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Patient-reported outcomes in moderate-to-severe allergic asthmatics treated with omalizumab: a systematic literature review of randomized controlled trials

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Abstract

Objective: Randomized controlled trials (RCTs) have established the safety and efficacy of omalizumab on clinical parameters, and have also evaluated its impact on patient-reported outcomes (PROs). The purpose of this systematic literature review was to review published data based on PRO endpoints in order to determine the benefit of omalizumab as add-on therapy to inhaled corticosteroids in patients with moderate-to-severe persistent allergic asthma.

Methods: A systematic literature review was conducted of reference databases and recent conferences. RCTs of add-on omalizumab therapy in adults, adolescents, and children with moderate-to-severe persistent asthma were included. Two researchers independently screened and reviewed articles with regards to inclusion and exclusion criteria for relevant studies.

Results: Twenty-six trials met the criteria for inclusion. Of these, PRO measures were included in 19 trials to capture the impact of omalizumab on symptoms, 11 assessed patients for health-related quality of life (HRQoL), and 4 evaluated asthma control. Other PROs related to global evaluation of treatment effectiveness and work productivity. Overall, results demonstrated a significant difference across most PROs in favor of omalizumab add-on therapy versus placebo or comparators.

Conclusions: PROs are an integral part of outcome assessment in clinical trials related to asthma. The RCTs reviewed demonstrate that omalizumab treatment improves PROs in patients with moderate-to-severe persistent allergic asthma, particularly symptom control and HRQoL.

Keywords: IgE response underlying allergic asthma and rhinitis; allergic asthma; omalizumab; patient reported outcome measures; patient reported outcomes

Short title: Patient-reported outcomes with omalizumab

Introduction

Asthma impacts over 330 million people worldwide[1], including approximately 24 million individuals in the United States (US) and 30 million in Europe.[2, 3] An allergic component, as evidenced by IgE antibodies to a relevant airborne allergen, manifests in approximately 80% of patients with asthma, and is often responsible for severe or treatment-refractory disease.[4, 5] Omalizumab (Xolair®; Novartis Pharmaceuticals Corporation and Genentech USA, Inc.), an anti-IgE monoclonal antibody, represented the first therapeutic agent that specifically addressed the role of allergy in moderate-to-severe asthma. Omalizumab was first approved by the Therapeutic Goods Administration in Australia for the treatment of adults and adolescents with moderate allergic asthma in 2002 and was subsequently approved in the US for adults and adolescents with moderate-to-severe persistent allergic asthma not controlled by inhaled steroids in 2003 and in Europe for severe persistent allergic asthma in 2005. Omalizumab was later approved for use in children aged 6 to 11 years in Europe (severe persistent allergic asthma) and the US in 2009 and 2016 respectively.

Randomized, double-blind, placebo-controlled studies have established the safety and efficacy of omalizumab on clinical parameters such as asthma exacerbations, systemic corticosteroid use, and lung function.[6, 7] In addition to the above endpoints, it is also important to accurately characterize the effects of omalizumab on the patients' subjective experience of asthma by PROs. According to the FDA Guidance for Industry, a PRO is defined as 'any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.'[8] PROs in clinical trials are captured by structured questionnaires called PRO measures (PROMs), also often referred to as 'PRO instruments'.[9]

The utility of PROMs in asthma has been well documented. In asthma, generic PROMs such as the Short-Form 36 Health Survey (SF-36) and the Health Utilities Index (HUI) may be used to evaluate general health status.[10] Disease-specific PROMs investigate and document the concerns, symptoms, and challenges in patients with asthma. These may be categorized into measures of quality of life (eg, Asthma Quality of Life Questionnaire [AQLQ]), symptoms (eg, Asthma Symptom Diary), or asthma control (eg, Asthma Control Test).[11, 12] Given the high number of PROMs that have been described in the literature and used in clinical studies in asthma, it is important to evaluate the entire body of patient-reported data to understand the potential impact of a treatment. As such, the rationale for this systematic literature review was to review the PRO data for omalizumab as add-on therapy to inhaled corticosteroids in patients with moderate-to-severe persistent allergic asthma.

Methods

A review of the literature evaluating PROs and their respective PROMs utilized in randomized controlled trials of omalizumab in adults, adolescents, and children with moderate-to-severe persistent asthma was conducted using MEDLINE (via PubMed), EMBASE, and the Cochrane Central Library of Controlled Trials (CENTRAL). The search was run on March 22, 2016, and no limits were placed on the publication date. The search was limited to English-language studies.

The population of interest for the review was patients diagnosed with moderate-to-severe allergic asthma, including children (6-11 years), adolescents (12-17 years), and adults (≥ 18 years). The intervention of interest was omalizumab (search terms 'omalizumab' or 'Xolair'). Study designs of interest were randomized controlled trials (RCTs) that had been published in peer-reviewed journals and had results presented. Conference websites were also searched to

identify late-breaking RCTs, including the Annual Meeting of the American Academy of Allergy, Asthma, and Immunology (AAAAI); Annual Scientific Meeting of the American College of Allergy, Asthma, & Immunology (ACAAI); Annual Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR); ISPOR Annual European Congress; Annual Academy of Managed Care Pharmacy (AMCP) Nexus; Annual Meeting and Expo of AMCP; and Annual International Conference of the American Thoracic Society (ATS). In addition, published systematic reviews were also evaluated for individual studies of relevance. Non-systematic reviews, editorials, commentaries, letters, case reports or cases series, and theses or dissertations were excluded. A further inclusion criterion was sample size: relevant RCTs were required to have $N \geq 10$ patients.

Quality assessment of each included study was undertaken independently by 2 separate reviewers, with any discrepancies in evaluation resolved by a third reviewer. The quality of included studies was assessed using the Cochrane Collaboration's tool (Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0) for assessing the risk of bias in RCTs. This tool scores a study based on the following types of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, or other sources of bias.

The search identified 1,380 studies, of which 1,261 were excluded for the following reasons: small sample size (<10); not a study design of interest; no outcomes of interest; not a population of interest; or was a duplicate study. Based on title and abstract screening, 119 studies potentially met the inclusion criteria for full-text review. After review of the full texts, 93 studies were excluded for the following reasons: not an RCT; presented baseline data only; did not have data on any PROs; not a patient population of interest; was a foreign language publication. The

selection process in detail is reported in Figure 1. This systematic literature review identified 26 RCTs for inclusion.

Results

Summary of studies included

A brief description of the RCTs utilizing PROMs is shown in Table 1. The studies had a broad global representation, with 10 multi-national RCTs included.[13, 14, 15, 16, 17, 18, 19, 20, 21, 22]. The majority of included analyses evaluated patients aged 12 years and older (15 of 26 studies)[13, 14, 15, 16, 17, 18, 20, 22, 23, 24, 25, 26, 27]; 5 trials included adults, aged 18 years and older only,[21, 28, 29, 30, 31] and 2 trials included children aged 6 to <12 years.[19, 32] The majority of RCTs were large (69% had N >300 patients). Study duration ranged widely from 16–60 weeks, with a median of 28 weeks (based on the longest follow-up duration reported for a given trial). A total of 85% (n=22) of studies compared the use of add-on omalizumab to standard of care, including inhaled corticosteroid (ICS) ± long-acting beta agonist (LABA), and other guideline-based treatment. Four studies had no placebo control group and evaluated omalizumab plus standard of care compared to standard therapy alone.[13, 16, 20, 26] Analyses in 2 studies isolated a group of patients designated as ‘responders’ to omalizumab, and included them as a third comparator, along with the placebo arm and either all omalizumab patients or those not responding to omalizumab therapy.[18, 25]

Overall, the risk of bias in the 26 RCTs reviewed was low across the evaluated domains (eg, blinding of study personnel and participants, complete outcome assessment, and selective reporting) (Table 2). Many studies did not report the randomization procedure for participants or the procedure for allocation to treatment assignment, both of which are included on the Cochrane Collaboration’s Tool, leading to an unclear assessment of the selection bias. Five of the 26

studies demonstrated a low risk of bias across all domains[15, 19, 28, 31, 33]; 2 studies had either high risk of bias[16] or the publication did not provide sufficient information to assess the risk of bias.[26]

PRO concepts evaluated

A wide variety of PRO concepts were assessed in the 26 RCTs reviewed, including symptoms, degree of asthma control, impact on daily life and functioning, and HRQoL. PROMs used to evaluate disease-specific HRQoL included the Asthma Quality of Life Questionnaire (AQLQ) and its derivatives, the mini-AQLQ and the pediatric Asthma Quality of Life Questionnaire (PAQLQ), as well as other measures. PROMs for asthma control included the Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ). Work impairment was also measured in 1 study using the Work Productivity Activity Impairment–Asthma (WPAI-A).[34] A diverse set of scoring systems and diaries were used for symptom assessment, including the Total Asthma Symptom Score (TASS) and the Wasserfallen symptom score. A brief summary of asthma-specific PROMs is provided in Table 3. No trends were evident in the use of specific PROMs across the studies, with the exception of a higher proportion of studies conducted in Europe (or international, multicenter studies) evaluating HRQoL (8 of 15 studies) compared with studies conducted in the US and/or Canada (4 of 11 studies).

In addition to reporting on the PROMs of interest, the corresponding minimal important difference (MID) was noted. The MID represents the smallest change in outcome that has been demonstrated to be clinically important. While several publications evaluated whether reported changes in PROMs met the established MID values, for studies without a specified achievement of a MID, the authors compared the change with an established MID value.

Asthma-specific quality of life

Asthma-specific quality of life in adults was measured using the AQLQ, or its derivative, the mini-AQLQ, in 9 studies. As shown in Table 4, adults with allergic asthma treated with omalizumab experienced improvements on the overall AQLQ score from baseline; the difference compared with placebo (and/or standard therapy for persistent severe asthma) was statistically significant in all but 2 studies[15, 30]; in these 2 studies, the change was numerically greater for omalizumab-treated patients, but statistical significance was not reported. The improvement was reported as early as 20 weeks (change of +1.3 vs -0.1 for placebo; $P<0.001$ [26]); similar improvement from baseline were reported in 52-week studies (+1.19[24] and +1.30[26]; both $P<0.001$ vs placebo). Domain analyses in 4 studies reported significant improvement from baseline at 16 weeks[30], at 28 weeks[14], and 52 weeks[17, 24] in the AQLQ scores of omalizumab-treated patients compared with placebo-treated patients for the following: symptoms, activity limitation, and environmental exposure. Emotional function was significantly improved with omalizumab compared with placebo in all but the 52-week study by Finn et al (2003).

Previous validation has suggested that a change of ≥ 0.5 points on the AQLQ indicates the MID in HRQoL; a change of ≥ 1.5 points indicates a large improvement in HRQoL.[35] Patients treated with omalizumab achieved at least the MID in AQLQ overall score; the mean change from baseline ranged from +0.91 points to +1.32 points at 20-52 weeks 28 weeks.[14, 24, 26, 27] Six of the 9 studies reported the percentage of patients achieving the MID for the overall AQLQ score; of these, 5 studies reported that significantly more omalizumab-treated patients had a ≥ 0.5 -point improvement from baseline compared with placebo or control (all $P<0.05$, as shown in Figure 2).[14, 15, 24, 26, 36] One study reported a marginal difference from placebo (78.8%

vs 69.8%; $P=0.05$).[27] However, in a subgroup analysis of the proportion of patients who achieved a large improvement in HRQoL, a significantly greater proportion of omalizumab-treated patients achieved ≥ 1.5 -point improvement compared with placebo (48.1% vs 33.3%; $P=0.003$).[27] In a similar assessment at 20 weeks in the study by Rubin et al (2012), 41.9% of omalizumab-treated patients achieved >1.5 -point improvement compared with only 2.8% of control patients ($P<0.001$).[26] The mini-AQLQ was used to evaluate the impact of add-on therapy with omalizumab on HRQoL.[20] At 12 months, patients treated with omalizumab compared to best standard care reported significantly greater improvements from baseline in overall score. A similar trend was observed for all individual domains. A significant difference in the percentage of patients achieving a MID (≥ 0.5 -point improvement) from baseline in overall score was reported for patients treated with omalizumab compared to controls (76.5% vs 41.7%, respectively; $P<0.001$).

Asthma-specific quality of life in children (age 6-12 years) was measured using the PAQLQ in 2 studies (Table 4).[19, 37] Significant improvement was reported in 1 study.[37] At 28 weeks (study end), patients treated with omalizumab experienced significantly greater changes from baseline as compared to placebo for overall PAQLQ score and the individual activities and symptoms domains ($P<0.05$). For the overall PAQLQ score and across all individual domains, more patients with add-on omalizumab therapy achieved a MID of ≥ 0.5 -point improvement at 20 weeks, with significant differences reported for overall score (46.9% vs 33.7%; $P<0.05$) and the activities domain (50.6% vs 39.5%; $P<0.05$) as compared to the control group.[37] The change in PAQLQ from baseline to 24 weeks in the clinical trial by Lanier et al (2009) did not achieve statistical significance from placebo ($P=0.676$), but the authors noted that baseline PAQLQ values were high.[19]

Rhinoconjunctivitis-related quality of life was also evaluated in 2 studies of patients with comorbid allergic asthma and rhinitis in order to assess whether an improvement in asthma response with omalizumab would also improve rhinitis symptoms.[25, 27] In both studies, a significantly greater proportion of omalizumab-treated patients had a rhinitis response (≥ 1.0 -point improvement on the RQLQ overall score) compared with placebo patients ($P < 0.001$ in both studies). The improvement from baseline was also statistically significantly greater for omalizumab vs placebo for all RQLQ domains (activities, sleep, non-nasal/non-ocular symptoms, practical problems, nasal symptoms, eye symptoms, and emotional function; $P < 0.05$ for all comparisons). [25, 27]

Asthma control

Asthma control was evaluated in 4 studies: 3 studies utilized the ACT and/or the C-ACT and 1 study utilized the ACQ. No significant differences were reported for the omalizumab-treated group vs placebo in the change from baseline at 24–48 weeks in total ACT (5.01 vs 4.36; $P = 0.178$)[23] or in the mean total ACT (22.5 vs 22.3; $P = 0.54$)[32]. In adolescents and children treated for 4 months with omalizumab, the difference in the mean change on the ACT (in patients ≥ 12 years of age) and the C-ACT (patients 4–11 years of age) was 0.94 (favoring omalizumab) and 0.73 (favoring omalizumab) compared with placebo; compared with an ICS boost alone, the difference on the ACT was minimal (0.05). Statistical significance was not reported for these comparisons.[33] However, the overall mean change from baseline on the ACT (across all treatment arms) was 2.4 points, which did not exceed the MID for the ACT (≥ 3.0 -point improvement). In a subgroup of children 4 to 11 years of age in the study by Busse et al (2011), a statistically significant difference in mean total C-ACT score in the previous month between omalizumab and placebo group was recorded at 48 weeks (23.0 vs 22.2, respectively;

$P=0.007$). It is important to note that while the results are statistically significant, the point estimates are close and likely not clinically meaningful. In adolescents (≥ 12 years of age), the difference in mean ACT score in the previous month between omalizumab and placebo groups was not significant.[32]

When asthma control was measured with the ACQ, omalizumab-treated patients experienced clinically meaningful and statistically significant improvement in control.[16] Patients receiving optimized asthma treatment plus omalizumab achieved a MID (≥ 0.4 -point reduction) in overall score from baseline to 16 weeks (-0.78) and at 32 weeks (-0.91); in comparison, patients receiving optimized asthma treatment alone did not (change from baseline of -0.11 and -0.04 at 16 and 32 weeks, respectively). The comparison between the omalizumab and optimized treatment group was statistically significant at both Week 16 and 32 ($P<0.001$).[16] While the ACT and the ACQ are commonly used PROMs for asthma control, it is important that results for each be interpreted separately, as a previous study has demonstrated that they are not interchangeable (kappa coefficient for agreement = 0.58).[38]

Symptom assessment

A total of 19 studies reported the impact of omalizumab on symptom occurrence. The majority of the studies were either double-blind placebo-controlled (13 of 19) trials or randomized open-label studies (3 of 19). In addition, there was 1 post hoc analysis of the INNOVATE study [18] and 2 subgroup analyses of previously conducted studies.[20, 21] All of the studies that reported symptom-related PROs varied by the time period over which the symptoms were measured (range: 4 weeks to 52 weeks) and by the type of assessment used to capture asthma symptoms.

The overall assessment of the effect of omalizumab on symptoms is complicated by the variation of scales used and the time in which the symptoms were monitored. Complex assessments, such as the Wasserfallen asthma symptom score, were used in 3 studies, and the Total Asthma Symptom Scale (TASS) was used in 5 studies. The Wasserfallen validated scale is a self-administered questionnaire (31 items rated on a 6-point Likert scale) including symptoms of inflammation[39], and the TASS is a patient assessment of daytime plus nighttime symptoms using a scale of 0 (none) to 4 (severe) plus morning score for symptoms upon wakening (yes/no) for a maximum score of 9. The Asthma Symptom Score (range, 0 to 4, where 4 is severe or breath problems at rest) was also used to record symptoms experienced during the day (4 studies) or night (3 studies). One study rated individual symptoms such as sneezing and chest symptoms, and 1 study simply counted frequency of night-time awakenings. Lastly, 5 studies recorded the percentage or number of days with asthma symptoms over a specific recall time period.

A summary of studies that assessed symptoms is provided in Table 5. In comparing the findings across studies, all 3 studies using the Wasserfallen asthma symptom score reported significantly greater changes from baseline in total score for patients in the omalizumab group compared to the control group,[13, 20, 27] with a significant difference in follow-up scores observed in 2 studies between treatment groups.[20, 27] Improvements in mean TASS were significantly greater for omalizumab treatment groups compared to placebo assessed at 28 weeks[14, 22, 40] and 48 weeks[15], and the total asthma scores at follow-up were significantly lower for patients with omalizumab therapy vs placebo up to 32 weeks.[36] Daytime and nighttime asthma symptom scores were evaluated utilizing a 0 (none) to 4 (severe) scale in 4 and 3 studies, respectively. While symptoms generally improved for patients using omalizumab compared to placebo, only 1 study reported significantly lower daytime and nighttime scores for

patients treated with omalizumab vs placebo at 26–28 weeks of follow-up ($P<0.05$).[22]. However, actual nighttime awakenings over the 2 weeks prior to the assessment were shown to significantly decrease at 32 weeks ($P=0.039$).[16] A study by Corren et al demonstrated a significant change in the mean area under the curve (AUC) in a chest symptom score (0, none; 3, severe) over 16 weeks in favor of omalizumab compared to placebo ($P<0.001$). Similar results were seen in the nasal-ocular symptom score (0, none; 3, severe) ($P=0.0002$) and the number of sneezes over a 1-hour allergen challenge (cat allergen) ($P=0.0169$) at 16 weeks.[29]

The number of days with asthma symptoms during the previous 2-week period was shown to be significantly lower with omalizumab compared with placebo in 2 of 3 studies that made this assessment.[32, 41] In Busse et al, the number of days with symptoms or limitations was evaluated for each 2-week interval, from the completion of the 12-week wash-in to the study completion. Across the 48 weeks of follow-up, omalizumab-treated patients had significantly fewer mean days (per 2-week interval) of wheezing, interference with activities, and nighttime sleep disruptions compared to placebo-treated patients ($P\leq 0.02$).[32] In a separate study, the percentages of symptom-free days and symptom-controlled days over each 2-week interval were significantly higher in patients who were considered responders to omalizumab therapy compared with those who were treated with omalizumab and placebo over 26-28 weeks ($P<0.001$).[18] However, when the number of days with asthma symptoms, nights with awakening, and days with impairment in daily activities were counted over a 1-week period on a patient diary card, the change from baseline to 16 weeks between omalizumab and placebo was not significant.[28]

Other patient-reported outcome measures

Global evaluation of treatment effectiveness (GETE) is a validated PROM that reflects clinical outcomes and HRQoL in patients with asthma, and has been shown to be positively correlated with clinical indices (except lung function), AQLQ, and HRQOL.[42]. The GETE can also be physician-reported, but only patient-reported outcomes were summarized here. The GETE was reported in 6 studies, usually alongside the investigator-rated GETE.[14, 16, 19, 26, 27, 43] This PROM evaluated perceived treatment effectiveness after 16 weeks of omalizumab therapy using the following ratings: excellent (complete control of asthma), good (marked improvement), moderate (discernible but limited improvement), poor (no appreciable change), or worsening.[43] In all 6 studies, significantly more patients reported their treatment effectiveness as excellent or good with omalizumab compared with placebo or optimized asthma treatment over 16-52 weeks (range, 64.3% to 81.4% reporting excellent or good with omalizumab vs 28.2% to 72.0% with placebo or optimized asthma treatment; all comparisons $P<0.01$).[14, 16, 19, 26, 27, 43] The impact of omalizumab on work impairment was measured as an exploratory endpoint in 1 study, using the Work Productivity and Activity Impairment Questionnaire-Asthma (WPAI-A).[23] At Week 24, there were no statistically significant differences between the omalizumab and placebo groups for any of the WPAI-A domains.

Discussion

PROs provide important insights into the patient's individual experience of a disease process.[44] In asthma, measures of lung function and rescue medication usage may not correlate well with a patient's actual disease experience, or the impact of treatment on a patient's HRQoL and functioning.[11, 12] As such, PRO data provide a chance for patients to provide their input into the impact of treatment, and may influence a patient's or a physician's treatment decision-

making process. For clinicians who routinely manage patients with asthma, PROs can thus be important indicators of a patient's perception of treatment's effectiveness. From a payer perspective, PROs can be useful to differentiate treatments with otherwise similar safety and efficacy profiles.

The utility of PROMs in asthma has been well documented and described in the literature.[11, 12] More than 30 validated PROMs have been utilized in RCTs of asthma. In a previously published systematic review, a total of 87 RCTs published between 1985 and 2006 were identified that reported on the clinical efficacy and safety of ICS and LABA treatment for adults or children with asthma. Of these 87 studies reviewed, 79 utilized at least 1 PROM to capture the patients' experiences during treatment for asthma.[12] In our review of omalizumab RCTs in adults, adolescents, and children with moderate-to-severe persistent asthma, PROs were reported by 8 PROMs. Across the wide range of studies included, omalizumab-treated patients reported improvement in symptoms, asthma control, and HRQOL that were generally greater than placebo or standard therapy, and were sustained for up to 52 weeks. Six RCTs reported that omalizumab-treated patients achieved clinically and statistically meaningful improvements on the AQLQ overall score; between 57.5% and 78.8% of omalizumab-treated patients achieved the MID of ≥ 0.5 -point improvement from baseline compared with between 22.2% and 69.8% of placebo or control patients.[14, 15, 24, 26, 27, 36] Omalizumab treatment also demonstrated sustained improvement for up to 48 weeks in asthma symptoms and night time awakenings, assessed with PROMs such as the asthma symptom score.[15, 36] The effect of omalizumab on asthma control was less consistent, as the studies did not show a consistent ability of omalizumab-treated patients to achieve the MID on the ACT. However, a study measuring

control using the ACQ reported a clinically meaningful and statistically significant improvement in omalizumab-treated patients ($P<0.001$).[16]

It should be noted that most of the PROMs included in this review pre-date the FDA guidance on the use of PROMs to support product labeling.[8] This guidance describes the necessary evidentiary standard required to ensure validity of PROMs, trial design, and statistical analysis plan recommended in order to support product labeling based on PRO-related endpoints. As such, while the PROMs identified in this review are widely used to demonstrate treatment benefit in asthma studies, they may not be acceptable for the purpose of product labeling in the United States. In general, the selection of a PROM is dependent on what outcome is being measured (eg, functioning, symptoms, or HRQoL), in what population (eg, pediatrics or adults), and in context of the use (eg, by a clinician assessing a patient or a study investigator in context of a clinical trial).

Limitations of this literature review include that studies published after the cut-off date of the literature search (March 22, 2016) may have been omitted. Of the studies included, while the majority were of good quality (i.e., low risk of bias), the reporting of PROM findings used in the studies was inconsistent. For example, in some studies symptom assessments were reported as ‘asthma symptom scores’ without information regarding the validation of the instrument. Similarly, the reporting of the MID poses an additional limitation, as not all studies reported whether changes from baseline met standard criteria for a clinically meaningful improvement. Finally, publication bias represents another potential source of bias, since studies demonstrating positive findings are reported more often than trials with negative results. In order to avoid inadvertently favoring positive studies associated with the use of omalizumab, the search protocol was designed to impartially select studies meeting the selection criteria, regardless of

negative or non-significant findings. The risk of bias within each study was then critically evaluated by 2 independent reviewers.

Conclusions

Overall, these RCTs have provided evidence that omalizumab treatment improves PROs in moderate-to-severe persistent allergic asthma, particularly symptoms and HRQoL.

Transparency

Declaration of funding: Novartis Pharmaceuticals Corporation funded this research.

Declaration of financial/other relationships: Drs. Kavati, Ortiz, and Vegesna are employees of Novartis Pharmaceuticals Corporation, which funded this research. Drs. Kavati, Ortiz, and Vegesna are stock shareholders of Novartis Pharmaceuticals Corporation. Dr. Corren has received grant or research funding from 3M Pharmaceuticals, Sanofi, Regeneron, Aimmune Therapeutics, and Circassia. Dr. Corren has been a consultant or advisor to MedImmune, AstraZeneca, Vectura Group, and Regeneron, and has participated in speakers bureaus for Teva Pharmaceutical Industries, Genentech, Novartis Pharmaceuticals Corporation, and AstraZeneca. Dr. Panettieri has received grant or research funding from Theratrophix, OncoArendi Therapeutics, Amgen, RIFM, Vertex Pharmaceuticals, Bristol-Myers Squibb, Gilead, Genentech, Sanofi, and Regeneron. Dr. Panettieri has been a consultant or advisor to AstraZeneca and MedImmune, and has participated in speakers bureaus for Boston Scientific and Teva. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials

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References

1. The Global Asthma Report 2014 Auckland, New Zealand: Global Asthma Network; 2014. Available from: <http://www.globalasthmareport.org/>.
2. ERS. Adult asthma. European Lung White Book [updated March 2017]. Available from: <http://www.erswhitebook.org/chapters/adult-asthma/>.
3. CDC. National - Current Asthma Prevalence (2015) 2017 [updated June 2017]. Available from: https://www.cdc.gov/asthma/most_recent_data.htm.
4. Ober C, Yao TC. The genetics of asthma and allergic disease: a 21st century perspective. *Immunological reviews*. 2011;242:10-30.
5. Lombardi C, Savi E, Ridolo E, Passalacqua G, Canonica GW. Is allergic sensitization relevant in severe asthma? Which allergens may be culprit? *The World Allergy Organization journal*. 2017;10:2.
6. XOLAIR (omalizumab) [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016.
7. XOLAIR Summary of Product Characteristics Nuremberg, Germany: Novartis Pharma GmbH; 2016.
8. FDA. Guidance for Industry. Patient-reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims 2009 [updated March 2017].
9. Weldring T, Smith SM. Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs). *Health services insights*. 2013;6:61-8.
10. Gibbons E, Fitzpatrick R. A structured review of patient-reported outcome measures (PROMs) for asthma: University of Oxford; 2009 [updated March 2017]. Available from: <http://phi.uhce.ox.ac.uk/>.

11. Worth A, Hammersley V, Knibb R, Flokstra-de-Blok B, DunnGalvin A, Walker S, Dubois AE, Sheikh A. Patient-reported outcome measures for asthma: a systematic review. NPJ primary care respiratory medicine. 2014;24:14020.
12. Frampton GK, Shepherd J. Patient-reported outcomes in clinical trials of inhaled asthma medications: systematic review and research needs. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2011;20:343-57.
13. Ayres JG, Higgins B, Chilvers ER, Ayre G, Blogg M, Fox H. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. Allergy. 2004;59:701-8.
14. Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, Beeh KM, Ramos S, Canonica GW, Hedgecock S, Fox H, Blogg M, Surrey K. 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. Allergy. 2005;60:309-16.
15. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, Rosen KE, Eisner MD, Wong DA, Busse W. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. Annals of internal medicine. 2011;154:573-82.
16. Bousquet J, Siergiejko Z, Swiebocka E, Humbert M, Rabe KF, Smith N, Leo J, Peckitt C, Maykut R, Peachey G. Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma. Allergy. 2011;66:671-8.
17. Buhl R, Hanf G, Soler M, Bensch G, Wolfe J, Everhard F, Champain K, Fox H, Thirlwell J. The anti-IgE antibody omalizumab improves asthma-related quality of life in patients with allergic asthma. The European respiratory journal. 2002a;20:1088-94.

18. Humbert M, Berger W, Rapatz G, Turk F. Add-on omalizumab improves day-to-day symptoms in inadequately controlled severe persistent allergic asthma. *Allergy*. 2008;63:592-6.
19. Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *The Journal of allergy and clinical immunology*. 2009;124:1210-6.
20. Niven R, Chung KF, Panahloo Z, Blogg M, Ayre G. Effectiveness of omalizumab in patients with inadequately controlled severe persistent allergic asthma: an open-label study. *Respiratory medicine*. 2008;102:1371-8.
21. Noga O, Hanf G, Kunkel G. Immunological and clinical changes in allergic asthmatics following treatment with omalizumab. *International archives of allergy and immunology*. 2003;131:46-52.
22. Solèr M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, Thirlwell J, Gupta N, Della Cioppa G. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *The European respiratory journal*. 2001;18:254-61.
23. Bardelas J, Figliomeni M, Kianifard F, Meng X. 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. *The Journal of asthma : official journal of the Association for the Care of Asthma*. 2012;49:144-52.
24. Finn A, Gross G, van Bavel J, Lee T, Windom H, Everhard F, Fowler-Taylor A, Liu J, Gupta N. Omalizumab improves asthma-related quality of life in patients with severe allergic asthma. *The Journal of allergy and clinical immunology*. 2003;111:278-84.

25. Humbert M, Boulet LP, Niven RM, Panahloo Z, Blogg M, Ayre G. Omalizumab therapy: patients who achieve greatest benefit for their asthma experience greatest benefit for rhinitis. *Allergy*. 2009;64:81-4.
26. Rubin AS, Souza-Machado A, Andradre-Lima M, Ferreira F, Honda A, Matozo TM. Effect of omalizumab as add-on therapy on asthma-related quality of life in severe allergic asthma: a Brazilian study (QUALITX). *The Journal of asthma : official journal of the Association for the Care of Asthma*. 2012;49:288-93.
27. Vignola AM, Humbert M, Bousquet J, Boulet LP, Hedgecock S, Blogg M, Fox H, Surrey K. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy*. 2004;59:709-17.
28. Chanez P, Contin-Bordes C, Garcia G, Verkindre C, Didier A, De Blay F, de Lara MT, Blanco P, Moreau JF, Robinson P, Bourdeix I, Trunet P, Le Gros V, Humbert M, Molimard M. Omalizumab-induced decrease of Fc ϵ RI expression in patients with severe allergic asthma. *Respiratory medicine*. 2010;104:1608-17.
29. Corren J, Wood RA, Patel D, Zhu J, Yegin A, Dhillon G, Fish JE. Effects of omalizumab on changes in pulmonary function induced by controlled cat room challenge. *The Journal of allergy and clinical immunology*. 2011;127:398-405.
30. Hoshino M, Ohtawa J. Effects of adding omalizumab, an anti-immunoglobulin E antibody, on airway wall thickening in asthma. *Respiration; international review of thoracic diseases*. 2012;83:520-8.
31. Ohta K, Miyamoto T, Amagasaki T, Yamamoto M. Efficacy and safety of omalizumab in an Asian population with moderate-to-severe persistent asthma. *Respirology (Carlton, Vic)*. 2009;14:1156-65.

32. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, Gruchalla RS, Kattan M, Teach SJ, Pongracic JA, Chmiel JF, Steinbach SF, Calatroni A, Togias A, Thompson KM, Szeffler SJ, Sorkness CA. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *The New England journal of medicine*. 2011;364:1005-15.
33. Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes SJ, Jr., Calatroni A, Wildfire JJ, Gergen PJ, Cohen RT, Pongracic JA, Kercksmar CM, Khurana Hershey GK, Gruchalla RS, Liu AH, Zoratti EM, Kattan M, Grindle KA, Gern JE, Busse WW, Szeffler SJ. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *The Journal of allergy and clinical immunology*. 2015;136:1476-85.
34. Andreasson E, Svensson K, Beerggren F. Validity of the work productivity and activity impairment questionnaire for patients with asthma (WPAI-asthma): results from a web-based study [PRP11]. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2003;6.
35. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *Journal of clinical epidemiology*. 1994;47:81-7.
36. Holgate ST, Chuchalin AG, Hebert J, Lotvall J, Persson GB, Chung KF, Bousquet J, Kerstjens HA, Fox H, Thirlwell J, Cioppa GD. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*. 2004;34:632-8.
37. Lemanske RF, Jr., Nayak A, McAlary M, Everhard F, Fowler-Taylor A, Gupta N. Omalizumab improves asthma-related quality of life in children with allergic asthma. *Pediatrics*. 2002;110:e55.

38. Vermeulen F, de Meulder I, Paesmans M, Muylle I, Bruyneel M, Ninane V. Asthma control measurement using five different questionnaires: a prospective study. *Respiratory medicine*. 2013;107:1314-21.
39. Wasserfallen JB, Gold K, Schulman KA, Baraniuk JN. Development and validation of a rhinoconjunctivitis and asthma symptom score for use as an outcome measure in clinical trials. *The Journal of allergy and clinical immunology*. 1997;100:16-22.
40. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, van As A, Gupta N. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *The Journal of allergy and clinical immunology*. 2001;108:184-90.
41. Sorkness CA, Wildfire JJ, Calatroni A, Mitchell HE, Busse WW, O'Connor GT, Pongracic JA, Ross K, Gill MA, Kattan M, Morgan WJ, Teach SJ, Gergen PJ, Liu AH, Szeffler SJ. Reassessment of omalizumab-dosing strategies and pharmacodynamics in inner-city children and adolescents. *The journal of allergy and clinical immunology In practice*. 2013;1:163-71.
42. Lloyd A.; Turk FL, T.; Canonica, G.W. Psychometric evaluation of Global Evaluation of Treatment Effectiveness: a tool to assess patients with moderate-to-severe allergic asthma. *Journal of Medical Economics*. 2007;2007.
43. Milgrom H, Berger W, Nayak A, Gupta N, Pollard S, McAlary M, Taylor AF, Rohane P. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics*. 2001;108:E36.
44. Blackwell LS, Marciel KK, Quittner AL. Utilization of patient-reported outcomes as a step towards collaborative medicine. *Paediatric respiratory reviews*. 2013;14:146-51.

TABLES

Table 1. Overview of RCTs Reviewed

Study	Patient Population (Severity)	N	Intervention	Study Design (Duration)	Study Duration	PRO Assessed and/or PROM Used		
						Symptoms / Control	HRQoL	Other
Ayres 2004	Poorly controlled, persistent moderate to severe allergic asthma in patients ≥ 12 years	312	- OMB + BSC - BSC	Randomized, open-label, multicenter, parallel-group	12 months	Wasserfallen asthma symptom score		
Bardelas 2012	Inadequately controlled, persistent allergic asthma treated w/ Step 4 or higher asthma maintenance therapy per 2007 NHLBI guidelines in patients ≥ 12 years	271	- OMB + current maintenance - PBO + current maintenance	Multicenter, randomized, double-blind, PBO-controlled	24 weeks	- ACT - e-Diary		WPAI-A
Bousquet 2011	Severe persistent allergic asthma in patients ≥ 12 years <75 years	404	- OMB + OAT - OAT	International, multicenter, randomized, open-label, parallel-group	32 weeks	- Nocturnal awakenings due to asthma - Patient's GETE - ACQ - e-Diary		
Buhl 2002a	Moderate-to-severe, symptomatic in patients ≥ 12 years <75 years (extension study of Solèr 2001)	546	- OMB + ICS (BDP) $\pm$ LABA - PBO + ICS (BDP) $\pm$ LABA	International, multicenter, randomized, double-blind, PBO-controlled, parallel-group (core study + double-blind extension)	52 weeks		AQLQ	
Busse 2001	Severe persistent in patients ≥ 12 years <75 years	525	- OMB + ICS (BDP) - PBO + ICS (BDP)	Multicenter, randomized, double-blind, PBO-controlled, parallel-group (Phase III)	28 weeks	TASS		
Busse 2011	Moderate or severe in patients 6-20 years	419	- OMB + guideline-based treatment - PBO + guideline-based treatment	Multicenter, randomized, double-blind, PBO-controlled, parallel-group; The Inner-City Anti-IgE Therapy for Asthma (ICATA) Study	60 weeks	- C-ACT - Number of days in 2 weeks preceding visit; interference w/activity		
Chanez 2010	Uncontrolled severe persistent in patients ≥ 18 years	31	- OMB + ICS (BDP equivalent) + LABA - PBO + ICS (BDP equivalent) + LABA	Multicenter, randomized, PBO-controlled, double-blind	16 weeks	- Number of days w/impairment in daily activities per week - Nights w/ awakenings - Change in number of days w/impairment in daily activities per week from baseline - ANAES definition of acceptable/optimal control		

Study	Patient Population (Severity)	N	Intervention	Study Design (Duration)	Study Duration	PRO Assessed and/or PROM Used		
						Symptoms / Control	HRQoL	Other
Corren 2011	Moderate asthma in patients 18-65 years	69	- OMB + stable asthma treatment - PBO + stable asthma treatment	Multicenter, randomized, double-blind, PBO-controlled, parallel-group	16 weeks	- Chest symptom score - NOSS Sneezes		
Finn 2003	Severe persistent in patients 12-75 years (extension study of Busse 2001)	525	- OMB + ICS (BDP) - PBO + ICS (BDP)	Data from core study (Busse 2001) + double-blind extension: multicenter, randomized, double-blind, PBO-controlled	52 weeks		AQLQ	
Hanania 2011	Severe in patients 12-75 years	850	- OMB + ICS (FCS) + LABA - PBO + ICS (FCS) + LABA	Multicenter, randomized, parallel-group, double-blind, PBO-controlled; the EXTRA study	48 weeks	TASS	AQLQ	
Hanania 2013	Severe in patients 12-75 years	850	- OMB + ICS (FCS) + LABA - PBO + ICS (FCS) + LABA	Prespecified and post hoc analyses of the EXTRA study (Hanania 2011)	48 weeks	TASS	AQLQ	
Holgate 2004	Severe in patients 12-75 years	246	- OMB + ICS (FCS) - PBO + ICS (FCS)	Multicenter, randomized, double-blind, PBO-controlled	32 weeks	TASS	AQLQ	
Hoshino 2012	Severe persistent in patients 20-75 years	30	- OMB + SAT - SAT	Randomized, controlled, open-label	16 weeks		AQLQ	
Humbert 2005	Severe persistent in patients 12-75 years	482	- OMB + ICS (BDP equivalent) + LABA - PBO + ICS (BDP equivalent) + LABA	Randomized, PBO-controlled, double-blind; the INNOVATE study	28 weeks	- Total clinical symptom score - Total asthma symptom score - Patients' GETE	AQLQ	
Humbert 2008	Severe persistent in patients 12-75 years (post-hoc analysis of Humbert 2005)	419	- OMB + ICS (BDP equivalent) + LABA - PBO + ICS (BDP equivalent) + LABA	Post-hoc analysis of the INNOVATE study (Humbert 2005)	28 weeks	- Symptom-free days - Symptom-controlled days	AQLQ*	
Humbert 2009	Moderate to severe in patients 12-75 years (post-hoc analysis of Vignola 2004)	399	- OMB + ICS (BUD ± LABA; Responders - PBO + ICS (BUD) ± LABA	Post-hoc analysis of the SOLAR study (Vignola 2004)	28 weeks	Total asthma symptoms score[†]	- AQLQ - RQLQ	

Study	Patient Population (Severity)	N	Intervention	Study Design (Duration)	Study Duration	PRO Assessed and/or PROM Used		
						Symptoms / Control	HRQoL	Other
Lanier 2009	Moderate to severe persistent in patients 6 to <12 years	627	- OMB + ICS (FCS propionate equivalent) - PBO + ICS (FCS propionate equivalent)	Multicenter, international, randomized, double-blind, PBO-controlled, parallel-group	52 weeks	- Daytime asthma symptom score - Nighttime awakenings requiring rescue medication - Change in nocturnal asthma symptom score - Patients' GETE	PAQLQ	
Lemanske 2002	Moderate to severe in patients 6 to 12 years (additional analysis of Milgrom 2001)	334	- OMB + ICS (BDP) - PBO + ICS (BDP)	Additional analysis of a multicenter, randomized, double-blind, PBO-controlled, parallel-group (Milgrom 2001)	28 weeks		PAQLQ	
Milgrom 2001	Moderate to severe in patients 6 to 12 years	334	- OMB + ICS (BDP) - PBO + ICS (BDP)	Multicenter, randomized, double-blind, PBO-controlled, parallel-group	28 weeks	- Daytime asthma symptom score - Nocturnal asthma symptom score - Morning asthma symptom score - Patients' GETE		
Niven 2008	Inadequately controlled, persistent moderate to severe allergic asthma in patients ≥12 years (post-hoc analysis of Ayres 2004)	164	- Subgroup: OMB + BSC (ICS >1000 µg/day BDP equivalent + LABA) - Subgroup: BSC (ICS >1000 µg/day BDP equivalent + LABA)	Post-hoc analysis of an open-label, randomized, multicenter, parallel-group study (Ayres 2004)	12 months	Wasserfallen asthma symptom score	Mini-AQLQ	
Noga 2003	Moderate to severe asthma in patients 12-75 (subgroup analysis of Solèr 2001)	35	- OMB + ICS (BDP) ± LABA - PBO + ICS (BDP) ± LABA	Subgroup analysis of an international, multicenter, randomized, double-blind, PBO-controlled, parallel-group study (Solèr 2001, Buhl 2002b)	7 months	Asthma symptom score		
Ohta 2009	Moderate to severe persistent asthma in patients 20-75 years	372	- OMB + ongoing asthma therapy [including high-dose ICS (BDP equivalent) ± other controller medications] - PBO + ongoing asthma therapy	Multicenter, randomized, double-blind, PBO-controlled	16 weeks	Asthma symptom score		
Rubin 2012	Uncontrolled, severe persistent asthma in patients	116	OMB + LABA +	Multicenter, randomized, open-label, parallel group	20 weeks	Patients' GETE	AQLQ	

Study	Patient Population (Severity)	N	Intervention	Study Design (Duration)	Study Duration	PRO Assessed and/or PROM Used		
						Symptoms / Control	HRQoL	Other
	≥12 years		ICS (FCS equivalent) • LABA + ICS (FCS equivalent)	(QUALITX)				
Solèr 2001	Moderate-to-severe, symptomatic in patients ≥12 years <75 years	546	• OMB + ICS (BDP) ± LABA • PBO + ICS (BDP) ± LABA	International, multicenter, randomized, double-blind, PBO-controlled, parallel-group	7 months	• Daytime score by patient diary: 0-4 (4 being worst) • Nighttime score by patient diary: 0-4 (4 being worst) • TASS		
Sorkness 2013	Moderate or severe asthma in patients 6 to 20 years (post-hoc analysis of Busse 2011)	419	• OMB + guideline-based treatment • PBO + guideline-based treatment	Post-hoc analysis of a multicenter, randomized, double-blind, PBO-controlled, parallel-group study; ICATA Study (Busse 2011)	60 weeks	• Asthma-related symptoms		
Teach 2015	Diagnosis or symptoms for more than 1 year, 1 or more asthma exacerbations (requiring systemic corticosteroids) or hospitalization within the prior 19 months, a positive skin test response to 1 or more perennial allergen in patients 6-17 years	513	• OMB (with inhaled PBO) + guidelines-based care • Guidelines-based care (with inhaled and injected PBO)	3-arm, randomized, double-blind, double PBO-controlled, multicenter clinical trial (PROSE)	4-9 month run-in phase, 4 month intervention phase	• ACT • C-ACT Asthma-related symptoms		
Vignola 2004	Moderate to severe in patients 12-75 years	405	• OMB + ICS (BUD) ± LABA • PBO + ICS (BUD) ± LABA	Multicenter, randomized, double-blind, parallel-group, PBO-controlled; the SOLAR study	28 weeks	• Wasserfallen total asthma symptom score • Wasserfallen total rhinitis clinical symptom score • Patient's GETE	• AQLQ • RQLQ	

*Baseline data only for QoL reported. † Baseline data only for symptom assessment reported.

Key: ACQ – Asthma Control Questionnaire; ACT – Asthma Control Test; AQLQ – Asthma Quality of Life Questionnaire; BDP – beclomethasone dipropionate; BSC – best standard care; BUD – budesonide; C-ACT – Childhood Asthma Control Test; FCS – fluticasone; ICS – inhaled corticosteroid; GETE – global evaluation of treatment effectiveness; HRQoL – health-related quality of life; ICATA – Inner-City Anti-IgE Therapy for Asthma; LABA – long-acting beta agonist; NOSS – nasal/ocular symptom scale; OAT – optimized asthma treatment; OMB – omalizumab; PAQLQ – Pediatric Asthma Quality of Life Questionnaire; PBO – placebo; RQLQ – Rhinoconjunctivitis Quality of Life Questionnaire; SAT – stable asthma treatment; TASS – Total Asthma Symptom Score; WPAI-A – Work Productivity and Activity Impairment Questionnaire-Asthma.

Table 2. Assessment of Risk of Bias Using the Cochrane Collaboration Tool*

Study	Data Years	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias
		Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Ayres 2004	NR	C	C	A	A	A	A	A
Bardelas 2012	NR	C	C	A	A	A	A	A
Bousquet 2011	NR	A	A	B	B	A	A	A
Buhl 2002a	NR	C	C	A	A	A	A	A
Busse 2001	NR	C	C	A	A	A	A	A
Busse 2011	2006-2008	C	C	A	A	A	A	A
Chanez 2010	2006-2008	A	A	A	A	A	A	A
Corren 2011	NR	C	C	A	A	A	A	A
Finn 2003	NR	C	C	A	A	A	A	A
Hanania 2011	NR	A	A	A	A	A	A	A
Holgate 2004	NR	C	C	A	A	A	A	A
Hoshino 2012	NR	C	C	A	A	A	A	A
Humbert 2005	NR	C	C	A	A	A	A	A
Humbert 2008	NR	C	C	A	A	A	A	A
Humbert 2009	NR	C	C	A	A	A	A	A
Lanier 2009	NR	A	C	A	A	A	A	A
Lemanske 2002	NR	C	C	A	A	A	A	A
Milgrom 2001	NR	C	C	A	A	A	A	A
Niven 2008	NR	C	C	A	A	A	A	A
Noga 2003	NR	C	C	A	A	A	A	A
Ohta 2009	NR	A	A	A	A	A	A	A
Rubin 2012	NR	C	C	C	C	A	A	A
Solèr 2001	NR	C	C	A	A	A	A	A
Sorkness 2013	2006-2008	C	C	A	A	A	A	A
Vignola 2004	NR	C	C	A	A	A	A	A

* Scoring key: A) Low Risk; B) High Risk; C) Unclear Risk. Cell color key: green generally indicates good quality, orange indicates poor quality, and clear cells indicate unclear or not determined.

Key: NR – not reported

Table 3. Characteristics of Disease-specific PROMs Identified in the 26 Studies Reviewed

Measure	Objective and Target Population	Content Validation	Domains	MID	# Items	Administration Mode	Recall Period
AQLQ	To measure the functional impairments that are most troublesome to adults with asthma Population age range: 17-70 years	Yes	Symptoms Activity limitations Emotional function Environmental stimuli	0.5	32	Self-administered Interviewer administered	2 weeks
Mini-AQLQ	To measure the functional impairments that are most troublesome to adults with asthma Population age range: 17-70 years	Yes	Symptoms Activity limitations Emotional function Environmental stimuli	0.5	15	Self-administered	2 weeks
PAQLQ	To measure the functional impairments that are most troublesome to children with asthma Population age range: 7-17 years	Yes	Symptoms Activity Emotional function	0.5	23	Self-administered Interviewer administered	1 week
ACT	To identify patients with poorly controlled asthma Population age range: ≥ 12 years	Yes	Asthma control	3.0	5	Self-administered Interviewer administered	4 weeks
C-ACT	To assess asthma control in children Population age range: 4-11 years	Yes	Child Caregiver	3.0	7	Self-administered (child) Interviewer administered	Child: 1 day Caregiver: 4 weeks
ACQ6	To measure the adequacy of clinical asthma control Population age: Adults	Yes	Symptoms Beta-agonist use	0.4	6	Self-administered	1 week
RQLQ	To measure the functional impairments that are most troublesome to adults as a result of rhinoconjunctivitis Population age: Adults	Yes	Overall Activity limitations Sleep impairment Non-nasal or non-ocular symptoms Practical problems Nasal symptoms Eye symptoms Emotional function	0.5	28	Self-administered	1 week
WPAI-A	To measure the loss of productivity due to asthma Population age range: ≥ 16 years	Yes	Work Daily activities	Not reported	6	Self-administered	1 week

Key: ACQ6 – Asthma Control Questionnaire; ACT – Asthma Control Test; AQLQ – Asthma Quality of Life Questionnaire; C-ACT – Childhood Asthma Control Test; MID – minimal important difference; PAQLQ – Pediatric Asthma Quality of Life Questionnaire; RQLQ – Rhinoconjunctivitis Quality of Life Questionnaire; WPAI-A – Work Productivity and Activity Impairment Questionnaire – Asthma.

Table 4. Studies that Used AQLQ (Overall Score), mini-AQLQ, or PAQLQ

Study	Intervention	Control	N	Baseline Scores	Change in Overall AQLQ / mini-AQLQ / Overall PAQLQ*	Time	Achieved MID [§]
Buhl 2002a	OMB + ICS ± LABA	PBO + ICS ± LABA	Core: 546 Ext.: 483	PBO: 4.36 OMB: 4.43	OMB scores were higher than PBO (P=NR) The change from baseline was greater for OMB vs PBO (P<0.001) ^A	52 weeks	Not reported
Finn 2003	OMB + ICS	PBO + ICS	Core: 525 Ext.: 460	Not reported	LSM change from baseline ^B PBO: 0.91 OMB: 1.19 P<0.01	52 weeks ^C	Yes
Hanania 2011	OMB + ICS + LABA	PBO + ICS + LABA	850	PBO: 3.9 OMB: 4.0	Difference in change from baseline for OMB vs PBO: 0.29 Significant (P=Not reported)	48 weeks	Not reported
Holgate 2004	OMB + ICS	PBO + ICS	246	Not reported	% of patients with ≥0.5 change from baseline: PBO: 38.6% OMB: 57.5% P<0.01	32 weeks	Yes
Hoshino 2012	OMB + SAT	SAT	30	Not reported	Median change from baseline: SAT: +0.28 OMB+SAT: +1.47 ^E P=Not reported	16 weeks	Yes
Humbert 2005	OMB + ICS + LABA	PBO + ICS + LABA	482	Not reported	LSM change from baseline: PBO: 0.46 OMB: 0.91 Difference: 0.45; P<0.001	28 weeks	Yes
Lanier 2009	OMB + ICS	PBO + ICS	627	Not reported	LSM difference in Overall PAQLQ score: 0.04 in favor of OMB P=0.676	52 weeks	No
Lemanske 2002	OMB + ICS	PBO + ICS	334	PAQLQ: PBO: 5.4 OMB: 5.5	% of patients with ≥0.5 change from baseline: PBO: 33.7% OMB: 46.9% P<0.05	28 weeks	Yes
Niven 2008	OMB + ICS + LABA	PBO + ICS + LABA	164	Not reported	Change from baseline on overall mini-AQLQ PBO: 0.17 OMB: 1.32 P<0.001	52 weeks	Yes
Rubin 2012	OMB + LABA + ICS	LABA + ICS	116	LABA+ICS: 3.1 OMB+ICS+LABA: 3.1	Mean score at 20 weeks: LABA + ICS: 3.0 OMB + ICS+ LABA: 4.4 P<0.001 Change from baseline: LABA+ICS: -0.1 OMB+ICS+ LABA: 1.3 ^F P<0.001	20 weeks ^D	Yes ^E
Vignola 2004	OMB + ICS ± LABA	PBO + ICS ± LABA	405	PBO: 4.0 OMB: 4.0	% of patients with ≥1.0-point change from baseline: PBO: 67.3%	28 weeks	Yes

Study	Intervention	Control	N	Baseline Scores	Change in Overall AQLQ / mini-AQLQ / Overall PAQLQ*	Time	Achieved MID [§]
					OMB: 50.0% P=0.001		

* Scores on the AQLQ, mini-AQLQ, and PAQLQ range from 1 to 7; a higher score indicates better quality of life. [§] Reported here whether the OMB group change from baseline achieved the MID (defined as ≥ 0.5) or the proportion of patients achieving this MID; ^A 15, 28 weeks available;

^B Baseline data available; ^C 16, 28 weeks available; significant findings reported at 28 weeks for change from baseline in Emotions domain ($P < 0.05$); ^D 12 weeks available; ^E MID reported at alternate timepoints.

Key: AQLQ – Asthma Quality of Life Questionnaire; ICS – inhaled corticosteroid; LABA – long-acting beta agonist; MID – minimal important difference; N/A – not available; OMB – omalizumab; PAQLQ – Pediatric Asthma Quality of Life Questionnaire; PBO – placebo; SAT – stable asthma treatment.

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Table 5. Studies that Used Patient-reported Symptoms

Study	Comparison	Symptom Measure	Reported Change	Timepoint	P-value
Ayres 2004	OMB + BSC vs BSC only	Wasserfallen total asthma symptom score (reduction from baseline indicates improvement)	Change from baseline, mean: OMB: -6.2 BSC: -0.7	52 weeks	<0.001
Bousquet 2011	OMB + OAT vs OAT only	Nighttime awakenings	Change from baseline: OMB: -4.05 OAT: -2.72	32 weeks	0.039
Busse 2001	OMB + ICS (BDP) vs PBO + ICS (BDP)	TASS (reduction from baseline indicates improvement)	OMB significantly improved asthma scores vs placebo after week 4	28 weeks	<0.01
Busse 2011	OMB + guideline-based treatment vs PBO + guideline-based treatment	Number of days with symptoms during the previous 2 weeks, mean $\pm$ SE	Asthma-related symptoms OMB: 1.48 ± 0.10 vs PBO: 1.96 ± 0.10 ; Difference: -0.48 (95% CI: -0.77, -0.20)	48 weeks	<0.001
			Wheezing OMB: 1.32 ± 0.09 vs PBO: 1.76 ± 0.09 ; Difference: -0.44 (95% CI: -0.70, -0.17)	48 weeks	0.001
			Interference with activity OMB: 0.70 ± 0.07 vs PBO: 0.59 ± 0.05 ; Difference: -0.17 (95% CI: -0.31, -0.03)	48 weeks	0.003
			Night-time sleep disruption OMB: 0.42 ± 0.05 vs PBO: 0.98 ± 0.07 ; Difference: -0.28 (95% CI: -0.47, -0.09)	48 weeks	0.02
			Subgroup analysis: sensitized and exposed to cockroach allergen OMB: -1.1 (95% CI: 0.4, 1.8); treatment effect: 48.5% Subgroup analysis: not sensitized to or exposed to cockroach allergen OMB: -0.4 (95% CI: 0.1, 0.7); treatment effect: 20.5%	48 weeks	0.06
			Reduction in number of days in 2 weeks preceding visit vs PBO Asthma-related OMB: 1.96 to 1.48; difference: 24.5% (1.04; 95% CI: 0.46, 1.62)	48 weeks	<0.001
Chanez 2010	OMB + ICS (BDP equivalent) + LABA vs PBO + ICS (BDP equivalent) + LABA	Number of days with asthma symptoms per week (diary card), median (range)	Change from baseline , OMB: -1.4 (-7 to 3) PBO: 0.0 (-4 to 2)	16 weeks	0.140
		Number of nights with awakening per week, median (range)	Change from baseline, OMB: -0.6 (-6 to 1) PBO: -0.3 (-4 to 2)	16 weeks	0.405
		Number of days with impairment in daily activities per week, median (range)	Change from baseline, OMB: -0.4 (-7 to 2) PBO: -0.3 (-7 to 2)	16 weeks	0.740
		ANAES definition of acceptable/optimal control (score=0)	OMB: 5 patients (25%) PBO: 1 patient (9.1%)	16 weeks	NR
Corren 2011	OMB + stable asthma treatment vs PBO + stable asthma treatment	Chest symptom score: chest tightness, wheezing, cough and SOB on a 4-point scale (0, none; 3, severe) (reduction from baseline indicates improvement)	AUC of change in score, mean OMB: 2.1; PBO: 5.6 Difference: -3.5 (95% CI: -4.8, -2.2)	16 weeks	<0.0001

Study	Comparison	Symptom Measure	Reported Change	Timepoint	P-value
		NOSS (nasal-ocular symptoms): nasal congestion, runny nose, itching of nose, itching of eyes, watery eyes on a 4-point scale (0, none; 3, severe) (reduction from baseline indicates improvement)	AUC of change in NOSS, mean OMB: 2.5; PBO: 5.2 Difference: -2.7 (95% CI: -4.0, -1.4)	16 weeks	0.0002
		Sneezes	Number of sneezes over 1-hour challenge, mean OMB: 3.5; PBO: 9.0 Difference: -5.4 (95% CI: -9.9, -1.0)	16 weeks	0.0169
Hanania 2011	OMB + ICS (FL) + LABA vs PBO + ICS (FL) + LABA	TASS (reduction from baseline indicates improvement)	Decrease in score for OMB vs PBO: Difference: -0.26 (95% CI: -0.42, -0.10)	48 weeks	NR
Holgate 2004	OMB + ICS (FL) vs PBO + ICS (FL)	TASS (reduction from baseline indicates improvement)	OMB lower than PBO	4, 8, 12, 32 weeks	<0.05
			OMB lower than PBO	16, 20, 24, 28 weeks	NS
Humbert 2005	OMB + ICS (BDP equivalent) + LABA vs PBO + ICS (BDP equivalent) + LABA	TASS (reduction from baseline indicates improvement)	Change from baseline: OMB significantly greater compared to PBO	28 weeks	0.039
Humbert 2008	OMB + ICS (BDP equivalent) + LABA vs OMB + ICS (BDP equivalent) + LABA responder group vs PBO + ICS (BDP equivalent) + LABA	Symptom-free days	OMB-treated: 37.2% OMB-responder: 45.8% PBO: 22.6%	26-28 weeks	<0.001
		Symptom-controlled days (total symptom score ≤ 1)	OMB-treated: 47.9% OMB-responder: 56.1% PBO: 35.3%	26-28 weeks	<0.001
		Symptom-controlled days: days w/ morning PEF rate $\geq 90\%$ of baseline, daytime asthma score ≤ 1 , and nighttime asthma score = 0	OMB-treated: 43.9% OMB-responder: 50.8% PBO: 28.0%	26-28 weeks	<0.001
Lanier 2009	OMB + ICS (FL equivalent) vs PBO + ICS (FL equivalent)	Nocturnal asthma symptom score (0-4), mean (SD) (reduction from baseline indicates improvement)	Change from baseline OMB: -0.63 (0.72) Placebo: -0.50 (0.71)	24 weeks	0.114
Milgrom 2001	OMB + ICS (BDP) vs PBO + ICS (BDP)	Daytime asthma symptom score (0-4), Mean (reduction from baseline indicates improvement)	OMB: 0.36 Placebo: 0.54	22 weeks	NR
Niven 2008	OMB + BSC (ICS >1000 $\mu\text{g/day}$ BDP equivalent + LABA) vs BSC (ICS >1000 $\mu\text{g/day}$ BDP equivalent + LABA)	Wasserfallen asthma symptom score (reduction from baseline indicates improvement)	Change from baseline: OMB: -6.7 vs BSC: 0.5	12 months	<0.01
			OMB had greater improvement compared to BSC	3 months	<0.05
				6 months	<0.01
				9 months	<0.05
Noga 2003	OMB + ICS (BDP) $\pm$ LABA vs PBO + ICS (BDP) $\pm$ LABA	Asthma symptom score: scale ranging from 0=no symptoms, to 4=breathing problems at rest (reduction from baseline indicates improvement)	Daily score, median (range): OMB: 0.5 (0 to 2.6) PBO: 0.9 (0 to 2.9)	16 weeks	NR

Study	Comparison	Symptom Measure	Reported Change	Timepoint	P-value
Ohta 2009	OMB + ongoing asthma therapy [high-dose ICS (BDP equivalent) ± other controller medications] vs PBO + ongoing asthma therapy	Asthma symptom score, Daily activity score (reduction from baseline indicates improvement)	Change from baseline: PBO had greater improvement compared to OMB	16 weeks	NS
		Asthma symptom score, Sleep score (reduction from baseline indicates improvement)	Change from baseline: OMB had greater improvement compared to PBO	16 weeks	NS
		Asthma symptom score (reduction from baseline indicates improvement)	Change from baseline: OMB had greater improvement compared to PBO	16 weeks	NS
Solèr 2001	OMB + ICS (BDP) ±LABA vs PBO + ICS (BDP) ±LABA	TASS (reduction from baseline indicates improvement)	Statistically significant differences in favor of OMB seen during the entire stable-steroid phase	28 weeks	≤0.001
		Daytime score by patient diary: 0-4 (4 being worst) (reduction from baseline indicates improvement)	Statistically significant differences in favor of OMB seen from week 4 through week 26	28 weeks	≤0.05
		Nighttime score by patient diary: 0-4 (4 being worst) (reduction from baseline indicates improvement)	Beneficial effect of OMB was evident for nighttime symptoms with statistically significant differences in favor of OMB seen from week 4 through week 26	28 weeks	<0.01
Sorkness 2013	OMB + guideline-based treatment vs PBO + guideline-based treatment	Days with asthma-related symptoms	OMB-treated patients had 0.86 less symptom days (per 2-week period)	4 weeks	0.04
Teach 2015	OMB + guideline-based care vs PBO + guideline-based care	Days with asthma-related symptoms	Number of days in 2 weeks preceding visit, mean (SD): OMB: 1.2 (0.09) PBO: 1.8 (0.16) Difference OMB vs PBO: -0.59 (-0.96, -0.23)	Unclear ('fall outcome period')	NR
Vignola 2004	OMB + ICS (budesonide) ± LABA vs PBO + ICS (budesonide) ± LABA	Wasserfallen total asthma symptom score (reduction from baseline indicates improvement)	Change from baseline Difference vs PBO: -1.8	28 weeks	<0.05 0.023
		Wasserfallen total rhinitis clinical symptom score (reduction from baseline indicates improvement)	Change from baseline Difference vs PBO: -3.53	28 weeks	<0.001 <0.001
		Wasserfallen total combined symptom score (reduction from baseline indicates improvement)	Change from baseline	28 weeks	<0.001

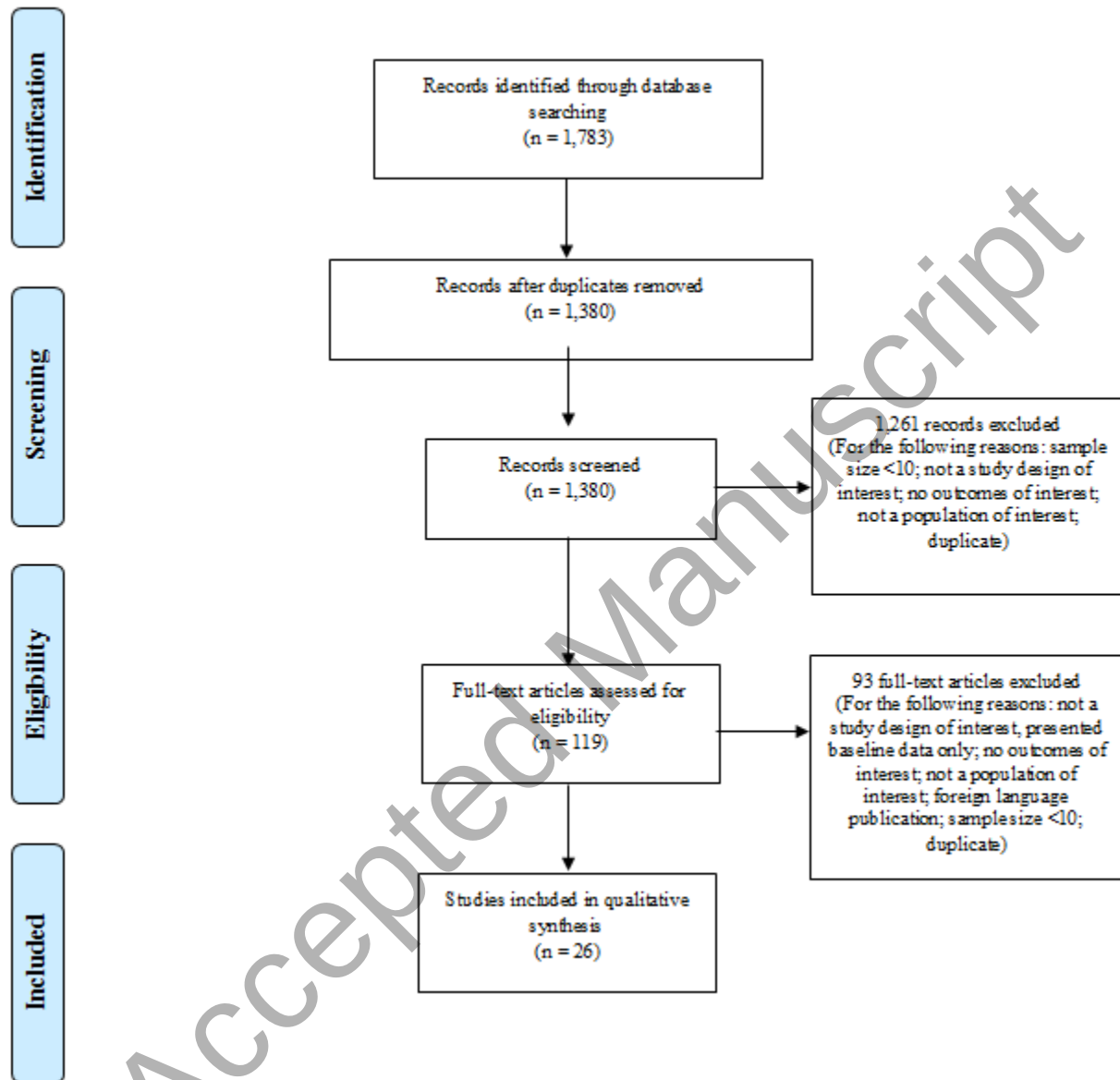
Key: ANAES - French National Agency for Accreditation and Evaluation in Healthcare; AUC – area under the curve; BDP – beclomethasone dipropionate; BSC – best standard care; GETE – global evaluation of treatment effectiveness; ICS – intravenous corticosteroids; LABA – long-acting beta2 agonist; NR – not reported; NS – not significant; OAT – optimized asthma therapy; OMB – omalizumab; PBO – placebo; SD – standard deviation; SOB – shortness of breath; TASS - Total Asthma Symptom Severity Score

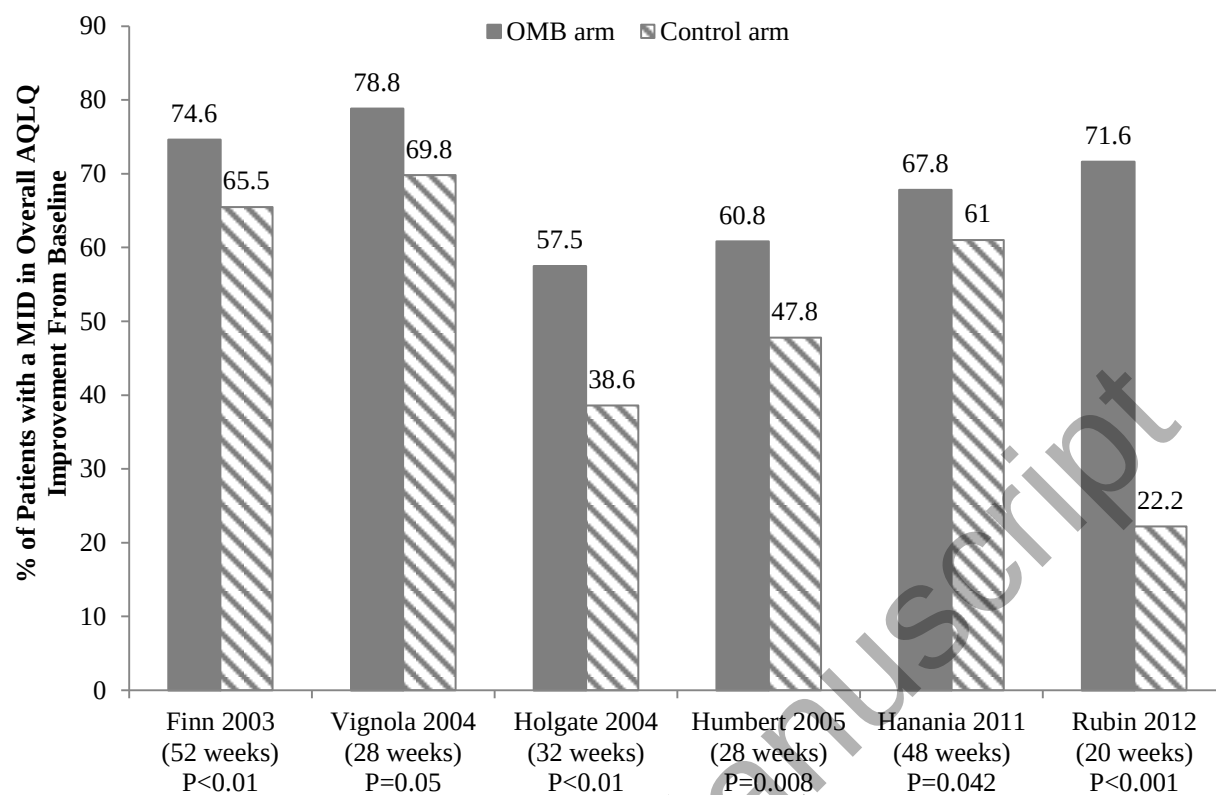
TASS: Total score (patient diary): daytime + nocturnal scores (each, 0-4) + morning score for symptoms upon waking (yes or no); max score=9.

FIGURES

Figure 1. PRISMA Study Flow

Figure 2. Percent of Patients Achieving MID on Overall AQLQ





Key: AQLQ – Asthma Quality of Life Questionnaire; MID – minimal important difference; OMB – omalizumab