National PBM Drug Monograph
Omalizumab (Xolair®)
VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

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INTRODUCTION
Omalizumab received FDA approval on June 20, 2003 and is the first biotechnology product for the treatment of asthma related to allergies. It is indicated for individuals 12 years of age and older with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Safety and efficacy have not been established in other allergic conditions. Omalizumab is manufactured by Genentech and will be jointly marketed with Novartis.

Many patients with asthma are atopic and possess specific IgE antibodies to allergens responsible for driving airway inflammation. Asthma is characterized by the early-phase response and the late-phase response upon exposure to allergen. The early phase response is IgE-mediated whereby IgE binds to FcεR1 receptors located on the surface of effector cells, ultimately leading to the release of stored inflammatory mediators from the effector cell. Although not well defined, it has been postulated that IgE may also be involved in the initiation of the late-phase response.

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that selectively binds to the Cε3 domain of IgE, which inhibits free IgE from binding to the mast cell FcεR1 receptor thereby preventing activation and subsequent release of cellular mediators.

PHARMACOKINETICS/PHARMACODYNAMICS
The absolute bioavailability after subcutaneous administration is 62%. Peak concentration is reached after 7-8 days. The volume of distribution is 78 ± 32 ml/kg, approximating plasma volume. Omalizumab is cleared by liver reticuloendothelial system and endothelial cells and has a half-life of ~ 26 days.

At recommended doses, serum free IgE is decreased by > 96%. Serum free IgE levels decrease in a dose-dependent fashion within 1 hour of the dose and are maintained between doses. Total serum IgE (omalizumab:IgE complex and free IgE) levels increase. After 16 weeks of treatment, total IgE levels were 5-fold higher than baseline levels. There appears to be no rebound in IgE levels after discontinuation of omalizumab. Total IgE levels do not return to pre-treatment levels for up to 1 year after discontinuation.

EFFICACY IN ALLERGIC ASTHMA
Pediatric trials and trials using IV administration of omalizumab were excluded from this review.

The 2 pivotal trials 008 and 009 utilized an identical protocol (see appendix for details on study design and results). [1,2] Patients had to be symptomatic despite treatment with inhaled corticosteroids (ICS), and had to have positive immediate response to skin prick test to $\geq$ 1 common allergen (mites, cockroach, dog, cat), total serum IgE $\geq$ 30 - $\leq$ 700 IU/mL, and FEV1 $\geq$40% - $\leq$ 80% predicted. Patients on other asthma controller drugs and current smokers were excluded. The patients' usual ICS was switched to an equivalent dose of beclomethasone (BDP). The trial was divided into 2 phases, a stable steroid phase (weeks 0-16) and a steroid reduction phase (weeks 16-28). During the stable steroid phase, the baseline BDP dose was maintained. During the steroid-reduction phase the dose of BDP was reduced by 25% every 2 weeks for 8 weeks until discontinued or worsening of asthma symptoms. For the last 4 weeks, the lowest effective dose of BDP that did not result in worsening of symptoms was maintained. Worsening of asthma symptoms was defined as: unscheduled physician visit; PEF < 50% of personal best; $\geq$ 20% in am PEF on $\geq$ 2 of 3 consecutive days; 50% increase in 24-h albuterol use (> 8puffs/ d) on $\geq$ 2 of 3 consecutive days, $\geq$ 2 of 3 consecutive nights with awakening due to asthma symptoms requiring medication.

The primary endpoint was the number of exacerbations during the stable steroid phase and the steroid reduction phase. An exacerbation was defined as worsening of asthma requiring treatment with systemic steroids or a doubling of the baseline inhaled steroid dose determined during the run-in period. In both trials, the number of exacerbations per patient was significantly lower in the patients receiving omalizumab compared to placebo (Table 1).

Table 1. Asthma exacerbations

	Study phase	Trial 008		Trial 009	
		Omalizumab	Placebo	Omalizumab	Placebo
Exacerbations/patient	Stable steroid phase	0.28*	0.54	0.28*	0.66
% of patients w/ ≥ 1 exacerbation	Stable steroid phase	14.6%*	23.3%	12.8%*	30.5%
Exacerbations/patient	Steroid reduction phase	0.39*	0.66	0.66*	0.75
% of patients w/ ≥ 1 exacerbation	Steroid reduction phase	21.3%*	32.3%	15.8%*	29.8%

*Significant versus placebo

Secondary endpoints included the percent reduction in the BDP dose at the end of the steroid-reduction phase, rescue albuterol use, asthma symptom score, peak expiratory flow rate and FEV1. The dose of inhaled steroids was significantly reduced in the group receiving omalizumab compared to placebo (Table 2). It is interesting to note that the placebo group also was able to substantially reduce their ICS dose. The difference from placebo in the mean reduction of rescue albuterol use was 0.5-1.5 puffs/day. There was approximately a 0.5-point difference in total asthma symptom score in favor of omalizumab. There was no appreciable difference in FEV1 or peak flow between omalizumab and placebo.

Table 2. Inhaled steroid use

	Trial 008		Trial 009	
	Omalizumab	Placebo	Omalizumab	Placebo
Mean baseline BDP dose (mcg/d)	570	568	769	772.1
Median % reduction of ICS	75%*	50%	75%*	50%
% of patients with ≥50% reduction in ICS dose	72.4%*	54.9%	79%*	55%
% of patients able to d/c ICS	39.6%*	19.1%	43%*	19%

*Significant versus placebo

The baseline demographics for urgent healthcare use in the previous year was relatively low suggesting that the study population had less severe disease. The mean number of unscheduled outpatient visits per patient in studies 008 and 009 was approximately 0.75 and 1.2 respectively and the mean number of ER visits per patient was approximately 0.2. The percent hospitalized in the previous year for asthma in study 008 was 2% and 4% in the omalizumab and placebo group respectively.[8] In study 009, the percent hospitalized for asthma was 4.1% and 7.5% respectively. Corren et al. presented the event rates/100 patient-years for unscheduled outpatient visits, emergency room treatment and hospitalizations for asthma exacerbation during 1 year of treatment[3]

Table 3. Event rates/100 patient-years

	Trial 008			Trial 009		
	Omalizumab	Placebo	Rate ratio [95% CI]	Omalizumab	Placebo	Rate ratio [95% CI]
Unscheduled outpatient visit	18.16	31.83	0.57* [0.35, 0.92]	14.84	32.07	0.46* [0.26, 0.8]
ER treatment	1.18	3.05	0.39 [0.00, 2.75]	1.14	2.92	0.39 [0.00, 2.75]
Hospitalization	0.39	1.31	0.30 [0.00, + inf]	0.38	4.16	0.09 * [0.00, 0.56]

*Significant

Trial 011 used a similar study design and dosing strategy as trials 008 and 009 with the following exceptions: fluticasone was the ICS used, included was an additional 4-week observation period after the steroid reduction phase, patients were considered as having severe asthma, patients taking oral steroids

were included, exacerbation was defined as the need for systemic steroids, and the primary endpoint was a decrease in ICS dose in those taking ICS only.[8]

The median percent decrease in ICS dose was 60% with omalizumab and 50% with placebo and was considered to be significant. Exacerbation rates, asthma symptom scores and spirometry were not significantly different compared to placebo. For the subgroup using both inhaled and oral steroids, the outcomes were not significantly different than that of placebo; however, the number of patients was relatively small. (See appendix for study details) [8]

Trials Q2143g (ALTO) and 1A04 are 2 randomized open-label trials comparing omalizumab to usual asthma care. There were no restrictions on concomitant asthma medications. They were primarily designed as safety trials; however, exacerbation rates, ER visits, urgent office visits, and hospitalizations for asthma were evaluated as secondary endpoints. In both trials, there were significantly less asthma exacerbations in the groups receiving omalizumab. Urgent office or ER visits and hospitalization did not greatly differ between groups in ALTO. In trial 1A04, there were less unscheduled office or ER visits in the omalizumab group; however, a statistical analysis was not done. (See appendix for study details)

Extension trials

In a 24-week extension, 483 patients continued randomized treatment from trial 009.[4] The lowest effective dose of BDP was continued and may be adjusted. Additional asthma medications may be used and/or switched if deemed necessary. The number of asthma exacerbations per patient was significantly reduced in the omalizumab group compared to placebo. Twenty-four percent of omalizumab patients had one or more exacerbations compared to 40.6% in the placebo group.

Fifty-seven percent of patients receiving omalizumab were able to decrease their dose of inhaled steroid by 50% or more compared to 32% receiving placebo. Similarly, 34% and 12% of omalizumab and placebo patients respectively were able to discontinue inhaled steroids.

QUALITY OF LIFE TRIALS

Asthma-related quality of life was also assessed in trials 008 and 009.[5,6] The Juniper Asthma Quality of Life Questionnaire (AQLQ) was used. This validated questionnaire is grouped into 4 domains: activity limitations (11 items), emotions (5 items), symptoms (12 items), and exposure to environmental stimuli (4 items). Each question is answered by the patient on a 7-point scale according to the level of impairment in the preceding 2 weeks. A lower score reflects greater impairment. An increase in domain or total score of $\geq$ 0.5 points is considered clinically meaningful and an increase $\geq$ 1.5 points is considered a large improvement. The AQLQ was assessed at the end of the steroid-stable, steroid-reduction, and extension phases. Total baseline scores in study 008 were 4.0 and 4.2 with omalizumab and placebo respectively and were 4.43 and 4.36 respectively in study 009. The omalizumab-treated patients had a larger increase in the AQLQ score and a greater percentage achieving a $\geq$ 0.5 or $\geq$ 1.5 point increase than did the placebo-treated patients.

Table 4. AQLQ results

	Trial 008		Trial 009	
	Omalizumab	**Placebo**	**Omalizumab**	**Placebo**
Steroid stable phase				
Mean change in AQLQ score	0.93*	0.66	0.9*	0.6
% with $\geq$ 0.5 point change	64.1%*	51.7%	62%	55%
% with $\geq$ 1.5 point change	28.3%*	18.6%	22%*	17%
Steroid reduction phase				
Mean change in AQLQ score	0.97*	0.7	1.02*	0.65
% with $\geq$ 0.5 point change	66.4%*	54.8%	68%*	57%
% with $\geq$ 1.5 point change	32.8%*	17.8%	30%*	18.5%
Extension trial				
Mean change in AQLQ score	1.19*	0.91	1.15*	0.8
% with $\geq$ 0.5 point change	74.6%*	65.5%	68%	70%
% with $\geq$ 1.5 point change	42.1%*	27%	32%*	24%

*Significant versus placebo; Results for study 009 estimated from graph

Evaluation of treatment effectiveness was assessed at the end of 28 weeks by both the patient and the investigators. Asthma control was rated as excellent (complete control), good (marked improvement), moderate (discernible but limited improvement), poor (no appreciable change), or worse. More than half the patients and clinicians considered the asthma control to be excellent or good.

Table 5. Patient and clinician assessment of asthma control

	Trial 008		Trial 009	
	Omalizumab	**Placebo**	**Omalizumab**	**Placebo**
Excellent/good (Patient/ clinician)	60.6% / 53.1%	38.1% / 33.3%	68% / 65%	40% / 33%
Moderate (Patient/ clinician)	21.9% / 28.9%	27% / 26.3%	19% / 20%	32% / 34%
Poor/ worse (Patient/ clinician)	17.6% / 18%	34.9% / 40.4%	11% / 12%	28% / 30%

Results for trial 009 estimated from graph

SEASONAL ALLERGIC RHINITIS

Omalizumab has been evaluated for prophylaxis of symptoms of seasonal allergic rhinitis (SAR) in a large 12-week trial.[7] Patients aged 12-75 years (n=536) with $\geq$ 2year history of ragweed-induced SAR and a baseline IgE level between 30-700 IU/ml were randomized to receive omalizumab or placebo. Treatment began just prior to ragweed season and continued throughout the pollen season. Patients with IgE levels between 151-700 IU/ml were given, 50mg, 150mg, or 300mg SQ every 3 weeks for a total of 4 doses. For IgE levels between 30-150 IU/ml, the dose was administered every 4 weeks for a total of 3 doses. The primary outcome measure was daily nasal symptom severity score. Compared to placebo, only the 300mg dose significantly resulted in a lower nasal score (0.75 vs. 0.98). Other endpoints included ocular symptom severity and rescue antihistamine use. All 3 doses resulted in improved ocular symptoms. Rescue antihistamine use was slightly lower in the omalizumab 300mg and 150mg groups versus placebo.

SAFETY AND TOLERABILITY

From a database of 2076 patients, of whom 1687 were exposed for 6 months and 555 were exposed for a year or more, the most frequent adverse events included injection-site reactions (45%), viral infection (23%), upper respiratory tract infection (20%), sinusitis (16%), pharyngitis (11%), or headache (15%).

It is not known whether IgE plays a role in surveillance in cancer prevention. If IgE is blocked there is a theoretical question of whether there is an associated increase in cancer incidence. The incidence of new or recurrent cancer was 0.5% with omalizumab and 0.2% with placebo. When expressed as 1000 patient-years of exposure the event rate was 6.3 and 3.3 respectively. The types of malignancies observed included breast, melanoma, non-melanoma skin, prostate, and parotid. Most patients were observed for less than a year. It is unknown if longer exposure or use in patients higher risk factors for malignancy increases the risk of developing cancer. It should be kept in mind that current smokers were excluded from the trials; therefore, it is unknown if their risk for cancer is further increased. The sponsor is planning long-term trials to determine whether there is a relationship between omalizumab treatment and cancer.

Anaphylaxis occurred in 4 omalizumab patients and in 3 control patients. In one of the omalizumab cases, the event was temporally associated with exposure to levofloxacin. In the 3 cases temporally related to omalizumab, the onset of the reaction began within 2 hours of the first or subsequent dose. Symptoms included urticaria, dyspnea, and throat and/or tongue edema.

Injection site reactions were common in both groups with an incidence of 45% in the omalizumab group and 43% in the placebo. Of these, 12% with omalizumab and 9% with placebo were considered severe. Symptoms included bruising, redness, warmth, burning, stinging, itching, hive formation, pain induration, mass, and inflammation. The reaction usually occurs within one hour of the injection, lasts less than 8 days and generally diminishes with subsequent injections.

No patient developed anti-omalizumab antibodies and there was no evidence of immune complex disease.

Only a small number of patients ≥ 65 years old (n=142) received omalizumab. It appears this group may have had a higher incidence of adverse events compared to those < 65 years old. Compared to the control group aged ≥ 65, the incidence of body as a whole, cardiovascular, digestive, musculoskeletal, nervous, and GU/reproductive adverse events were higher.

DRUG INTERACTIONS
No formal drug interaction trials have been conducted.

DOSAGE
Omalizumab is administered subcutaneously. Dose and dosing frequency is based on serum total IgE level measured before the start of treatment and body weight (Table 6). No more than 150mg is injected at a single site. Doses > 150mg are to be divided among more than 1 injection site. Dosage adjustments may be made based on changes in body weight. Repeat IgE levels cannot be used to adjust dose as total levels which measure both the omalizumab:IgE complex and free IgE are elevated.

Table 6. Omalizumab dosing

Pre-tx serum IgE (IU/mL)	Body weight (kg)				Dosing frequency
	30-60	>60-70	>70-90	>90-150	
30-100	150mg	150mg	150mg	300mg	Q4 weeks
>100-200	300mg	300mg	300mg	225mg	Q2 weeks
>200-300	300mg	225mg	225mg	300mg	
>300-400	225mg	225mg	300mg	Do not dose	
>400-500	300mg	300mg	375mg		
>500-600	300mg	375mg	Do not dose		
>600-700	375mg	Do not dose			

PREPARATION FOR ADMINISTRATION
Omalizumab is for single use only and contains no preservatives. The solution should be used for SC administration within 8 hours following reconstitution when stored in the vial at 2-8°C (36-46°F), or within 4 hours of reconstitution when stored at room temperature.

The lyophilized product takes 15-20 minutes to dissolve. The fully reconstituted product will appear clear or slightly opalescent and may have a few small bubbles or foam around the edge of the vial. The reconstituted product is somewhat viscous; in order to obtain the full 1.2 mL dose, ALL OF THE PRODUCT MUST BE WITHDRAWN from the vial before expelling any air or excess solution from the syringe.

A vial delivers 1.2 mL (150 mg) of omalizumab. For a 75 mg dose, draw up 0.6 mL into the syringe and discard the remaining product.

COST
The FSS cost for each 150mg vial is $323.29.

Dose	# of vials/ month	Cost/year
150mg	1	$3879.49
300mg	2	$7758.96
450mg (administered as 225mg twice monthly)*	4	$15, 517.92
600mg (administered as 300mg twice monthly	4	$15, 517.92
750mg (administered as 375mg twice monthly*	6	$23,276.88

*For a 75mg dose, withdraw 0.6ml and discard remaining product

SUMMARY

In the 2 pivotal trials, the omalizumab group had half as many exacerbations, when defined as worsening of asthma requiring treatment with systemic steroids or a doubling of the ICS dose, compared to placebo. The omalizumab treated patients were also able to reduce their baseline dose of ICS by about 1/4 more than the placebo group. Unscheduled outpatient visits were less frequent in the omalizumab treated group than the placebo group; however, hospitalization or ER visits due to asthma were not significantly different between the groups. It should be kept in mind that the pivotal trials enrolled a relatively "less sick" population who were taking, on average, moderate doses of ICS, not taking any other asthma controller drugs including oral steroid maintenance and had few urgent office or ER visits or hospitalizations in the year prior to enrollment.

Patients in trial 011 had more severe asthma than those in the pivotal trials. Unfortunately, asthma exacerbation, defined as need for systemic steroids, was a secondary endpoint. Nevertheless, the exacerbation rates did not differ significantly between groups. The median decrease in ICS dose was about 10% greater in the omalizumab group versus placebo. In contrast, the 2 open label trials did show benefit in a population with more severe disease; however, the open-label nature makes it difficult to draw firm conclusions.

Omalizumab does not have an effect on FEV1 or PEF and a relatively small favorable effect on asthma symptoms scores and rescue albuterol use.

Given the cost of this drug, it is unlikely that it will be used in patients with moderate allergic asthma. Blinded trials evaluating a population of severe asthmatics are needed, particularly in those who are oral steroid dependent.

Other areas where data are needed are in individuals who are $\geq$ 65y/o, smokers, non-white, and who have COPD with an asthmatic component. Also needed are long-term efficacy and safety data beyond one year of exposure and blinded trials evaluating omalizumab in patients whose asthma and allergy treatments have been optimized.

The safety of omalizumab use in those traveling to endemic parasitic regions is unknown. There is an ongoing study in Brazil evaluating omalizumab in patients who have intestinal helminthic exposure.

REFERENCES

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6. Finn A, Gross G, van Bavel J, et al. Omalizumab improves asthma-related quality of life in patients with severe allergic asthma. J Allergy Clin Immunol 2003; 111: 278-84.

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8. FDA Advisory Committee Briefing documents for Omalizumab for asthma. April 18, 2003 http://www.fda.gov/ohrms/dockets/ac/03/briefing/3952b1.htm

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Date: **August 2003**

APPENDIX. SUMMARY OF CLINICAL TRIALS

<table>
<tr><th>TRIAL</th><th>INCLUSION</th><th>DOSE</th><th>PATIENT CHARACTERISITICS</th><th>STUDY ENDPOINTS</th><th>RESULTS</th></tr>
<tr>
<td>Trial 008
Busse 2001
R, DB, PC, PR
Multicenter
Omalizumab vs placebo
N=525
28 weeks</td>
<td>Asthma ≥ 1 year per ATS criteria

12-75y/o

Symptomatic despite tx with ICS

+ immediate response on skin prick testing to ≥ 1 common allergen (mites, cockroach, dog, cat)

Total serum IgE ≥ 30 - ≤ 700 IU/mL and
body weight ≤ 150kg

FEV1 w/o bronchodilators ≥ 40 and ≤ 80% predicted

FEV1 reversibility of ≥ 12% post-albuterol 90-180mcg

Daily sx score ≥ 3 (maximum 9)

Inhaled beclomethasone 420-840mcg/day (or equivalent) for ≥ 3 months

No acute exacerbation for ≥ 1 month prior to screening

No regularly scheduled oral corticosteroids

No smoking within 2 years or history of ≥ 10 pack-yrs</td>
<td>4-6 week run-in where patients usual steroid was switched to equivalent BDP and titrated to maintain previous asthma control

2 study phases:
Stable steroid phase weeks 0-16 – Randomized to OM or PL; baseline BDP dose maintained unchanged

Steroid-reduction phase weeks 16-28 – BDP reduced by 25% every 2 weeks for 8 weeks until d/c or worsening of asthma sxs. For the last 4 weeks, pt. maintained on lowest effective dose of BDP that did not result in worsening of sxs.

Omalizumab ≥ 0.016mg/kg/IgE IU·ml. Dose given q 4 weeks if 150-300mg. If dose 450-750mg, it is divided into 2 equal portions and given q 2 weeks

Rescue albuterol (max 8 puffs/d) allowed, stable doses of immunotherapy continued; other asthma meds were not allowed</td>
<td>% male- OM 38.8%; PL 43.2%
Age (yrs)- OM 39.3 (12-73); PL 39 (12-74)
Duration of asthma (yrs)- OM 20.6 (1-61); PL 22.7 (2-60)
BDP dose (mcg/day)- OM 570 (420-1008); PL 568 (336-840)
Serum total IgE (IU/mL)- OM 172.5 (20-860); PL 186.3 (21-702)
FEV1 %pred – OM 68.2 ± 14.9;
PL 67.7 ± 14.3
FEV1 (L/s) – OM 2.3 ± 0.67; PL 2.4 ± 0.69)
AM PEF run-in (L/min)- OM 321 ± 88; PL 328 ± 90.2
PRN albuterol during run-in (puffs/ day)- OM 4.9 ± 2.65; PL 4.8 ± 2.51
Total sx score during run-in- OM 4.31 ± 1.17; PL 4.24 ± 1.17

Data presented as mean (range) or mean ± SD</td>
<td>Primary endpoint
# of exacerbations/ patient during stable steroid phase and steroid reduction period

Secondary endpoints
Patients with ≥ 1 exacerbation during stable steroid phase and steroid reduction period

Reduction in BDP dose at end of steroid-reduction phase

Rescue albuterol use

Asthma sx score

Morning PEF
FEV1 % predicted

IgE concentrations

Exacerbation defined as worsening of asthma requiring treatment with systemic steroids or doubling of baseline ICS dose</td>
<td>
<table>
<tr><th></th><th>Omalizumab N=268</th><th>Placebo N=257</th></tr>
<tr><td>Discontinuations</td><td>7.1%</td><td>13.2%</td></tr>
<tr><td># of exacerbations per pt. (stable steroid phase/steroid reduction phase)</td><td>0.28* / 0.39*</td><td>0.54 / 0.66</td></tr>
<tr><td># of days per exacerbation (Stable steroid phase/ steroid reduction phase)</td><td>7.8* / 9.4*</td><td>12.7 / 12.6</td></tr>
<tr><td>% of pts. w/ ≥ 1 exacerbations (stable steroid phase/steroid reduction phase)</td><td>14.6%* / 21.3%*</td><td>23.3% / 32.3%</td></tr>
<tr><td>Median % reduction of ICS dose</td><td>75%*</td><td>50%</td></tr>
<tr><td>% of pts. w/ ≥50% ICS dose reduction</td><td>72.4%*</td><td>54.9%</td></tr>
<tr><td>% of pts. who d/c ICS</td><td>39.6%*</td><td>19.1%</td></tr>
<tr><td>PRN albuterol use stable steroid phase/ steroid-reduction phase (puffs/d)^</td><td>-1.5* / -1.65*</td><td>-1.15 / -1.0</td></tr>
<tr><td>Asthma sx score stable phase/ reduction phase</td><td>-1.8* / -1.95*</td><td>-1.3 / -1.5</td></tr>
<tr><td>Δ in morning PEF at end of stable steroid phase</td><td>+18.5L</td><td>+6.9L</td></tr>
<tr><td>FEV1 % pred</td><td>+4.33%</td><td>+1.4%</td></tr>
<tr><td>Free IgE</td><td>6-8 IU/ml</td><td>>62 IU/ml</td></tr>
</table>
*Significant vs. placebo
Mean values unless otherwise indicated
^Results estimated from graph
</td>
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<table>
<tr>
<td>Trial 009
Soler 2001
R, DB, PC, PR
Multicenter
Omalizumab vs. placebo
N=546
7 months
ITT</td>
<td>As in Busse 2001 except:

Inhaled beclomethasone 500-1200mcg/day (or equivalent) for ≥ 3 months</td>
<td>Same study design and dosing protocol as described in Busse 2001</td>
<td>% male- OM 51.4%; PL 46.7%
Age (yrs)- OM 40.0 (12-76); PL 39 (12-72)
Duration of asthma (yrs.)- OM 20.3 (2-68); PL 19.1 (1-63)
BDP dose (mcg/day)- OM 769 (500-1600); PL 772.1 (200-2000)
Serum total IgE (IU/mL)- OM 223.1 (21-785); PL 205.6 (22-814)
FEV1 %pred – OM 69.8 (30-112); PL 69.9 (22-109)
FEV1 (L/s) – OM 2.53 (1.0-5.05); PL 2.52 (0.64-5.05)
FEV1 % reversibility – OM 26.4 (10-86); PL 25.8 (11-103)
Morning PEF (L/min)- OM 374; PL 376
% moderate asthma – OM 78.1%; PL 78.3%
% severe asthma*- OM 21.9; PL 21.7
PRN albuterol (puffs/d) – OM 4.0; PL 4.2

* FEV1 ≤ 65% pred and mean total sx score >4 for last 14 days of run-in
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Mean (range)</td>
<td>See Busse 2001</td>
<td>
<table>
<tr><th></th><th>Omalizumab N=274</th><th>Placebo N=272</th></tr>
<tr><td>Discontinuations</td><td>6.9%</td><td>14.7%</td></tr>
<tr><td>Exacerbations/pt Stable steroid phase</td><td>0.28*
[0.15, 0.41]</td><td>0.66
[0.49, 0.83]</td></tr>
<tr><td>Exacerbations/pt Steroid-reduction phase</td><td>0.66*
[0.49, 0.83]</td><td>0.75
[0.58-0.92]</td></tr>
<tr><td>% of pts. w/ ≥ 1 exacerbations stable steroid phase/steroid reduction phase</td><td>12.8%* / 15.8%*</td><td>30.5% / 29.8%</td></tr>
<tr><td>Median BDP dose (Interquartile range)</td><td>100mcg*
(0-400mcg0</td><td>300mcg
(100-600)</td></tr>
<tr><td>% of pts. w/ >50% ICS dose reduction</td><td>79%</td><td>55%</td></tr>
<tr><td>% of pts. who d/c ICS</td><td>43%</td><td>19%</td></tr>
<tr><td>PRN albuterol use stable steroid phase/ steroid-reduction phase (puffs/d)^</td><td>2* / 1.9*</td><td>3.6 / 3</td></tr>
<tr><td>Asthma sx score stable steroid phase/ steroid-reduction phase^</td><td>2.4* / 2.3*</td><td>3.1/ 2.75</td></tr>
<tr><td>Morning PEF at end of stable steroid phase</td><td>395</td><td>382</td></tr>
<tr><td>FEV1 % pred ^</td><td>71</td><td>69</td></tr>
<tr><td>Median free IgE</td><td>5-8 IU/ml</td><td>Data not shown</td></tr>
</table>
*Significant vs. placebo
^Results estimated from graph
Mean [95% CI] values unless otherwise indicated
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<tr>
<td>Buhl 2002
R, DB
N=483
24-week

Extension of trial by Soler 2001</td>
<td>See Soler 2001</td>
<td>Patient continued on randomized treatment from core trial 009.

Lowest effective dose of BDP continued and may be adjusted

Additional asthma meds may be used and/or switched if deemed necessary.</td>
<td>See Soler 2001</td>
<td>Asthma exacerbations
FEV1
BDP use
Concomitant asthma med use</td>
<td>
<table>
<tr><th></th><th>Omalizumab</th><th>Placebo</th></tr>
<tr><td>d/c</td><td>3.9%</td><td>11.4%</td></tr>
<tr><td>Exacerbations/pt</td><td>0.48*
[0.3, 0.66]</td><td>1.14
[0.81, 1.46]</td></tr>
<tr><td>% of pts. w/ ≥1 exacerbations</td><td>24*</td><td>40.6</td></tr>
<tr><td>Mean BDP dose (mcg/d)</td><td>253*</td><td>434</td></tr>
<tr><td>% of pts. w/ >50% ICS dose reduction</td><td>57%*</td><td>32%</td></tr>
<tr><td>% of pts. who d/c ICS^</td><td>34%*</td><td>12%</td></tr>
<tr><td>% using LABA/LTI</td><td>11% / 0.4%</td><td>17% / 3.5%</td></tr>
<tr><td>FEV1</td><td colspan="2">Difference NS. Data not shown</td></tr>
</table>
^Results estimated from graph
</td>
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<table>
<tr>
<td>Trial 011
R, DB, PC, PR
Omalizumab vs. placebo
N=341
32 weeks
Data from FDA transcripts and product package insert</td>
<td>12-75y/o

Asthma ≥ 1 year

+ skin prick test to ≥ 1 common allergen or + RAST test to specific allergen

Total serum IgE ≥ 30 - ≤ 700 IU/mL

FEV1 reversibility of ≥ 12%

Fluticasone dose ≥ 1000mcg/d with or without prednisolone up to 20mg/d</td>
<td>Same study design and dosing strategy as in Trials 008 and 009 plus a 4 week follow up period

Fluticasone inhaler was used as the ICS

Separate randomization for those only on ICS and those requiring oral steroids

Rescue albuterol allowed, stable doses of immunotherapy continued; other asthma meds were not allowed</td>
<td>% Male- OM 36%; PL 40%
Age (yrs.)- OM 42.7 (12-75); PL 42.4 (12-74)
Duration of asthma (yrs.)- OM 22.3 (2-70); PL 22.3 (1-64)

<u>ICS only group (n=246)</u>
FTC dose (mcg/day)- OM 1375 (750-2000); PL 1363 (1000-2000)
Serum total IgE (IU/mL)- OM 267 (31-1055); PL 266 (19-815)
FEV1 %pred – OM 63 (17-119); PL 66 (8-123)
Hosp admission in past year- OM 13%; PL 6.7%
ER visit per patient in past year- OM 0.7 (0-8); PL 0.6 (0-10)
Office visit in past year- OM 2.1 0-20); PL 1.7 (0-10)

<u>ICS + p.o group (n=95)</u>
FTC dose (mcg/day)- OM 1490 (750-2500); PL 1411 (500-2000)
Serum total IgE (IU/mL)- OM 205 (26-610); PL 234 (23-701)
FEV1 %pred – OM 60 (16-98); PL 57 (32-98)
Mean prednisolone dose- 10mg/day
OM 13%; PL 6.7%
Hosp admission in past year- OM 23%; PL 23%
ER visit per patient in past year- OM 1.0 (0-10); PL 1.3 (0-20)
Office visit in past year- OM 2.2 (0-10); PL 1.7 (0-12)</td>
<td><u>Primary endpoint</u>
Decrease in ICS dose in the ICS –only group

<u>Secondary endpoint</u>
Asthma exacerbations
Decrease in oral steroids
Rescue albuterol
Spirometry
Asthma sx scores</td>
<td>
<table>
<tr><th></th><th>Omalizumab</th><th>Placebo</th></tr>
<tr><td>d/c stable phase / reduction phase/ followup phase</td><td>6 / 2.8 / 5.7%</td><td>3/ 5.4 / 5.4%</td></tr>
<tr><td>Median % decrease in ICS dose</td><td>60%*</td><td>50%</td></tr>
<tr><td>% of pts. who d/c ICS</td><td>21%</td><td>15%</td></tr>
<tr><td>Median % decrease in oral steroid dose</td><td>69%</td><td>79%</td></tr>
<tr><td>% of pts. who d/c oral steroids</td><td>42%</td><td>42%</td></tr>
<tr><td>% of pts. w/ ≥1 exacerbations (stable phase) ICS / ICS + p.o</td><td>15.9% / 32%</td><td>15% / 22.2%</td></tr>
<tr><td>% of pts. w/ ≥1 exacerbations (reduction phase) ICS / ICS + p.o</td><td>22.2% / 42%</td><td>26.7% / 42.2%</td></tr>
<tr><td>Asthma sx score</td><td colspan="2">Minimum difference between groups</td></tr>
<tr><td>FEV1 / am PEF</td><td colspan="2">Minimum difference between groups</td></tr>
<tr><td>Rescue albuterol (puffs/d) ICS / ICS + p.o.</td><td colspan="2">0.5-1 puff difference vs. PL/ 0.4-2.8 puff difference vs. PL</td></tr>
</table>
*Significant vs. placebo
</td>
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<table>
<tr>
<td>Trial Q2143g
ALTO
R, Open label
Multicenter
Omalizumab vs. usual asthma care
N=1899
24 weeks

Data from FDA transcripts</td>
<td>6-75y/o
FEV1 < 80% predicted OR history of FEV1 < 80% predicted

Using moderate dose of ICS ± stable dose of oral steroids

On at least one of the following: LABA, leukotriene receptor antagonist, theophylline, cromolyn

IgE ≥ 30 - ≤ 1300 IU/mL
Weight ≥ 20 - ≤ 150kg

No smoking within 2 years or history of ≥ 10 pack years</td>
<td>2:1 randomization

No restrictions on concomitant asthma medications</td>
<td>% Male- OM 42.8%; control 42.6% Age (yrs.)- OM 41 ± 17; control 40 ± 17 (~ 7% of patient were aged 6-11)
Serum total IgE (IU/mL)- OM 193 ± 173; control 194± 177
FEV1 %pred – OM 75 (16-138); control 76 (24-185)
ICU admission- OM 8%; control 9%
Previous intubation/ ventilator- OM 7.8%; control 8.3%
Overnight hosp stay- OM 11.4%; control 10.8%
ER visit in past year- OM 21.3%; control 19.3%
Urgent office visit in past year- OM 45.6%; control 44.8%</td>
<td>Primary endpoint
Incidence of serious adverse events

Secondary endpoints
Asthma exacerbations

Exacerbation defined as required urgent office or ER visit AND ≥ 1 of the following: doubling ICS dose, increase in p.o. steroid dose (if on maintenance), initiation of systemic steroids</td>
<td>
<table>
<tr><th></th><th>Omalizumab N=1262</th><th>Control N=637</th></tr>
<tr><td>Discontinuations</td><td>14.2%</td><td>11%</td></tr>
<tr><td>% of pts. w/ ≥1 exacerbations</td><td>21.5%*</td><td>28%</td></tr>
<tr><td>Exacerbation rate/24 weeks</td><td>0.35*</td><td>0.44</td></tr>
<tr><td>% of pts. w/ ≥1 hosp for asthma</td><td>2.2%</td><td>3.1%</td></tr>
<tr><td>Hospitalization rate/24 weeks</td><td>0.027</td><td>0.041</td></tr>
<tr><td>% of pts. w/ ≥1 ER visit for asthma</td><td>2.9%</td><td>3.5%</td></tr>
<tr><td>ER visit rate/24 weeks</td><td>0.04</td><td>0.047</td></tr>
<tr><td>% of pts. w/ ≥1 urgent visit for asthma</td><td>19.8%</td><td>25.5%</td></tr>
<tr><td>Urgent visit rate/24 weeks</td><td>0.31</td><td>0.38</td></tr>
<tr><td>Use of concomitant asthma medications</td><td colspan="2">No notable inter treatment difference</td></tr>
<tr><td>FEV1/ PEF</td><td colspan="2">No notable inter treatment difference</td></tr>
</table>
</td>
</tr>
<tr>
<td>Trial IA04
R, open label
Multicenter
Omalizumab vs. usual asthma care
N=312
52 weeks

Data from FDA transcripts</td>
<td>12-75 y/o
Moderate-severe persistent asthma ≥ 2yrs.

≥ 1 asthma-related hospitalization or ER visit AND ≥ 1 course of oral steroids in the previous yr.

BDP ≥ 800mcg or equivalent (non-peds)

+ skin test to ≥ 2 allergens FEV1 reversibility of ≥ 12%

Total serum IgE ≥ 30 - ≤ 700 IU/mL

Suitable weight for dosing

Smoking > 10 pack years excluded</td>
<td>2:1 randomization
Same dosing as in trials 008 and 009

No restrictions on concomitant asthma medications except immunotherapy was not allowed</td>
<td>% Male- OM 28.2%; control 32.1% Age (yrs.)- OM 38.2 (12-73); control 39.3 (12-71)
FEV1 %pred – OM 71.4 ± 21.4; control 71.6 ± 21.9
Serum total IgE (IU/mL)- OM 204 ± 153; Control not done
% w/ ≥ hospitalization- OM 42.2%%; control 45.3%
% w/ ≥ 1 ER visit in past year- OM 90.3%%; control 91.5%
% w/ ≥ 1 course of oral steroid in past year- OM 100%; control 99.1%
Median ICS dose (BDP equivalent)- OM 2000mcg (0-10,000); control 2000 (400-8000)</td>
<td>Primary endpoint
Deterioration of asthma

Secondary endpoints
Systemic corticosteroid requiring exacerbations

Asthma deterioration defined as need for curse of antibiotics, oral steroids, missing school/work, unscheduled office visit, ER visit, hospitalization

Exacerbation defined as need for systemic steroids</td>
<td>
<table>
<tr><th></th><th>Omalizumab N=206</th><th>Control N=106</th></tr>
<tr><td>Discontinuations</td><td>17%</td><td>31.1%</td></tr>
<tr><td>% of pts. w/ ≥1 asthma-related deterioration</td><td>64%*</td><td>80%</td></tr>
<tr><td>% of pts. w/ ≥1 exacerbations</td><td>50.5%*</td><td>73.6%</td></tr>
<tr><td>Unscheduled office visit</td><td>33.5%</td><td>50.6%</td></tr>
<tr><td>% of pts. w/ ER visit</td><td>12.6%</td><td>19.1%</td></tr>
<tr><td>% of pts. w/ hospitalization</td><td>8.4%</td><td>9%</td></tr>
<tr><td>% of pts. school/work absenteeism</td><td>43.5%</td><td>57.3%</td></tr>
<tr><td>FEV1 % predicted</td><td>+4%</td><td>-2%</td></tr>
<tr><td>ICS dose at end of study</td><td>-342mcg</td><td>+68mcg</td></tr>
<tr><td>Concomitant asthma meds</td><td colspan="2">No notable inter treatment difference</td></tr>
</table>
* significant versus control
</td>
</tr>
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