptom score: 20.12 Changes in total “yes” responses on the HRQOL questionnaire: -1.7 ± 3.93

Japan ¹⁸¹	Natural history and risk factors of obstructive changes over a 10-year period in severe asthma	Retrospective cohort study Natural history of asthma patients regularly attending a clinic over 10 years who were uncontrolled (according to ATS definition) despite treatment with daily high-dosage ICS+ controller medication EX: Events that required urgent action for worsening asthma including unscheduled office visits, ED visits, or hospitalization requiring systemic steroids therapy	N=54	NS SCG vs. PBO, $p=0.539$ Annual EX rate over a mean follow-up period of 12.7 years: 0.48 ± 0.51 Annual EX rate over a 10-year period: 0.48 ± 0.51 Blood eosinophil count (%) mean $\pm$ SD: All patients: $13.8 \pm 6.9\%$ Patients with slow (≤ 20 mL) annual decline in FVC: $13.5 \pm 5.6\%$ Patients with fast (>20 mL) annual decline in FVC: $14.6 \pm 9.4\%$, $p=0.61$
Japan ¹⁸²	The position of pranlukast, a cysteinyl leukotriene receptor antagonist, in the long-term treatment of asthma. 5-year follow-up study	Prospective cohort study	Pranlukast (n=27)	Baseline OCS use (mg/day): 8.6 (SEM: 1.5) 5-year follow up OCS use (mg/day): 5.8 (SEM: 1.8) PEFR % predicted, mean $\pm$ SEM: Baseline: 60.2 ± 2.1 ; Change at 16 weeks: $+15.2 \pm 3.8$ Proportion with PEF % predicted $\geq 80\%$ (normal lung function): 1 year: 45.5%
South Korea ¹⁸³	Role of neutrophils in persistent airway obstruction due to refractory asthma	Retrospective cohort study (n=2,298) ATS criteria used to assess refractory asthma	Asthma patients who were registered in an asthma cohort at the Genome Research Center for Allergy and Respiratory Diseases in Korea	Incidence of SUA in asthma patient population: 4.3% (98/2,298)
India ¹⁸⁴ Meeting abstract	Efficacy and safety of omalizumab in real-world clinical practice in Indian patients with allergic (IgE-mediated) asthma: Analysis by baseline severity of asthma	Prospective cohort study	Omalizumab (n=64)	% of patients with EX at baseline: 9.3% (time period NR); % of patients with EX at follow up: 1.1% <u>ACQ (mean, SD):</u> ACQ-5: Baseline: NR Change at 28 weeks: -1.5 , $p=0.000$ <u>ACT (mean, SD):</u> Baseline: NR Change at 28 weeks: $+10.2$, $p=0.000$
India ¹⁸⁵	Effectiveness of vitamin D3 in severe persistent asthmatic patients: A double blind, randomized, clinical study	RCT	Usual care group (n=69): budesonide (800 μ g) with formoterol (24 μ g) daily Intervention care group (n=72): the same as usual care plus vitamin D3	<u>Other HRQOL:</u> SGRQ: Symptom score: Between group comparison showed statistically significant improvement ($p<0.001$) from Day 30 onward. Activity score: No significant difference was

			tablet (1,000 IU; once daily)	observed between the groups <i>Impact score:</i> A statistically significant difference was observed from Day 30 through the end of final follow up <i>Total score:</i> Between group comparison showed no statistically significant improvement from baseline to Day 150. However, on the final follow-up day, a statistically significant improvement ($p<0.05$) was observed Statistically significant improvement is observed in symptom score, activity score, impact score, and total scores of SGRQ within group comparison. The findings of this study suggest that the addition of vitamin D3 to the regular treatment regimen does not improve pulmonary function. However, statistical as well as clinical improvement is seen with respect to HRQOL
Israel ¹⁸⁶	National asthma observational survey of severe asthmatics in Israel: The no-air study	Cross-sectional study (n=123) Control assessed by GINA 2006 criteria	A survey administered at a single patient visit conducted in 12 Israeli centers by pulmonologists who were all members of the Israeli Pulmonary Society	Incidence of SUA in SA patient population: 43.9% (541/123)
Israel ¹⁸⁷	Omalizumab reduces corticosteroid use in patients with severe allergic asthma: Real-life experience in Israel	Retrospective cohort study	Omalizumab (n=33)	Total number of hospital admissions in the previous year: 9; incidence of 0.316 admissions per person-year Prior hospitalization reported at baseline: The number of days spent in the hospital: 32 days Prior ED visits reported at baseline: Total number of ED visits in the previous year: 15; incidence of 0.526 ED visits per person-year
Jordan ¹⁸⁸	Relationship between lung function and asthma symptoms in patients with difficult to control asthma	Prospective cohort study	N=59	Median hospitalization in the previous year: 1 (range 1–8)
Mexico ¹⁸⁹	Omalizumab in the treatment of persistent moderate to severe asthma in the context of allergic and non-allergic asthma	Prospective cohort study EX: Requiring use of systemic corticosteroids (severe)	Omalizumab (n=35)	<u>Number of EX:</u> Baseline: 22 8 weeks: 20 16 weeks: 17 32 weeks: 15 52 weeks: 5
Mexico ¹⁹⁰	Real life study of three years omalizumab in patients with	Prospective open, observational, cohort study (difficult-to-control	Omalizumab (n=52)	<u>ACT (mean, SD):</u> Baseline mean score was 12.4 (very poorly controlled

	difficult-to-control asthma	asthmatic patients from the outpatient clinic of the Regional Hospital Licenciado Adolfo López Mateos [ISSSTE], Mexico City)		asthma) 3-year (n=47) mean score was 20.47 (controlled asthma) Mean personal improvement was 8.06 points (median 8, SD 3.57) 35 patients (74.4%) reached a 20–25 score (well-controlled asthma) 12 patients maintained a 15–19 score (uncontrolled asthma)
Russia ¹⁹¹	[Life quality control in patients with severe bronchial asthma]	Cross-sectional study	Treatment group: NR (n=50 with SUA)	<u>AQLQ (mean, SD):</u> Symptoms: 3.0 Activity limitation: 2.9 Emotional function: 3.1 Environmental stimuli: 3.0 Total: 3.0 <u>Other HRQOL:</u> SF-36: Physical activity: 40 Role physical: 25 Pain: 50 General perception of health: 49 Vitality: 48 Social activity: 50 Role emotional: 30 Mental health: 55 Self-assessment compared with previous year: 39 NR
Russia ¹⁹²	[Monitoring and treatment of severe bronchial asthma in adults: Results of national multicenter trial NABAT]	Prospective cohort study	NR	<u>Hospitalization rate per treatment period: mean ± SD:</u> Men: 1.0 ± 0.1 Women: 1.3 ± 0.1 <u>LOS (days):</u> Men: 15.9 ± 2.2 Women: 22.5 ± 1.5 <u>Mean number of emergency medical treatment calls per year:</u> Men: 2.8 ± 0.6 Women: 9.7 ± 2.3 <u>Number of physician visits for worsening condition per year:</u> Men: 3.1 ± 0.4 Women: 4.8 ± 0.3

Australia ¹⁹³	Effectiveness and response predictors of omalizumab in a severe allergic asthma population with a high prevalence of comorbidities: The Australian Xolair Registry	Retrospective cohort study	Omalizumab (n=180)	ACQ (mean, SD): ACQ-5: Nonresponder, n=21 Baseline: 3.38 (0.87) 6 months: 3.10 (1.23), $p=0.285$ Responder, n=138 Baseline: 3.57 (0.96) 6 months: 1.78 (1.08), $p<0.0001$
Australia ¹⁹⁴	Real-life effectiveness of omalizumab in severe allergic asthma above the recommended dosing range criteria	Prospective cohort	Omalizumab 6 months (n=180)	Serious adverse events: 20%
Egypt ¹⁹⁵	The effect of omalizumab in treatment of inadequate controlled severe persistent asthma patient	Randomized, double-blind, parallel-group study	Omalizumab (n=30)	Omalizumab significantly reduced the rate of asthma EX by 40% ($p<0.0001$ vs. control) and the rate of total ED visits by 44% ($p<0.0001$ vs. control). Omalizumab significantly improved asthma-related quality of life, morning PEF, and asthma symptom scores

.A&E, accident and emergency; ABPA, allergic bronchopulmonary aspergillosis; ABPM, allergic bronchopulmonary mycosis; ACQ-5/6/7, Asthma Control Questionnaire version 5, 6, or 7; ACT, Asthma Control Test; AE, adverse event; AMB, ambulatory; AQLQ, Asthma Quality of Life Questionnaire; AQLQ(S)+12, Asthma Quality of Life Questionnaire for 12 years and older; ASUI, Asthma Symptom Utility Index; ATAQ, Asthma Therapy Assessment Questionnaire; ATC, Anatomical Therapeutic Chemical Classification; ATS, American Thoracic Society; BDP, beclomethasone dipropionate; BMI, body mass index; BTS, British Thoracic Society; CAE, clinical asthma exacerbation; CCS, continuous corticosteroids; CI, confidence interval; DLQI, Dermatology Life Quality Index; EX, exacerbation(s); ED, emergency department; EPR-3; Expert Panel Report 3; EQ-5D, EuroQoL-5D; EQ-VAS, EuroQoL-visual analog scale; ERS, European Respiratory Society; ESS, Epworth Sleepiness Scale; FENO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FP, fluticasone propionate; FS, fungal sensitivity; FVC, forced vital capacity; GETE, global evaluation of treatment effectiveness; GEMA, Spanish Guidelines for Asthma Management; GINA, Global Initiative for Asthma; GORD, gastroesophageal reflux disease; GP, general practitioner; HADS, Hospital-Anxiety Depression Scale; HDICS; high-dosage inhaled corticosteroid; HI, high intensity; HICS; high-intensity corticosteroids; HRQOL, health-related quality of life; ICER, incremental cost-effectiveness ratio; ICD-9, International Classification of Diseases, Ninth Revision; ICS, inhaled corticosteroid; ICT; IgE, immunoglobulin E; IgG1, immunoglobulin G1; IL-13, interleukin 13; IMI, Innovative Medicine Initiative; IQR, interquartile range; ITT, intention-to-treat; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; LOS, length of stay; LSM, least squares mean; LSM-TD, least squares mean treatment difference; LTRA, leukotriene receptor antagonist; mAb, monoclonal antibody; MARS, Medication Adherence Report Scale; MMF; NAEPP, National Asthma Education and Prevention Program; NAFLD, nonalcoholic fatty liver disease; NHLBI, National Heart, Lung, and Blood Institute; NHS, National Health Service; NR, not recorded; NS, nonsignificant; OAT, other asthma therapy; OCS, oral corticosteroid; OPCR, Optimum Patient Care Research Database; OR, odds ratio; PA, persistent asthma; PAO, pulmonary airway obstruction; PBO, placebo; PEF, peak expiratory flow; Q4W, every 4 weeks; Q8W, every 8 weeks; QALY, quality-adjusted life-year; RCT, randomized controlled trial; RR, rate ratio; Rx, prescription; SA, severe asthma; SABA, short-acting β_2 agonist; SD, standard deviation; SE, standard error; SEA, severe eosinophilic asthma; SEM, standard error of the mean; SF-36, Short Form 36 Health Survey; SFC, salmeterol/fluticasone propionate combination; SGRQ, St. George's Respiratory Questionnaire; SoC, standard of care; SNOT, Sino-nasal Outcome Test; SRA, severe refractory asthma; STAI, State-Trait Anxiety Inventory; SUA, severe uncontrolled asthma; TASS, Total Asthma Symptom Score; tx, treatment; VAS, visual analog scale.

*significant at $p<0.05$

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