Cipla

PRODUCT MONOGRAPH

In severe allergic asthma

℞ emzumab

embrace life

Omalizumab injection 150mg

PREFACE:

Asthma is a common disease affecting around 358.2 million people worldwide and 37.9 million in India, and the incidence is predicted to rise in the next few decades[1]. It is recognized that around 5-10% of patients with asthma have severe disease that remains inadequately controlled; despite high-dose inhaled corticosteroids plus long-acting $ß_2$-agonists (ICS/LABA) and additional controller medication if required (Global Initiative for Asthma 2016 step 4 therapy)[2]. Such patients, who have exhausted their therapeutic options, are at a higher risk of serious exacerbations and asthma-related mortality. They represent the greatest unmet medical need among the asthmatic population today. However, a key challenge in managing this group of severe asthmatics is to identify appropriate patients that will respond best to existing and evolving therapies.

IgE bound to high-affinity IgE receptors (FcεRI) on mast cells is cross-linked by allergen leading to the release of pro-inflammatory mediators, which give rise to the symptoms of asthma Omalizumab, the first anti-IgE treatment, suppresses IgE-mediated allergic reactions by binding to free IgE in patients with allergic asthma. The clinical efficacy and safety of Omalizumab has been extensively evaluated in clinical trials involving patients with severe persistent allergic asthma and has shown benefits in reducing exacerbations, requirement of oral corticosteroids, improvement in asthma control and quality of life. Analysis of safety and tolerability of Omalizumab in completed Phase I/II/III trials has shown that the frequency and nature of adverse events were generally similar between Omalizumab and control groups.

Emzumab is a biosimilar biologic, which is similar in terms of quality, safety and efficacy to the Innovator Omalizumab. It has undergone extensive tests, analyzing (i.e., characterizing) the structure, quality, purity, pharmacodynamic, pharmacokinetic, toxicology,efficacy and safety studies which help to prove it is similar to the Innovator Omalizumab. This monograph is a compilation of efficacy and safety of anti-IGE therapy and Emzumab in patients with severe allergic asthma.

May 2020

CONTENTS:

CHAPTER 1
SEVERE ASTHMA: THE UNMET NEED

- Globally, 5–10% of the total asthma population suffers from severe asthma[3,4]
- Approximately 2 million people suffer from severe asthma in the United States and yet it remains poorly understood[5]
- The average cost per patient with severe asthma is reportedly six times that of mild asthma[6]
- Medication usage is high in patients with severe asthma, with almost 26% using three or more controllers[8]
- Approximately 10% of patients with severe asthma have reported a history of intubation for asthma[7]
- The mortality rate amongst individuals with severe asthma is estimated to be 6.7 per 100 person-years[9]

Despite an increased understanding of the inflammatory basis of asthma and a growing acceptance of standardized disease management guidelines, asthma remains associated with substantial morbidity, mortality and economic costs. The Asthma UK survey estimated that 2.6 million of the 5.1 million people in the UK suffering from asthma experience serious asthma symptoms. Patients with severe asthma are at increased risk of hospitalization for exacerbations, or of asthma death, and account for more than 50% of total asthma-related costs. Patients with severe asthma, particularly the estimated 5% of patients whose asthma is inadequately controlled despite best available therapy, have limited therapeutic options.

GINA 2002 guidelines[8] classify asthma severity as intermittent, mild persistent, moderate persistent or severe persistent asthma. For optimum control of asthma GINA 2016[9] guidelines recommend that treatment be given in a stepwise fashion (step 1–4), increasing medications until symptoms are adequately controlled. It is recognized that complete control may not be achievable for patients with severe persistent asthma. Patients with severe persistent asthma that is inadequately controlled despite GINA step 4 therapy are a challenging patient population with few therapeutic options available. A clear unmet need exists for an effective and safe treatment of severe persistent asthma that is inadequately controlled despite GINA step 4 therapy.

DEFINITION OF SEVERE ASTHMA

The term, severe asthma, has undergone several changes in definition since the first attempt by the Global Initiative for Asthma Management (GINA) guidelines in 1995. Various societies and organizations such as the European Respiratory Society (ERS), American Thoracic Society (ATS), World Health Organization (WHO) and Innovative Medicines Initiative (IMI) have tried to define severe asthma using various terminologies such as ‘difficult asthma’, ‘severe refractory asthma’, poorly controlled asthma’, and ‘uncontrolled asthma’.

Recently, a joint ERS/ATS taskforce has defined severe asthma as “Asthma that requires treatment with guidelines-suggested medications for GINA guidelines steps 4–5 (high-dose inhaled corticosteroids (ICS) and long-acting ß2-agonist (LABA) or leukotriene modifier/theophylline) for the previous year or systemic corticosteroids (CS) for ≥50% of the previous year to prevent it from becoming 'uncontrolled' or which remains ‘uncontrolled despite this therapy’.[3] Further, the WHO recommends that severe asthma because of no treatment or undertreatment should be considered as untreated severe asthma, especially in the developing parts of the world.[11]

IDENTIFYING SEVERE ASTHMA IN CLINICAL PRACTICE

Recognizing severe asthma can be quite tricky in real-life practice. Severe asthma has been described as asthma that requires step 4 or step 5 treatment as described in the GINA guidelines— that is, high-dose ICS/LABA to prevent it from becoming uncontrolled or if it remains uncontrolled despite this treatment.[17]

Severe asthma is also defined by GINA as asthma that is uncontrolled despite adherence with maximal optimized therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased.[15]

The word 'severe' is also used by the patients to describe the intensity or frequency of their symptoms, which may not necessarily indicate a severe disease as it may be possible to control the symptoms using the right doses of ICS. Hence, it is quite important to explain the term 'severe' to the patient when diagnosing severe asthma.

The first step towards diagnosing severe asthma is its differentiation from uncontrolled asthma. Uncontrolled asthma is a very common reason for persistent symptoms and frequent exacerbations of asthma and may be easily improved.

The following problems, which contribute to 'difficult' asthma, need to be excluded before considering the diagnosis of severe asthma:[17]

- Ability to use inhalers correctly
- Adherence issues
- Confirmed diagnosis of asthma
- Ruling out the alternate diagnosis of asthma
- Comorbidities and contributory conditions
- Exposure to irritants and allergens

FIGURE 1 DESCRIBES IN DETAIL THE STEPS TOWARDS DIAGNOSING SEVERE ASTHMA IN CLINICAL PRACTICE. THESE STEPS MAINLY HELP TO IDENTIFY TREATMENT-RESISTANT OR REFRACTORY ASTHMA.

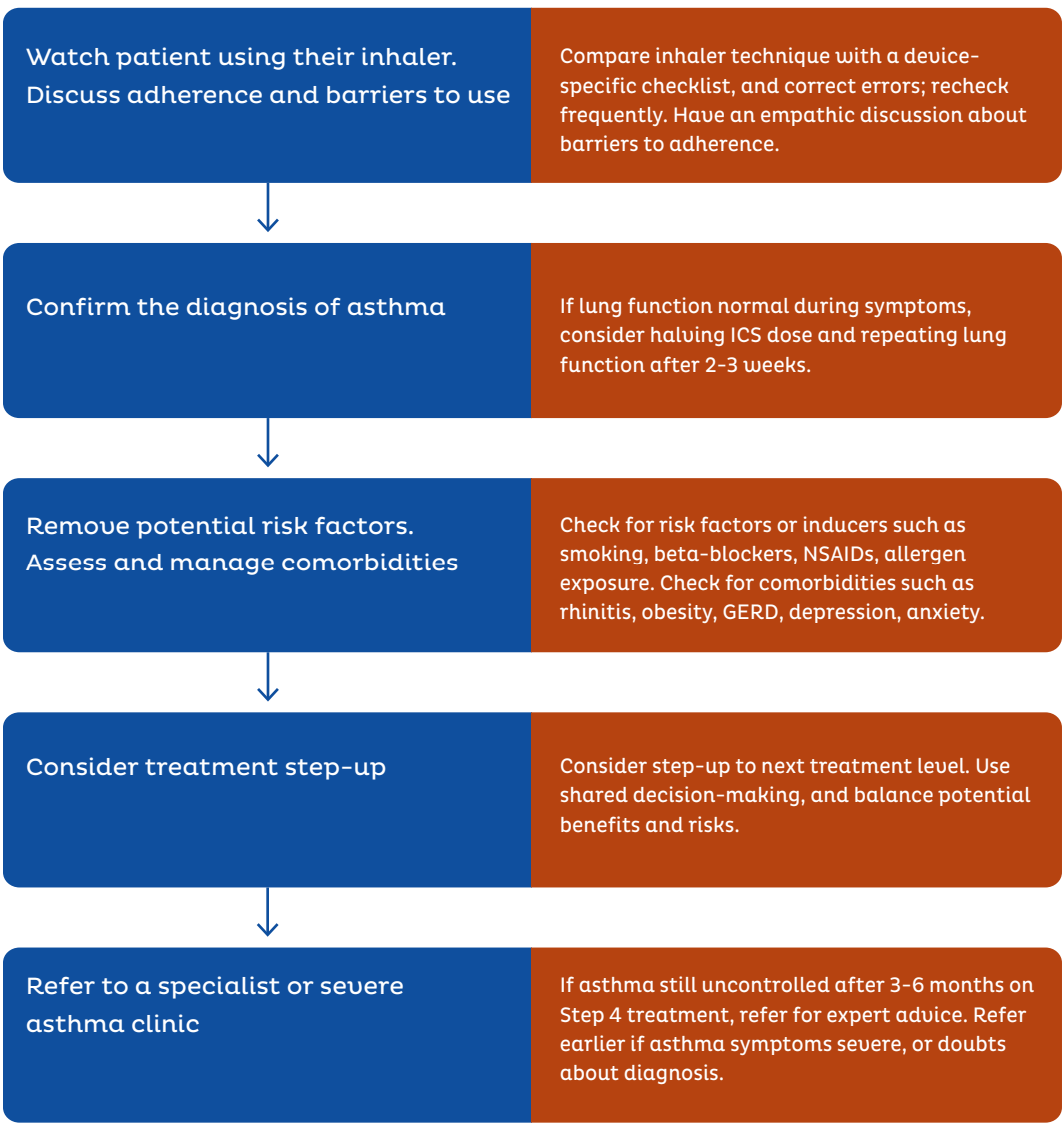


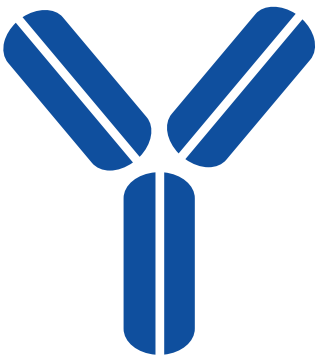
Figure 1: Steps for diagnosing severe asthma

One of the key differences between difficult asthma and treatment-resistant/refractory severe asthma is that difficult asthma can be managed by modification of the common problems mentioned in Figure 1.[17]

Treatment-resistant/refractory severe asthma probably needs more than the traditional treatment options and, hence, is now the focus of research in the development of targeted therapies in the form of monoclonal antibodies.

SUMMARY:

- Severe asthma represents a significant problem for patients and physicians – it is associated with high morbidity and mortality, considerable economic costs and a detrimental effect on patients' QoL.
- Patients with severe asthma are at an increased risk of hospitalization for exacerbations or of asthma death and account for more than 50% of total asthma-related costs.
- Patients with severe asthma, particularly the estimated 5% of patients whose asthma is inadequately controlled despite best available therapy, have limited therapeutic options. Patients with inadequately controlled severe persistent asthma despite maximal optimized therapy treatment have exhausted their therapeutic options and have a significant unmet medical need.
- Targeted therapies are now in focus for the treatment of severe persistent asthma that is adequately controlled despite treatment with high-dose ICS and LABA.



CHAPTER 2
ROLE OF IgE IN ASTHMA

- Immunoglobulin E (IgE) is one of the five classes of immunoglobulins or antibodies that have evolved to play differing roles in the body's immune system

- IgE plays a key role in the inflammatory process by virtue of binding to high-affinity (FcεRI) receptors on key inflammatory cells, including mast cells

- Activation of mast cells leads to the release of a variety of preformed and newly generated pro-inflammatory mediators and cytokines, including histamine, interleukins (IL), leukotrienes and prostaglandins (Type I hypersensitivity reaction), and the release of cytokines IL-4, IL-13 (increasing IgE synthesis) and IL-5 (increasing eosinophil accumulation) that contribute to the chronic inflammatory response

- The prevalence of asthma is closely related to the level of serum IgE

- High-affinity IgE receptors are upregulated on eosinophils, mast cells, macrophages and dendritic cells (DC) in patients with allergic asthma
- Expression of high-affinity IgE receptors is increased in fatal asthma. IgE may enhance mast-cell survival
- Asthma is almost always associated with some type of IgE-related reaction and therefore has an allergic basis
- IgE plays a key role in the inflammatory response that characterizes both the acute and chronic clinical manifestations of asthma

IgE AND THE INFLAMMATORY RESPONSE

IgE is one of the five classes of immunoglobulins or antibodies that have evolved to play differing roles in the body's immune system. When cell-bound IgE molecules are cross- linked (e.g. by allergen) the mast cell is activated. This activation releases a variety of preformed and newly generated pro-inflammatory mediators and cytokines, including histamine, interleukins, leukotrienes and prostaglandins (Type I hypersensitivity reaction), and the release of IL-4, IL-13 (increasing IgE synthesis) and IL-5 (increasing eosinophil accumulation) that contribute to the chronic inflammatory response. Indeed, eosinophilia is a well-recognized feature of inflammation in asthma and reflects asthma severity and the risk of exacerbations. In addition, IgE binds to Dentaitic cells (DC) and enhances allergen uptake and presentation to T cells, leading to increased T-cell proliferation and eosinophil differentiation and activation. (Figure 3).

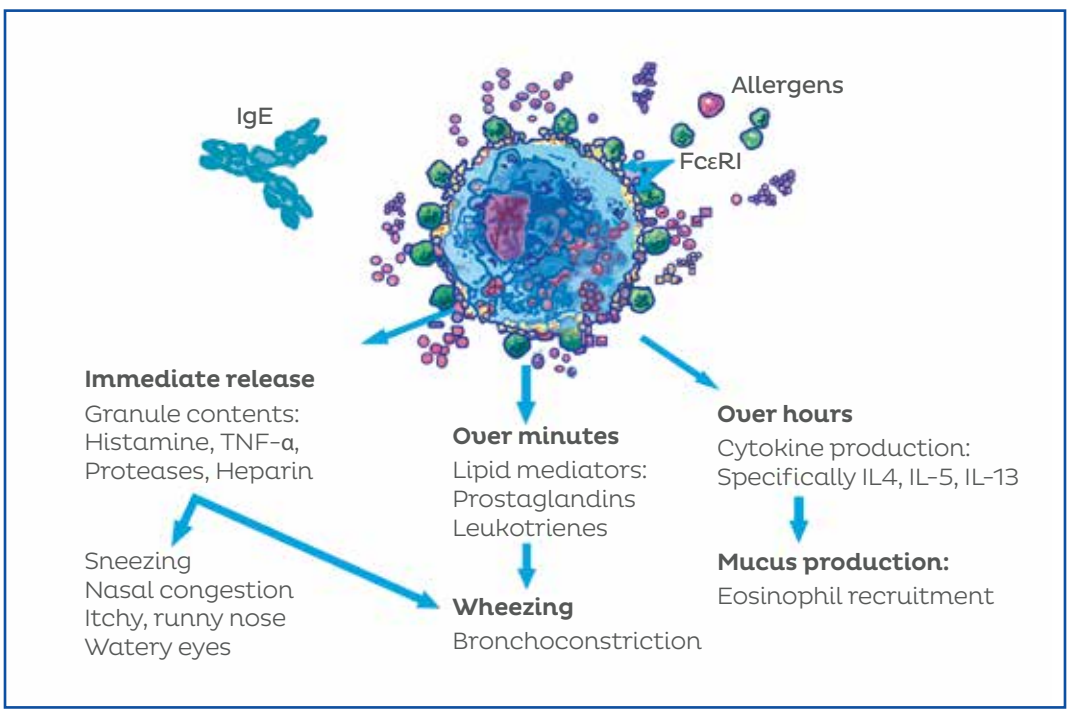


Figure 2: IgE dependent release of Inflammatory Mediators

IgE itself upregulates FcεRI on mast cells/basophils.[35, 36] The upregulation of FcεRI expression in the presence of higher concentrations of serum IgE results in mast-cell stimulation and mediator release at lower concentrations of allergen, and/or in the release of increased amounts of mediators and cytokines for a given level of stimulus.[37] The presence of FcεRI receptors on various other cell types can account for a range of pro-inflammatory activities.

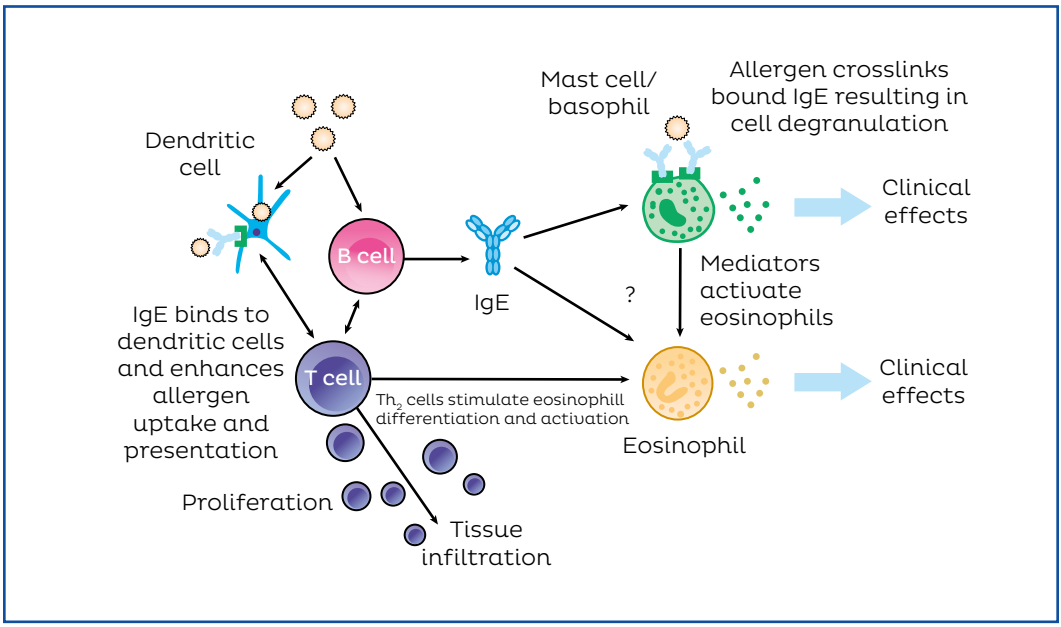


Figure 3: IgE plays a central role in the inflammatory cascade

IgE IN ALLERGIC ASTHMA

In patients with allergic asthma, exposure to allergen can trigger mast-cell degranulation. Bronchoconstrictor mediators such as histamine, prostaglandins, leukotrienes and thromboxanes act on the smooth muscle of the airways resulting in immediate bronchoconstriction. This leads to the development of typical asthma symptoms within minutes of exposure to allergens. Many patients with asthma also experience a late-phase reaction some hours later due to the recruitment of inflammatory cells, particularly eosinophils.

The prevalence of asthma is closely related to the level of serum IgE. Burrows and colleagues[38] identified a close association between asthma and serum IgE level. (Figure 4). Elevated IgE levels are associated with persistent wheezing. In addition, IgE has been shown to predict human airway reactivity in vitro.[39]

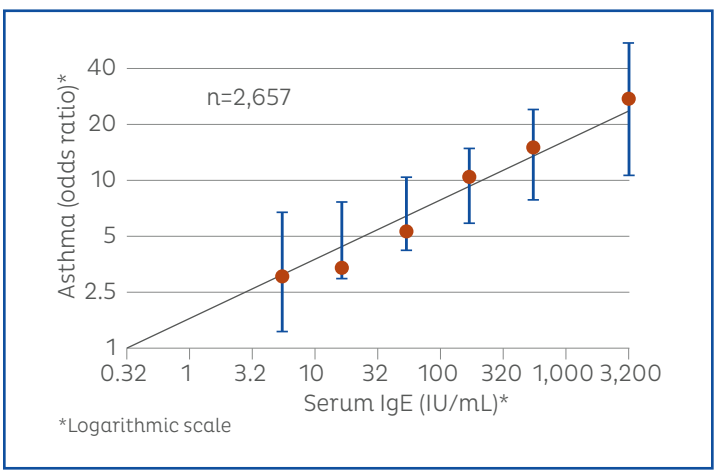
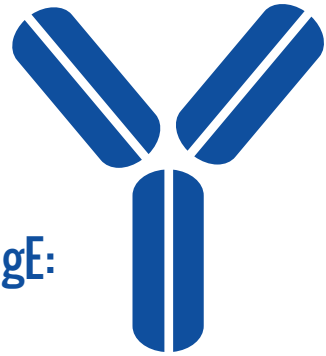


Figure 4:
The likelihood of having asthma increases with increasing levels of serum IgE

SUMMARY:

- IgE plays a key role in the inflammatory process by virtue of binding to high-affinity (FcεRI) receptors on key inflammatory cells, including mast cells.
- IgE levels are elevated in patients with asthma, which is almost always associated with some type of IgE-related reaction and therefore has an allergic basis.
- In addition, IgE upregulates the high-affinity IgE receptors on key anti-inflammatory cells such as mast cells/basophils, eosinophils and DCs.
- IgE may also enhance mast-cell survival.
- IgE plays a central role in allergic asthma and there is also growing evidence indicating a role in non-allergic (intrinsic) asthma.



CHAPTER 3
TARGETING IgE: ROLE OF OMALIZUMAB

- Omalizumab is the first of a new class of agents that specifically target human IgE.
- Omalizumab removes serum free-IgE, but does not bind to cell-surface IgE, thus avoiding the FcεRI cross-linking that could potentially lead to anaphylaxis.
- By removing free IgE, Omalizumab downregulates IgE receptors on mast cells/basophils and inhibits the release of pro-inflammatory mediators.
- Omalizumab significantly reduces eosinophilia in patients with allergic asthma.
- Omalizumab inhibits allergen-induced early and late asthmatic responses in patients with allergic asthma.
- Omalizumab significantly reduces submucosal IgE cells and FcεRI cells in patients with allergic asthma.
- Omalizumab reduces FcεRI expression on DCs and may inhibit antigen processing and presentation to T cells.
- Omalizumab reduces inhaled corticosteroid (ICS) use.
- The anti-inflammatory effects of Omalizumab provide proof of concept of the importance of IgE in allergic respiratory disease.

STRUCTURAL AND BINDING CHARACTERISTICS OF OMALIZUMAB:

The molecule is made up of a human immunoglobulin G (IgG) framework on to which is grafted the CDR from the anti-IgE antibody raised in mice.(Figure 5). The humanized monoclonal antibody contains only 5% non-human residues, minimizing the potential for the development of allergic responses to the animal proteins. This improves the safety profile. Additionally, both pharmacokinetics and therapeutic efficacy are enhanced. Omalizumab binds to the region of the IgE molecule that interacts with IgE receptors (Figure 6)

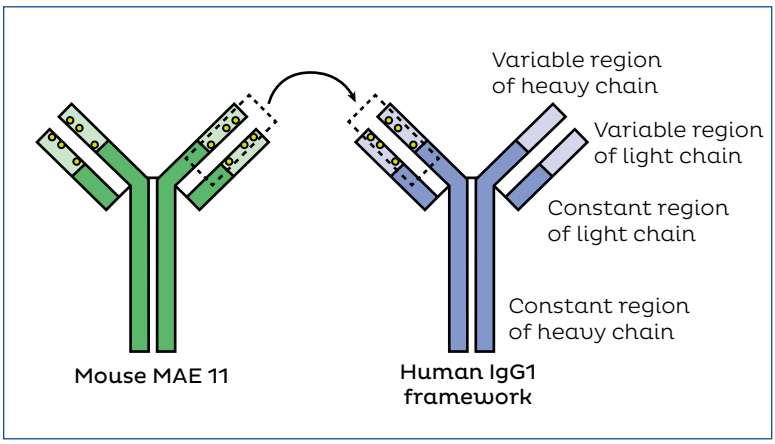


Figure 5: Humanizing the monoclonal anti-IgE antibody

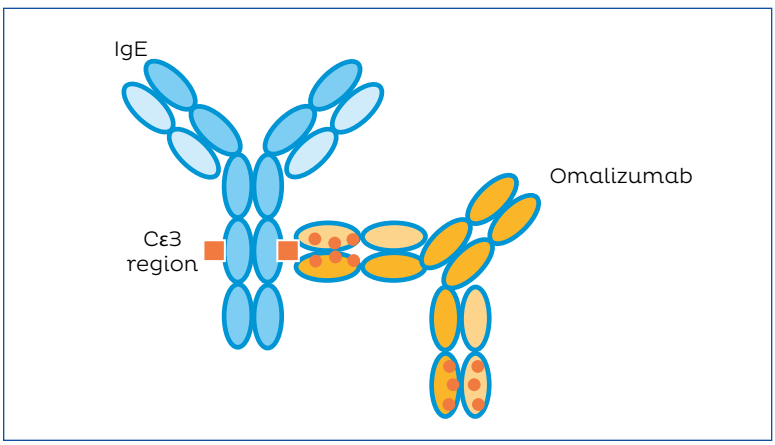
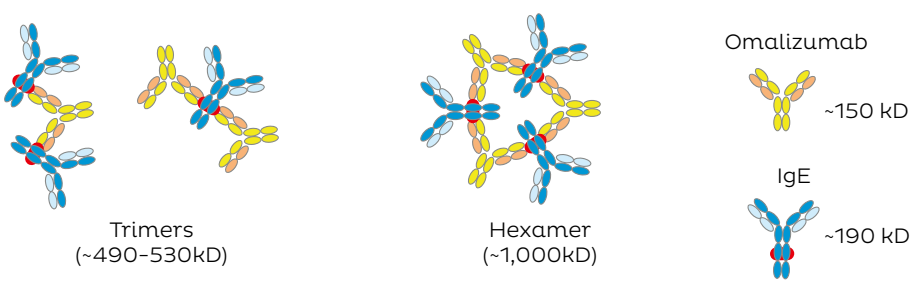


Figure 6: Humanized monoclonal anti-IgE antibody: Omalizumab

OMALIZUMAB: CLINICAL PHARMACOLOGY

- Omalizumab binds to IgE and prevents binding of IgE to FcεRI, thereby reducing the amount of free IgE that is available to trigger the allergic cascade. Treatment of atopic subjects with omalizumab resulted in a marked down-regulation of FcεRI receptors. Furthermore, the in vitro histamine release from basophils isolated from Omalizumab treated subjects was reduced by approximately 90% following stimulation with an allergen compared to pre-treatment values.
- Following subcutaneous (s.c.) administration, Omalizumab is slowly absorbed (7–8 days to peak serum concentration) and slowly removed (terminal half-life averaged approximately 3 weeks) in adult and adolescent patients with asthma, with little accumulation in peripheral tissues.
- No clinically important changes in Omalizumab pharmacokinetics were observed as a result of differences in age, sex, or race.



- Heterotrimers at Omalizumab: IgE molar ratios > 1 (Omalizumab excess) or <1 (IgE excess)
- Hexamers at Omalizumab:IgE molar ratios of ~ 1:1
- Complexes are small and present no safety risk

Figure 7: Omalizumab: IgE Complexes

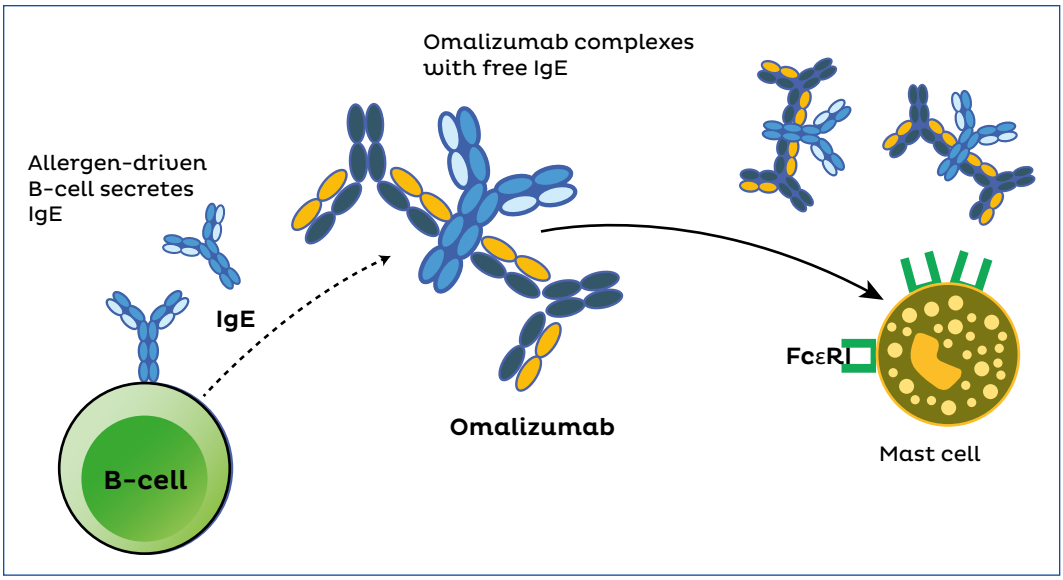


Figure 8: Mode of action of omalizumab

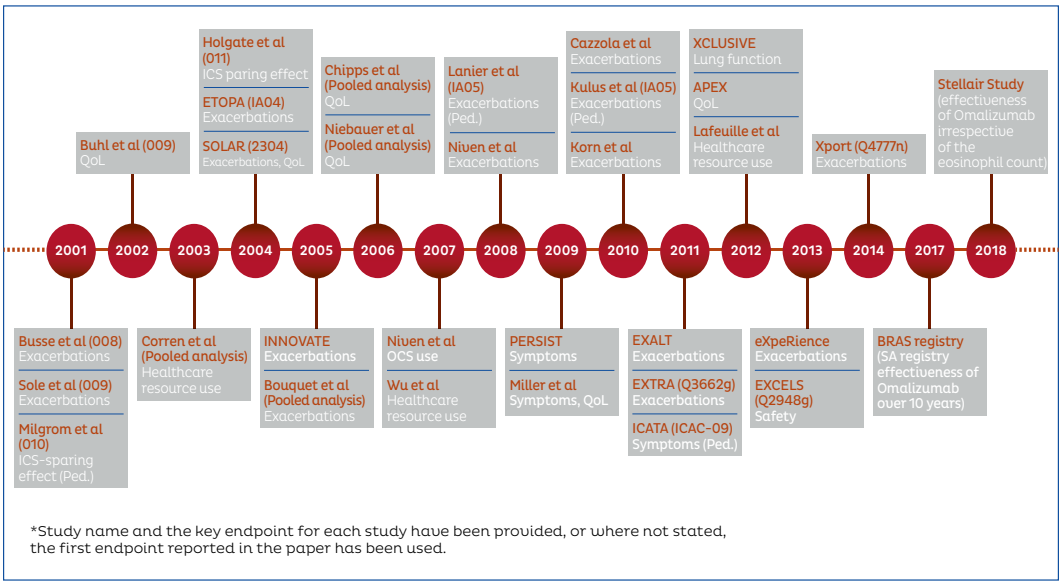
- In clinical studies in asthma patients, free IgE levels in serum were reduced in a dose-dependent manner within one hour following the first dose and maintained between doses. Mean decrease in free IgE in serum was greater than 96% using recommended doses. Total IgE levels (i.e., bound and unbound) in serum increased after the first dose due to the formation of omalizumab: IgE complexes which have a slower elimination rate compared with free IgE.
- Omalizumab reduced serum free-IgE concentrations in a dose- and baseline IgE-dependent manner within 1 hour of dosing. Omalizumab:IgE complexes cannot bind IgE receptors, so lack the biological activity of IgE.
- In Phase III studies, Omalizumab produced average maximal decreases from baseline in serum free-IgE of >96%. Paradoxically, total IgE is increased as this includes both bound and unbound IgE. The decreases in free IgE and increases in total IgE caused by Omalizumab were reversible upon treatment discontinuation, with no rebound in IgE levels.
- To ensure that the vast majority of patients achieve a free IgE level <50 ng/mL (20.8 IU/mL), the target free IgE level with Omalizumab therapy is 25 ng/mL (10.4 IU/mL). This can be achieved using an individualized dosing approach.

SUMMARY:

- Omalizumab treatment results in reduced levels of free IgE and downregulation of FceRI on basophils and mast cells, and other inflammatory cells. This dual effect on mast cells results in decreased mast-cell activation and sensitivity, leading to a reduction in eosinophil influx and activation.
- In addition to reducing the number of IgE and FceRI cells in the bronchial mucosa of patients with allergic asthma, Omalizumab had effects downstream in the allergic cascade including a marked reduction in inflammatory cell influx in the airways, most notably eosinophils.
- The anti-inflammatory effects of Omalizumab provide proof of concept of the importance of IgE in allergic respiratory disease.

CHAPTER 4
CLINICAL EFFICACY OF OMALIZUMAB

The clinical efficacy of add-on Omalizumab therapy has been extensively evaluated in patients with severe persistent allergic asthma.



*Study name and the key endpoint for each study have been provided, or where not stated, the first endpoint reported in the paper has been used.

Figure 9: Wealth of evidence generated on Omalizumab supports its use as an add-on therapy for inadequately controlled severe allergic asthma

KEY OUTCOMES FROM THESE STUDIES ARE HIGHLIGHTED HERE:

1. Immunomodulation

Omalizumab significantly reduces IL 13 and histamine release from basophils ($p<0.01$ for both) vs. placebo after 16 weeks' treatment, and significantly reduces blood eosinophil count ($p<0.01$) vs. placebo after 16 and 50 weeks[23]

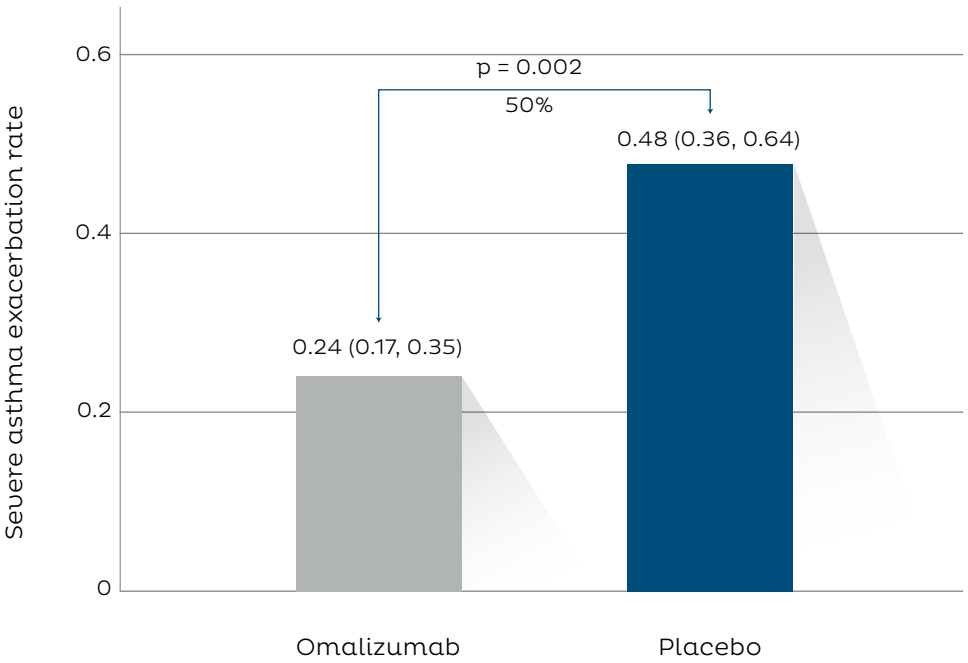
Omalizumab significantly reduces submucosal cellular IL 4 expression vs. baseline and placebo[24]

Omalizumab significantly reduces sputum eosinophil count and tissue esinophils[24]

Omalizumab reduces expression of IL5[24]

2. Significant reduction in exacerbations in moderate-severe asthma

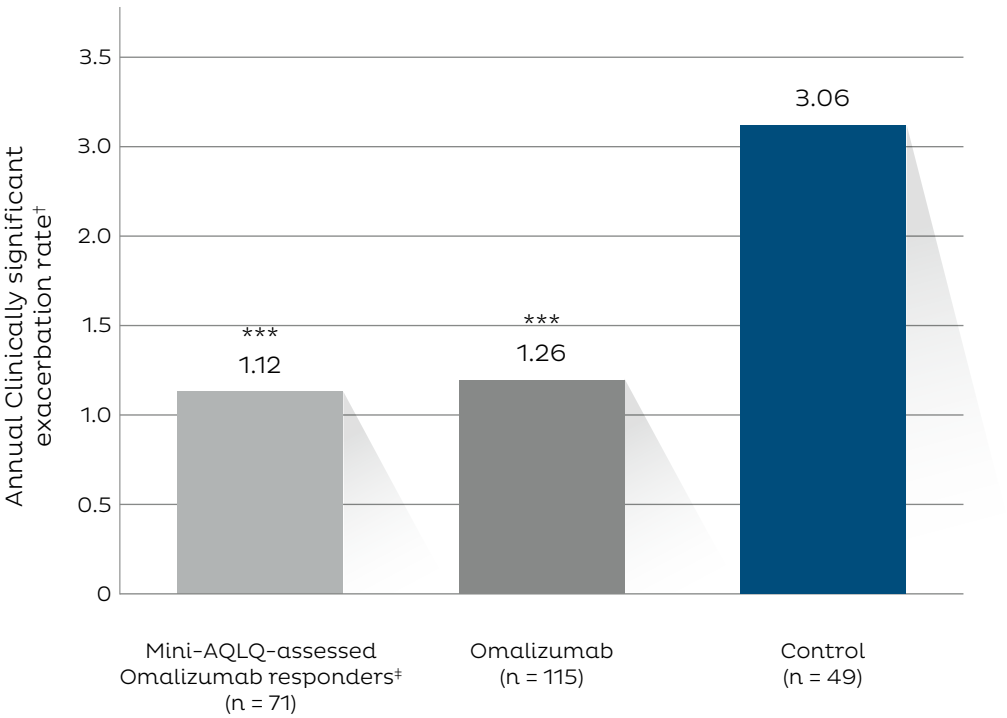
a) INNOVATE was a multinational, multicenter, randomized, double-blind, parallel-group, 28-week study conducted to assess the efficacy, safety and tolerability of OMALIZUMAB in 419 patients (12–75 years) with severe persistent allergic asthma who were inadequately controlled, despite GINA Step 4 treatment, in which OMALIZUMAB or placebo was added to ICS + LABA (primary endpoint).[25]



† Severe exacerbation were defined as PEF/FEV_1 to <60% of personal best, requiring systemic corticosteroids.

Severe exacerbation rate decreased by 50% in the omalizumab treated group vs. placebo

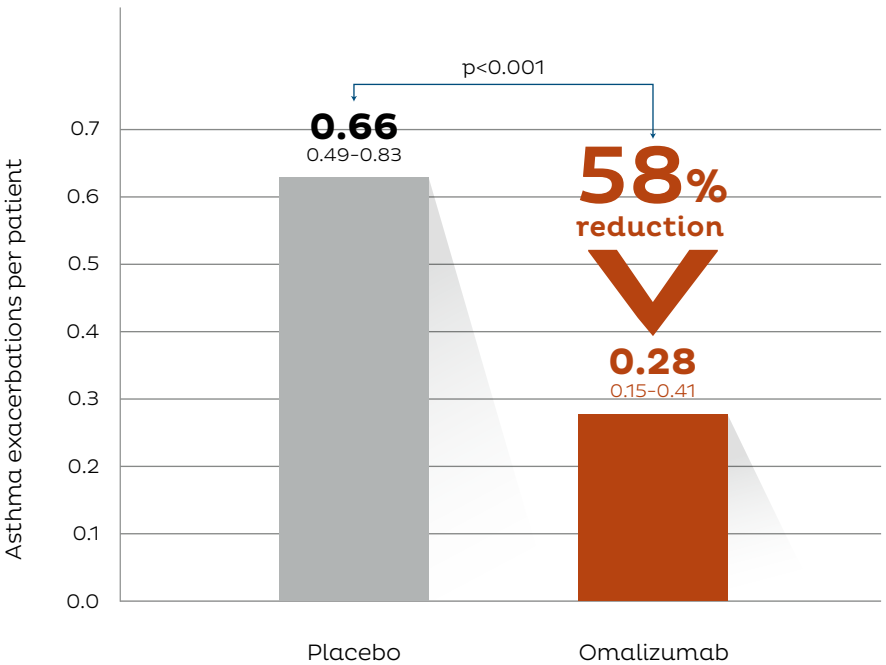
b) This was a subgroup analysis of a randomized, open-label, multicentre, parallel-group trial designed to evaluate the efficacy and tolerability of Omalizumab in patients who were symptomatic despite treatment with ICS. This subgroup analysis in patients with severe allergic asthma despite treatment with ICS + LABA. Efficacy variables assessed in this subgroup analysis included the annual rate of clinically significant asthma exacerbations, defined as asthma worsening requiring treatment with systemic corticosteroids.[26]



‡ Asthma worsening requiring treatment with systemic corticosteroids;
† ≥ 0.5-Point improvement in Mini-AQLQ overall score

Annual asthma exacerbation rate was significantly reduced by 59% in the omalizumab group vs. control

c) This was a multicenter, double-blind trial designed to evaluate the efficacy, safety, and steroid-sparing effect of Omalizumab in 546 people aged 12–76 years with moderate-to-severe persistent allergic asthma who were symptomatic, despite treatment with ICS. An asthma exacerbation was defined as a worsening of asthma that required treatment with systemic corticosteroids or a doubling of the patient's baseline ICS dose. The primary endpoints were the number of exacerbations experienced per patient in the stable-steroid and steroid-reduction phases. Data shown are from the stable-steroid phase.

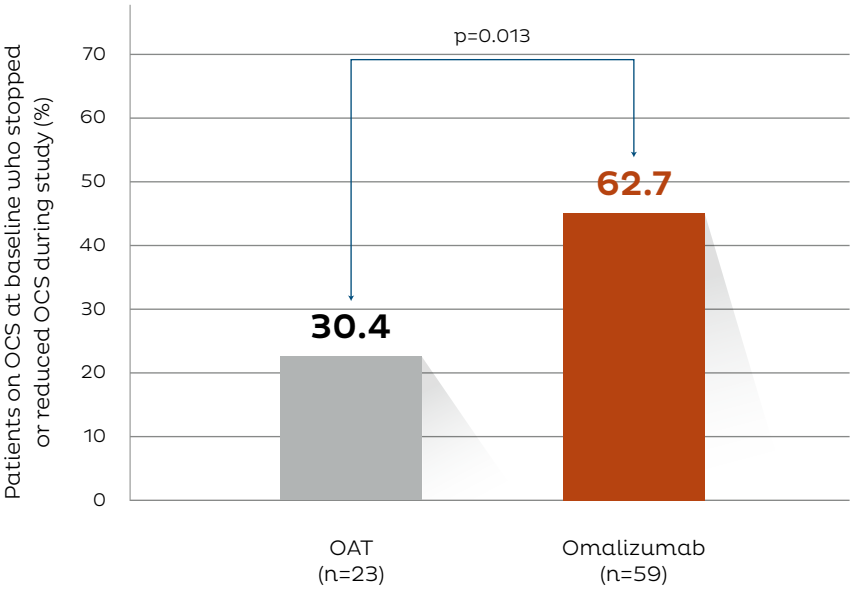


58% fewer exacerbations were observed per patient with Omalizumab + ICS vs. ICS+ Placebo

3. Significant decrease in oral corticosteroid use

a) EXALT: This subgroup analysis of a randomized, open-label, parallel-group study evaluated the OCS-sparing effect of omalizumab added to optimized asthma therapy (OAT), compared with OAT alone. Patients (n=82, aged 12–75 years) with persistent severe allergic asthma, uncontrolled despite GINA 2004 Step 4 treatment, received omalizumab or standard therapy for 32 weeks. The primary endpoint was the change from baseline in OCS use by Week 32 in patients requiring maintenance OCS at baseline, which was assessed in terms of percentage OCS dose change and numbers of patients with reduced/stopped or maintained/increased OCS.[28]

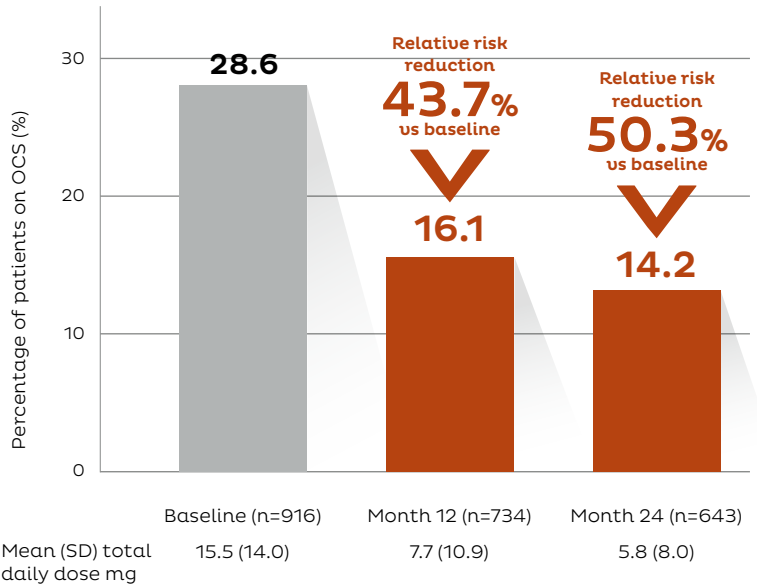
EXALT sub-group analysis; Omalizumab reduced/stopped OCS use in 63% of patients



63% patients in Omalizumab group were able to reduce/stop OCS use, compared to 30% in the Optimized Asthma Therapy (OAT) group, at week 32

b) eXpeRience Study:
eXpeRience was a 2-year, international, single-arm, open-label, observational registry that evaluated real-world effectiveness, safety and use of OMALIZUMAB therapy in 943 patients with uncontrolled persistent allergic asthma. Effectiveness variables (physician's Global Evaluation of Treatment Effectiveness and change from baseline in exacerbation rate, symptoms, rescue medication use, and oral corticosteroid use) were evaluated at pre-specified time-points. Safety data were also recorded. Clinically significant exacerbations were defined as any worsening of asthma considered by the treating physician to require systemic corticosteroids, and were regarded as severe if there was a reduction in peak expiratory flow to <60% of the patient's predicted or personal best.[29]

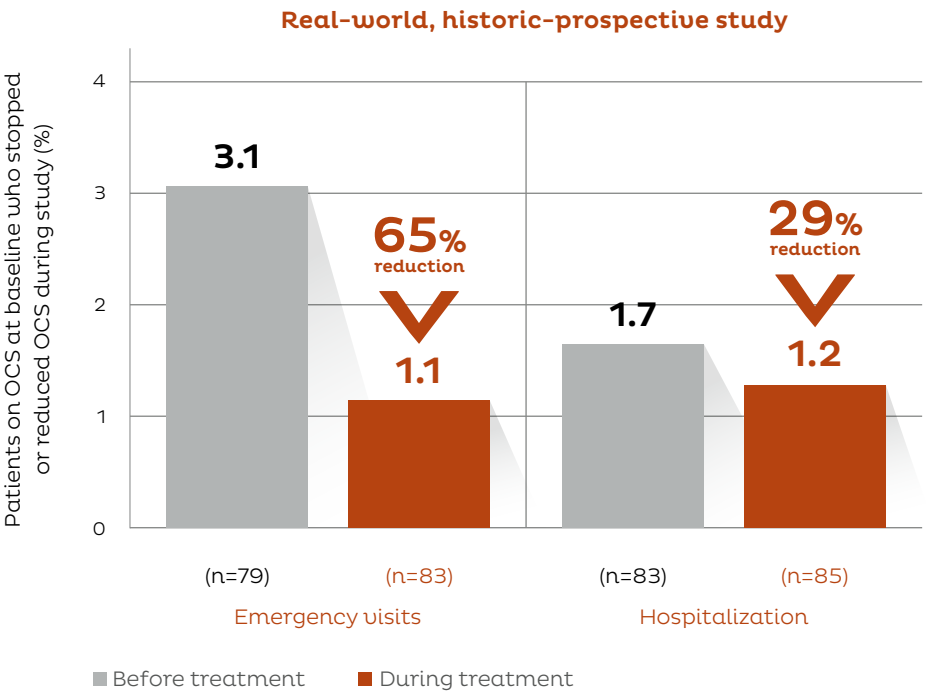
eXpeRience: Omalizumab led to a 50% relative reduction in the percentage or patients using OCS



50% of patients stopped using OCS at 2 years from baseline (28.6% of patients were on OCS at baseline vs. 14.2% at month 24)

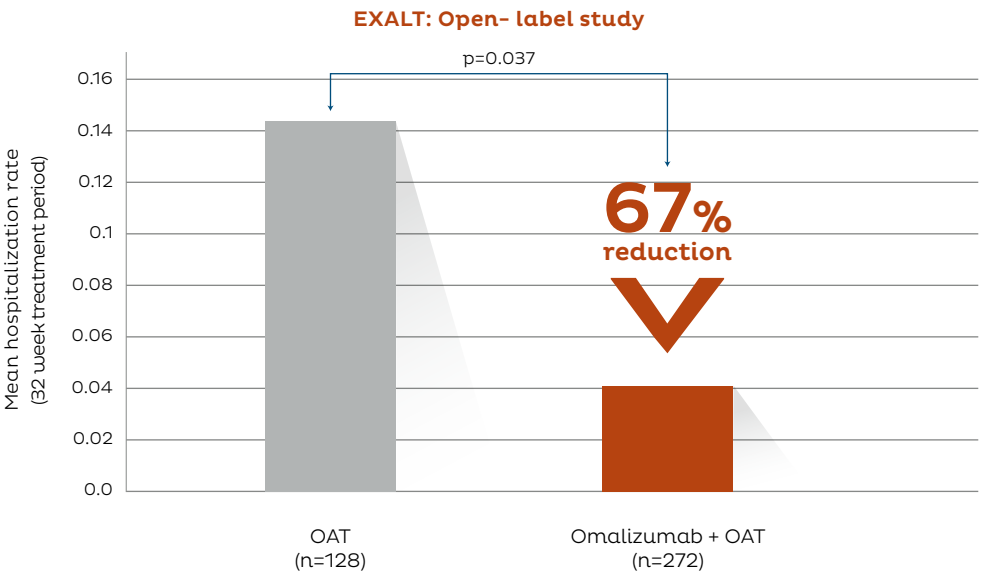
4. Significant reduction in emergency visits and hospitalizations due to asthma

a) This was an historic-prospective, observational, French study assessing the effectiveness of Omalizumab in people with uncontrolled severe allergic asthma (n=146).[30]



Omalizumab showed 65% reduction in asthma- related emergency visits after more than 5 months of treatment

b) EXALT was a 32-week, randomized, open-label, parallel-group study evaluating the persistency of treatment responder classification in patients with severe allergic asthma aged 12–75 years (n=400) receiving Omalizumab added to optimized asthma therapy.[31]



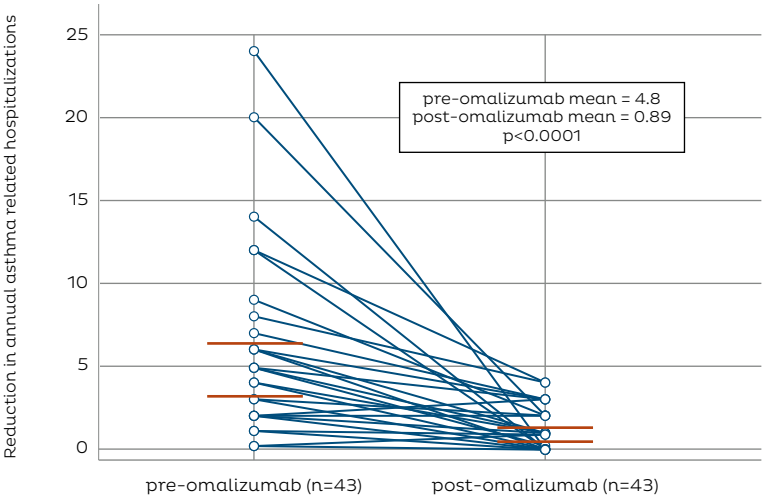
Omalizumab reduces the rate of asthma-related hospitalization by 67% vs. OAT (Optimized Asthma Therapy) over 32 weeks

c) The Birmingham regional severe asthma service (BRAS) - provides experience in the clinical use of omalizumab over 10 years.

Retrospective analysis of 45 patients from severe asthma registry.[36]

Patients treated with Omalizumab 150-600 mg every 2 or 4 weeks for longer than 23 months were included.

BRAS Registry: Reduction in hospitalization

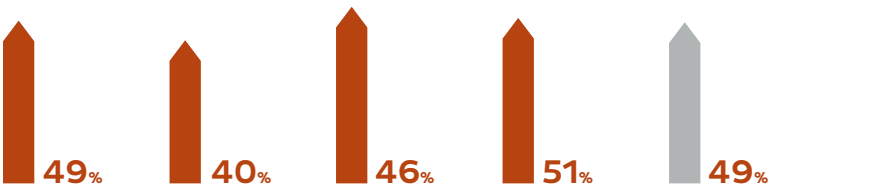


Reduction in annual asthma related hospitalization following omalizumab therapy

80.7% and 48.5% reduction in hospital admissions and emergency attendances, respectively

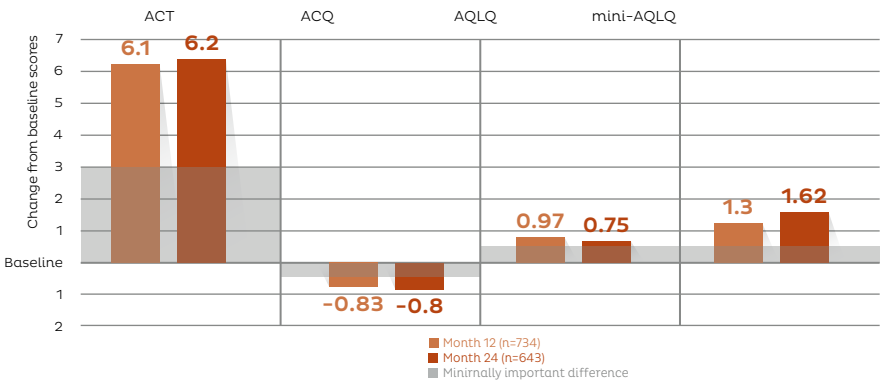
5. Significantly improving Asthma-related QoL

Relative improvement vs. placebo in QoL scores from baseline[25]



Omalizumab improves asthma-related QoL compared to placebo

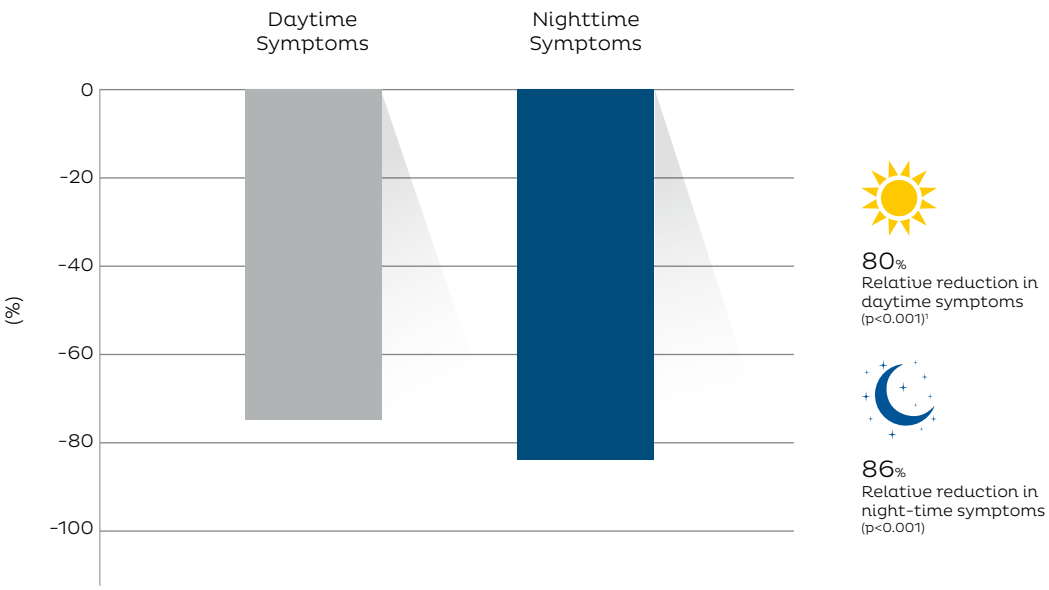
eXpeRience: a real-world observational study in 943 people with uncontrolled persistent allergic asthma[29]



*Pre-treatment is for 12 months prior to the start of ornallzurnab treatment. Annualised data are presented for 'Month 12' (combining week 16, Month 8, and Month 12 time-points) and 'Month 24' (combining week 18, Month 8, and Month 24 time-points). n=number or evaluable patients at baseline. Months 12 and 24, respectively.

6. Significantly improving asthma symptoms

a) German observational study of 280 patients with uncontrolled severe allergic asthma treated with OMALIZUMAB for up to 6 months: prospective, post-marketing, surveillance trial to verify the efficacy and tolerability of Omalizumab in a real-life setting.[32]

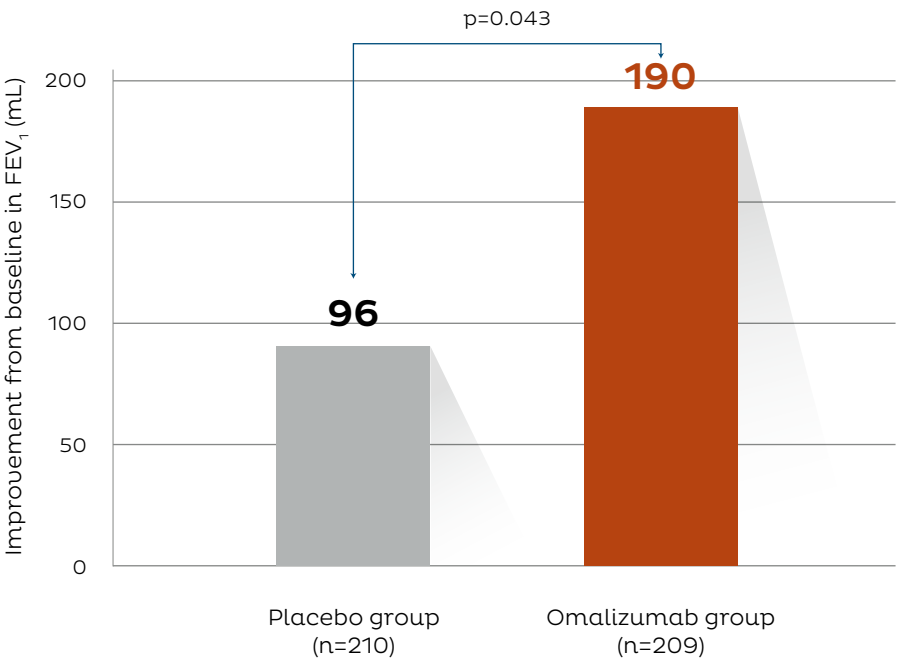


Omalizumab reduces the rate of asthma-related hospitalization by 67% vs. OAT (Optimized Asthma Therapy) over 32 weeks

7. Significant improvement in lung function

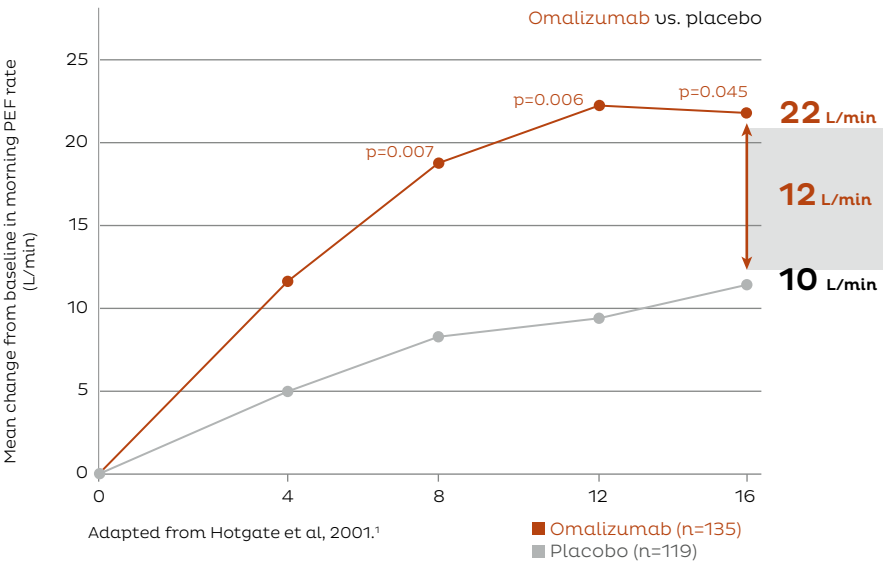
a) INNOVATE was a multinational, multicenter, randomized, double-blind, parallel-group, 28-week study conducted to assess the ecacy, safety and tolerability of Omalizumab in 419 patients (aged 12–75 years) with severe persistent allergic asthma who were inadequately controlled despite GINA Step 4 treatment, in which OMALIZUMAB or placebo was added to ICS + LABA (primary endpoint).[25]

INNOVATE: randomized, double-blind study



FEV_1 (% predicted) was significantly improved with Omalizumab compared with placebo at study completion (p=0.043)

b) This was a meta-analysis of three randomized, double-blind, placebo-controlled studies that enrolled 1,412 patients with moderate or severe allergic asthma, all requiring daily treatment with ICS.[33]

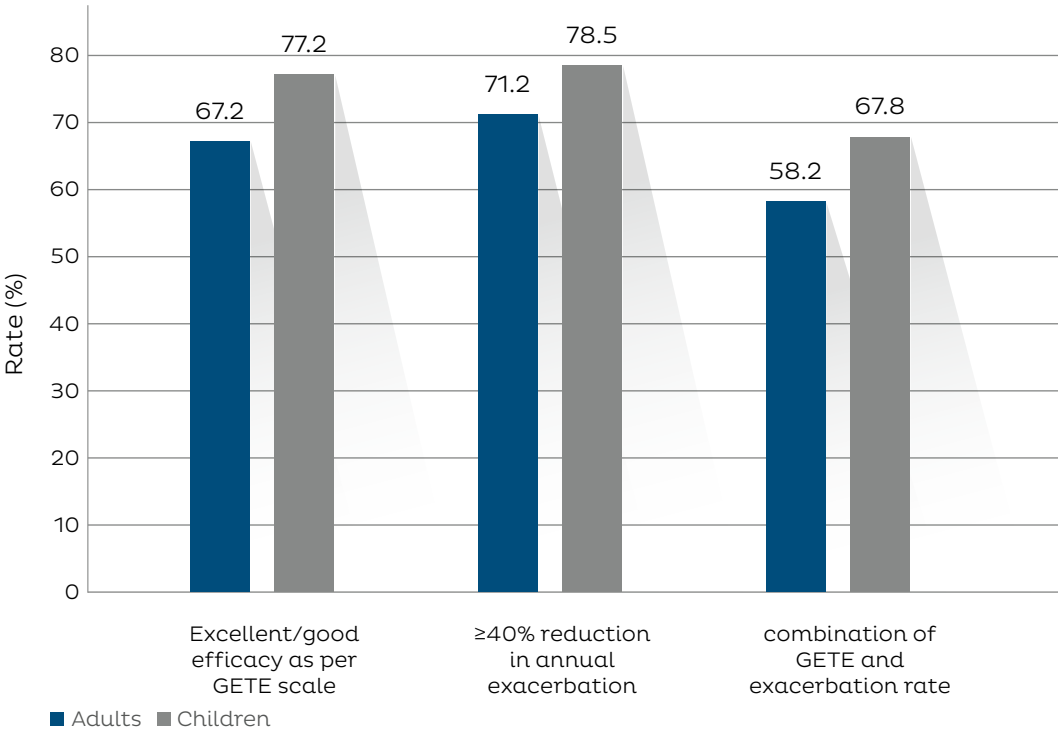


12L/min improvement in morning PEF rate after 16 weeks vs. placebo (p=0.026)

8. Effectiveness of omalizumab in severe allergic asthma (SAA) regardless of eosinophil levels - The STELLAIR study[37]

The STELLAIR study aimed at evaluating whether response to omalizumab is affected by blood eosinophil counts in patients with SAA.

Proportion of patients classified as responders having excellent/good efficacy to omalizumab as determined by Global Evaluation of Treatment Effectiveness scale were 67.2% adults and 77.2% children.



Effect of omalizumab therapy on primary study outcomes in adults and children with severe allergic asthma

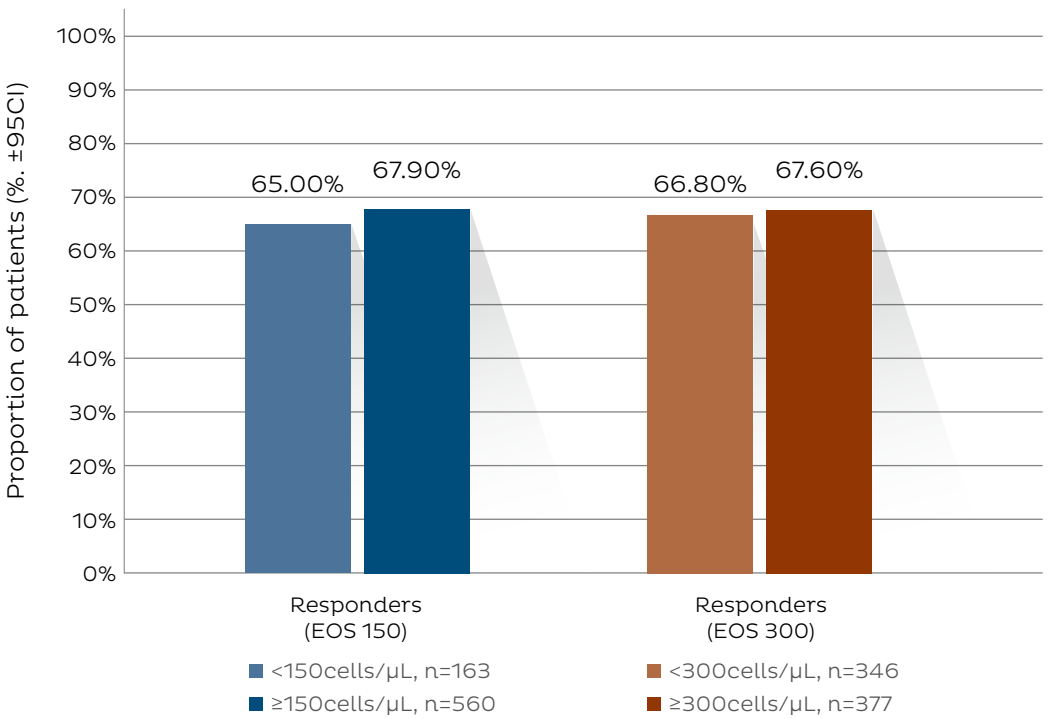
It was found that rates of overall response, ≥40% reduction of exacerbation and combined response to omalizumab treatment were comparable irrespective of the blood eosinophil count.

In addition, the proportion of combined response was reported to be similar for low (<300 cells/μL) as well as high (≥300 cells/μL) eosinophil counts in all adults with SAA

There were significant reductions in asthma exacerbations following treatment with omalizumab in patients with SAA having blood eosinophils <300 or ≥300 cells/μL and IgE <75 or ≥75 IU/μL (Figure 2)

Thus, omalizumab was found to be effective in all adults with SAA irrespective of blood eosinophil counts.

A – RESPONDERS BASED ON PHYSICIAN'S GLOBAL EVALUATION (GETE)



SUMMARY

Taken together, these findings clearly indicate that add-on Omalizumab therapy is effective for patients with severe persistent allergic asthma that is inadequately controlled despite best available therapy.

Omalizumab reduces asthma exacerbation rates, hospitalization rates and corticosteroid usage in patients suffering from severe allergic asthma.

It is also effective in patients with severe allergic asthma regardless of blood eosinophil counts.

CHAPTER 5
CLINICAL SAFETY OF OMALIZUMAB

- The safety and tolerability of Omalizumab in completed Phase I/II/III studies involving >7,500 adult and adolescent patients with asthma, rhinitis or related conditions have been analyzed
- The frequency of adverse events (AEs) was similar between Omalizumab and control groups
- AEs with Omalizumab were generally of mild to moderate severity and of short duration
- Omalizumab is not associated with an increased risk of hypersensitivity reactions or immune complex disease
- Clinical data do not suggest a causal link between Omalizumab and cancer
- An exploratory study found no evidence to suggest an increased risk of geohelminth infection in high-risk patients receiving Omalizumab to treat allergic asthma or Perennial Allergic Rhinitis (PAR)

OMALIZUMAB IS WELL TOLERATED

In controlled studies, 2,111 patients received Omalizumab for 24 weeks and 555 for 52 weeks. Nasopharyngitis, upper respiratory tract infection, headache and sinusitis were the most frequently reported AEs in the Omalizumab and control groups (Table 1).

Table 1 Omalizumab safety summary. Most frequent AEs (≥5% patients); all controlled studies[40]

Adverse event	Omalizumab (%) n=3,678	Control (%) n=2,452
Any adverse event	74.8	75.2
Upper respiratory tract infection	15.7	15.7
Headache	15.5	15.6
Nasopharyngitis	14.4	15.9
Sinusitis	10.1	12.0
Cough	5.9	7.1
Bronchitis	5.2	5.6
Influenza	5.0	6.6

Any differences observed between the groups were small and not indicative of specific organ toxicity. AEs were generally of mild to moderate severity and of short duration. Severe AEs occurred more frequently in the control group than in the Omalizumab group (Omalizumab 10.8%, control 12.6%). (Table 2). Serious AEs occurred infrequently (Omalizumab 4.2%, control 3.8%). Few patients discontinued due to AEs (Omalizumab 2%, control 1%).

Table 2 Omalizumab safety summary. Most frequent AEs (≥0.5% patients); all controlled studies[11]

Adverse event	Omalizumab (%) n=3,678	Control (%) n=2,452
Any severe adverse event	10.8	12.6
Headache	1.5	1.6
Upper respiratory tract infection	0.7	0.6
Sinusitis	0.5	1.0
Influenza	0.3	0.7
Nasopharyngitis	0.2	0.5

ADVERSE EVENTS[34]

Immune system effects

- As Omalizumab is a protein, it might be expected to be associated with hypersensitivity reactions and related immunological effects. However, because Omalizumab is a humanized monoclonal antibody, the potential for hypersensitivity reactions should be minimal. Indeed careful analysis of the clinical safety database has shown that Omalizumab is not associated with an increased risk of hypersensitivity reactions or immune complex disease.
- Skin rash (urticaria) is a common manifestation of allergic reactions. In Phase II and Phase III trials the incidence of urticaria was similar in patients treated with Omalizumab (1.1%) and control patients (1.2%) and the incidence of severe systemic hypersensitivity was 0.1% in both groups. As Omalizumab is an immunoglobulin designed to bind to the patient's IgE, there is a theoretical possibility of immune-complex mediated AEs following administration. There has been no incidence of immune complex disease in clinical trials with Omalizumab.

Malignant neoplasia

- An in-depth clinical and statistical analysis of malignant neoplasia reported in multiple-dose clinical studies of Omalizumab of up to 4 years' duration has been conducted. In addition, a literature review and a comparison of cancer rates with the National Institutes of Health (NIH) Surveillance, Epidemiology, and End Results (SEER) database were undertaken.
- Malignant neoplasms were reported in 25 of 5,015 (0.5%) Omalizumab-treated patients and in five of 2,854 (0.2%) control patients. No cases of malignant neoplasia were considered drug-related by a panel of independent oncologists, blinded to treatment assignment. Malignancy rate per 1,000 patient-years in the Omalizumab group was comparable with control ($p>0.5$).
- The range of relative risk estimates across Omalizumab Phase I–III clinical trials (0.75–5.14) was consistent with estimates for asthmatic populations reported in the literature (0.75–2.1). A meta-analysis of five cohort studies in asthmatic populations 102–106 found no association between asthma and cancer rates (incidence ratio [95% confidence interval (CI)]: 0.95 [0.69, 1.30]), suggesting that asthma is neither a risk factor nor a protective factor for cancer.

Parasitic infection

IgE, the molecular target for Omalizumab, is believed to be involved in host defence mechanisms against parasitic infections, although its precise role remains unclear. An exploratory, multicentre, randomized, double-blind, placebo-controlled trial was conducted to evaluate the effect of Omalizumab treatment on the incidence of intestinal helminth (geohelminth) infection in adult and adolescent patients with allergic asthma and/or PAR and at high risk of helminth infection. The results of this

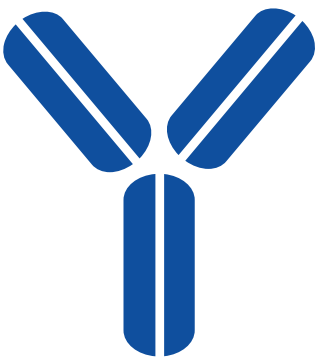
study showed a slight increase in infection rate with Omalizumab, although the course, severity and response to treatment of infection was unaltered. The helminth infection rate in the overall Omalizumab clinical trial programme was less than 1 in 1,000 patients.

Post-marketing experience

- Post-launch safety data from the USA (launched June 2003) are consistent with those obtained in the Omalizumab clinical trial programme; there has been no increase in cancer rates, and hypersensitivity reactions remain rare. One case of thrombocytopenia has been reported (relationship to Omalizumab not confirmed) and there have been 27 reported cases of alopecia (0.1%).
- When compared with those from population studies, reporting rates for alopecia were lower in patients receiving Omalizumab. Currently, more than 45,000 patients have been prescribed Omalizumab in the USA.

SUMMARY

- Omalizumab has demonstrated an excellent safety and tolerability profile in clinical trials involving >7,500 adults and adolescents with asthma, rhinitis or related conditions. The frequency and nature of AEs was similar in the Omalizumab and control treatment groups, with AEs generally mild to moderate in severity and of short duration.
- There is no evidence of an increased risk of hypersensitivity reactions, immune complex disease, cancer, or geohelminth infection.
- Post-launch safety data are consistent with those obtained in clinical trials



CHAPTER 6
EMZUMAB
BIOSIMILAR BIOLOGIC

Emzumab is the biosimilar of the Innovator Omalizumab.

BIOSIMILAR BIOLOGICS

What is a biosimilar drug?

Biosimilar is a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.

A biosimilar drug as the name suggests is similar but not exactly identical to the reference product. Therefore, it undergoes extensive tests, analyzing (i.e., characterizing) the structure and function compared to the reference product. State-of-the-art technology is used to compare characteristics of the products, such as purity, chemical identity, and bioactivity. The results from these comparative tests, along with other information, helps to demonstrate that the biosimilar is highly similar to the reference product.[35]

MOLECULAR COMPLEXITY OF BIOLOGICS

A biological medicine i.e. biologics is a medicine whose active substance is made by or derived from a living organism. These are large, complex molecules comprising over 25,000 atoms and difficult to characterize. Hence it is impossible to develop an exact copy of the biologic.

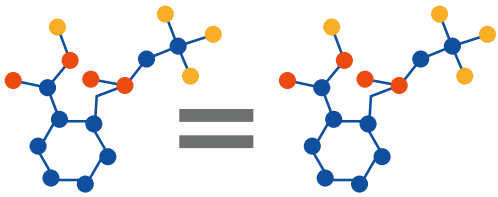
A small molecule drug, such as aspirin, has 21 atoms, biologics can be made of over 25,000 atoms.

Since manufacturing of biologics uses living cells every batch of a biologic may have slight variations, hence strict controls on quality, purity, efficacy and safety.

CAN SMALL-MOLECULE MEDICINES BE REPRODUCED?

Yes, Small molecule drugs are relatively small in structure and can typically be completely defined, very well-characterized, and entirely reproduced.

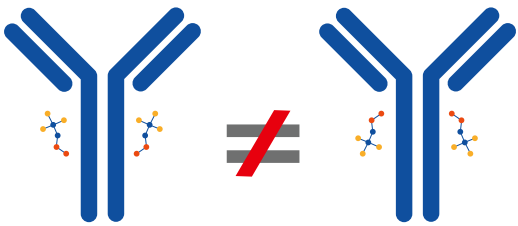
Source: http://fdabiosimilars.e-paga.com/course/framework/index.html



CAN LARGE-MOLECULE MEDICINES (BIOLOGICS) BE REPRODUCED?

No, In contrast to most small molecule drugs that are chemicallysynthesized and more easily characterised, most biological (large-molecule) products are complex molecules that are not easliy characterized. In addition, biological products come with unique challenges that need to be managed throughout the manufacturing process.

Source: http://fdabiosimilars.e-paga.com/course/framework/index.html



BIOSIMILARS ARE ONLY "SIMILAR" TO INNOVATIVE REFERENCE PRODUCTS, NOT IDENTICAL

Minor differences between the reference product and the biosimilar product in clinically inactive components are acceptable.

Because the manufacturing of biologics uses living cells, it is impossible to guarantee that each batch of a biologic will be identical to the last, which means every dose of the innovator biologic also has slight variations (i.e., acceptable within-product variations). Therefore, for both reference products and biosimilars, lot-to-lot differences (i.e., acceptable within-product differences) have to be carefully controlled and monitored.[34]

A biosimilar product has to ensure that there are no clinically meaningful differences from the reference product in terms of safety, purity, and potency (safety and effectiveness). This is generally demonstrated through human pharmacokinetic (exposure) and pharmacodynamic (response) studies, an assessment of clinical immunogenicity, and, if needed, additional clinical studies.

EMZUMAB – PHASE III CLINICAL TRIAL

Emzumab is the biosimilar of the Innovator Omalizumab. Prospective, multi-centre, randomized, double-blind, comparative clinical study was done to evaluate efficacy and safety of biosimilar omalizumab (Emzumab gp) Vs reference omalizumab in patients with moderate to severe persistent asthma.

The primary objective was to determine whether Emzumab is comparable to reference product in efficacy as determined by the incidence of clinically significant asthma exacerbation in patients with moderate to severe persistent asthma. Secondary Objectives were to evaluate other efficacy parameters, pharmacokinetics, pharmacodynamics as well as safety and tolerability of study drug/ reference up to Week 16.

In this study, a total of 112 subjects were randomized in this study (73 subjects in the Emzumab gp and 39 subjects in the reference arm) in order to dose 105 subjects with the study medication i.e. 70 subjects in the study arm and 35 subjects in the reference arm. Eligible subjects were randomized to receive Emzumab/ reference product as per randomization schedule. Omalizumab was administered at a dose of 150 mg to 375 mg subcutaneously every two or four weeks as recommended in prescribing information. Doses (mg) and dosing frequency were determined based on baseline serum total IgE level (IU/mL) measured before the start of treatment and body weight (kg).

All responders at Week 16 received study drug in open-label phase of the study as per their dosing schedule till week 24.

Demographic Details

Parameter	Statistics	Emzumab (N=69)	Innovator Omalizumab (N=35)	Overall (N=104)
Gender				
Male	n (%)	30 (43.5%)	7 (20.0%)	37 (35.6%)
Female	n (%)	39 (56.5%)	28 (80.0%)	67 (64.4%)
Age (years)	N	69	35	104
	Mean	38.96	42.57	40.17
	Std Dev	12.02	13.18	12.48
	Median	37	43	38
	Range	(19.0 , 61.0)	(19.0 , 63.0)	(19.0 , 63.0)
	p-value (between arms)	0.1638		
Height (cm)	N	69	35	104
	Mean	157.44	154.54	156.47
	Std Dev	9.50	8.29	9.18
	Median	156	153	155
	Range	(135.0 , 184.5)	(136.0 , 173.0)	(135.0 , 184.5)
	p-value (between arms)	0.1287		
Weight(kg)	N	69	35	104
	Mean	55.41	58.13	56.32
	Std Dev	12.66	10.69	12.05
	Median	55	58	56
	Range	(37.3 , 113.0)	(37.0 , 84.0)	(37.0 , 113.0)
	p-value (between arms)	0.2788		
BMI(kg/m2)	N	69	35	104
	Mean	22.35	24.44	23.05
	Std Dev	4.67	4.71	4.77
	Median	21.90	24.45	22.64
	Range	(14.5 , 37.8)	(16.0 , 33.5)	(14.5 , 37.8)
	p-value (between arms)	0.0343		

RESULTS

In primary efficacy analysis, in Emzumab gp , 4 (5.80%) asthma exacerbations were reported till week 16 compared to 1 (2.86%) asthma exacerbation in reference arm. In Emzumab gp, 3 (4.35%) subjects had at least one asthma exacerbations compared to 1 (2.86%) subject in reference arm (reference arm case required hospitalization and was reported as a SAE). The difference in incidence of clinically significant asthma exacerbations between the two treatment arms was not statistically significant (p>0.05).

Primary Endpoint - Reduction in Exacerbations

	Biosimilar Omalizumab (n=69), n(%)	Innovator Omalizumab (n=35), n(%)	95% CI of treatment difference	P value
Number of exacerbations	4 (5.8%)	2 (2.86%)	(-0.0489, 0.1061)	0.06
Number of patients with at least one exacerbation	3 (4.35%)	1 (2.86%)	(-0.0585, 0.0871)	0.1835
Number of exacerbations requiring hospitalizations	0 (0.00%)	1 (2.86%)	NE	NE

NE - Not Evaluable
Data on file, Reliance Life Sciences

In the secondary efficacy analysis, in Emzumab gp, the time to first asthma exacerbation was 53 days compared to 62 days in reference arm. In Emzumab and reference arm, the mean change from baseline in FEV1(%) was 7.51 and 5.98 at week 4; 9.48 and 8.93 at week 8; 12.06 and 7.93 at week 12; 12.30 and 8.94 at week 16 respectively. The difference in change from baseline in FEV1(%) was not statistically significant (p>0.05) between the two arms at any visit. The mean change from baseline in FEV1/FVC(%) was 4.20 and 4.06 at week 4; 5.13 and 6.52 at week 8; 6.48 and 4.90 at week 12; 6.77 and 7.10 at week 16 respectively for Emzumab gp and reference arms. The difference in change from baseline in FEV1/FVC(%) was not statistically significant (p>0.05) between the two arms at any visit.

At week 16, 4 (5.80%) subjects in Emzumab gp had 50-75% ICS dose reduction compared to 2 (5.71%) subjects in reference arm and one (1.45%) subject in Emzumab gp had 25-50% ICS dose reduction compared to 3 (8.57%) subjects in reference arm.

Secondary Endpoint - Reduction in ICS dose and GETE Score

Reduction in ICS Dose at week 16

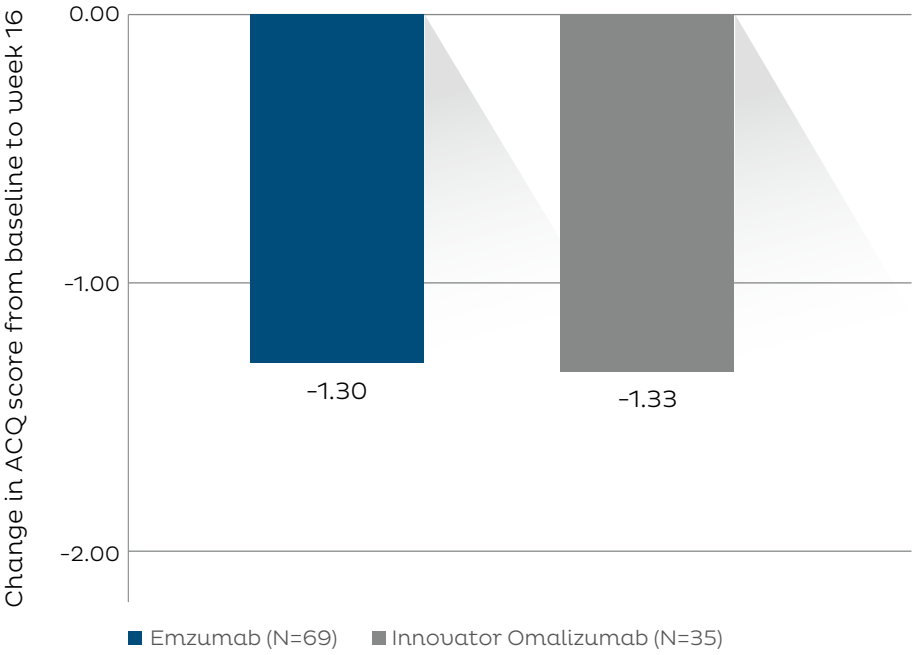
% Reduction in ICS	Biosimilar Omalizumab (n=69)	Innovator Omalizumab (n=35)
50% to < 75%	4 (5.80%)	2 (5.71%)
25% to < 50%	1 (1.45%)	3 (8.57%)
0% to < 25%	58 (84.06%)	24 (68.57%)

Global Evaluation of Treatment Effectiveness (GETE) score at week 16

Score	Biosimilar Omalizumab (n=69)	Innovator Omalizumab (n=35)
Responder (Excellent +Good)	57 (82.61%)	30 (85.71%)
P-value (between arms)	0.1088	

In the Emzumab arm, the proportion of subjects with meaningful improvement in Asthma Quality of Life Questionnaire (AQLQ) (improvement in overall AQLQ score _0.5) was 36.23% and 34.29% at week 4; 49.28% and 57.14% at week 8; 49.28% and 68.57% at week 12; 57.97% and 77.14% at week 16 respectively. In this study, the proportion of patients with minimal important difference (MID) in AQLQ score was comparable between the two treatment arms at all the visits.

ACQ Score



In Emzumab gp and reference arm, the mean change in overall ACQ score was -0.58 and -0.34 at week 4; -0.85and -0.62 at week 8; -1.10 and -0.96 at week 12; -1.30 and -1.33 at week 16 respectively. The difference in mean change in ACQ score between the two treatment arms was not statistically significant (p>0.05) at any visit. Based on Global Evaluation of Treatment Effectiveness (GETE), at week 16, the proportion of responders (sum of excellent and good response) was 82.61% in Emzumab gp, compared to 85.71% in reference arm. The difference between two arms was statistically not significant (p>0.05).

PHARMACODYNAMICS

In the pharmacodynamics assessment during phase III Comparative study of biosimilar omalizumab (Emzumab) / reference omalizumab in patients with moderate to severe persistent asthma, concentrations of free and total IgE were determined in serum samples by a specific enzyme-linked immunosorbent assay (ELISA).

The difference in Cmin, Tmin and maximum percent decrease from baseline level for free IgE was statistically not significant between two arms (p>0.05). Fig

Pharmacodynamic Parameters

		Free IgE			Total IgE		
Treatment Arm	Statistics	C_{min} (ng/ml)	T_{min} (hrs.)	Max% decrease from BL	C_{max} (ng/ml)	T_{max} (hrs.)	Max% increase from BL
Emzumab	Mean	23.43	124.50	74.05	589.65	296.73	112.60
	SD	20.15	96.05	12.53	272.51	104.63	75.23
	CV%	85.99%	77.15%	16.92%	46.22%	35.26%	66.81%
	Range	(4.99, 93.33)	(12, 360)	(41.92, 93.54)	(106.7, 1000.1)	(0, 360)	(0, 291.49)
Innovator Omalizumab	Mean	24.88	97.09	69.515	678.51	278.86	137.408
	SD	19.38	95.78	22.880	298.92	103.08	106.032
	CV%	77.89%	98.65%	32.91%	44.05%	36.97%	77.17%
	Range	(1.39, 93.33)	(12, 360)	(20.75, 97.34)	(80.6, 1000.1)	(120, 360)	(0.00, 368.32)
	P value	0.807	0.344	0.271	0.306	0.568	0.378

For total IgE, the difference in Cmax , Tmax and maximum percent increase from baseline level for total IgE was statistically not significant between two arms (p>0.05). Fig. The similar reduction seen in Free IgE level after study and reference treatment further strengthens the hypothesis that the two products have comparable efficacy profiles. Formation of complexes of IgE with omalizumab shifts IgE clearance from the relatively fast clearance of free IgE to the slower complex clearance. This results in elevation in serum total IgE levels after omalizumab treatment. Elevation of total IgE was seen in the majority of dosed patients. Emzumab and reference gp showed very similar effects with respect to reduction in serum Free IgE and elevation in serum Total IgE reduction in serum Free IgE and elevation in serum Total IgE was maintained during subsequent doses with Emzumab.

PHARMACOKINETICS

Emzumab was evaluated on various parameters viz. Cmax, area under the curve (AUC0-360) for comparability vs the innovator Omalizumab showed comparable pharmacokinetic profile. Fig

Safety

Pharmacokinetic Parameters

Parameter	Treatment Arm	Mean	SD	Median	Minimum	Maximum	CV (%)
Cmax (mcg/ml)	Emzumab (N=24)	60.46	15.77	58.36	39.88	112.93	26.08
	Innovator Omalizumab (N=22)	68.11	17.58	64.24	44.12	120.29	25.81
AUC $_{0-360}$ hrs (mcg.hr/ml)	Emzumab (N=24)	19108.04	4684.8	18540.94	12487.7	35028.24	24.52
	Innovator Omalizumab (N=22)	20716.27	4704.32	20181.73	14468.95	34430.45	22.71

Emzumab showed comparable pharmacokinetic profile based on Cmax, AUC parameters

SAFETY

In this study, 105 randomized subjects received at least one dose of study medication (Innovator Omalizumab) as per protocol. Therefore, 105 subjects (70 in Emzumab arm and 35 in Innovator Omalizumab arm) were included in safety analysis.

Safety evaluation was performed at week 24 based on physical examination, vital signs, laboratory investigations, and adverse events monitoring during the study. Safety results are summarized below:

- In this study, a total of 102 adverse events were reported out of which 63 were reported in the Emzumab arm and 39 were reported in the Innovator Omalizumab arm.
- There were 28 (40.00%) subjects in Emzumab arm and 19 (54.29%) subjects in the Innovator Omalizumab arm with at least one treatment emergent adverse event.
- In this study, 02 serious adverse events (SAEs) were reported. Out of these, one SAE (acute exacerbation of bronchial asthma) was reported in Innovator Omalizumab arm and one SAE (spontaneous abortion) was reported in Emzumab arm. No deaths occurred during this study.
- One subject from Innovator Omalizumab arm and one subject from Emzumab arm was discontinued from the study due to treatment emergent adverse events.
- As per the available literature, the safety observations are consistent with the known safety profile of Omalizumab. Therefore, considering the disease

condition and the safety profile of the study medication, the adverse events reported during this study do not raise any new safety concern.

IMMUNOGENICITY

Immunogenicity samples were collected from all subjects at baseline (pre-dose), at Week 16 and Week 24 or at withdrawal visit. All the samples analyzed in this study were negative for anti-Omalizumab antibodies. There were no apparent immunologically mediated safety or efficacy concerns reported in this study.

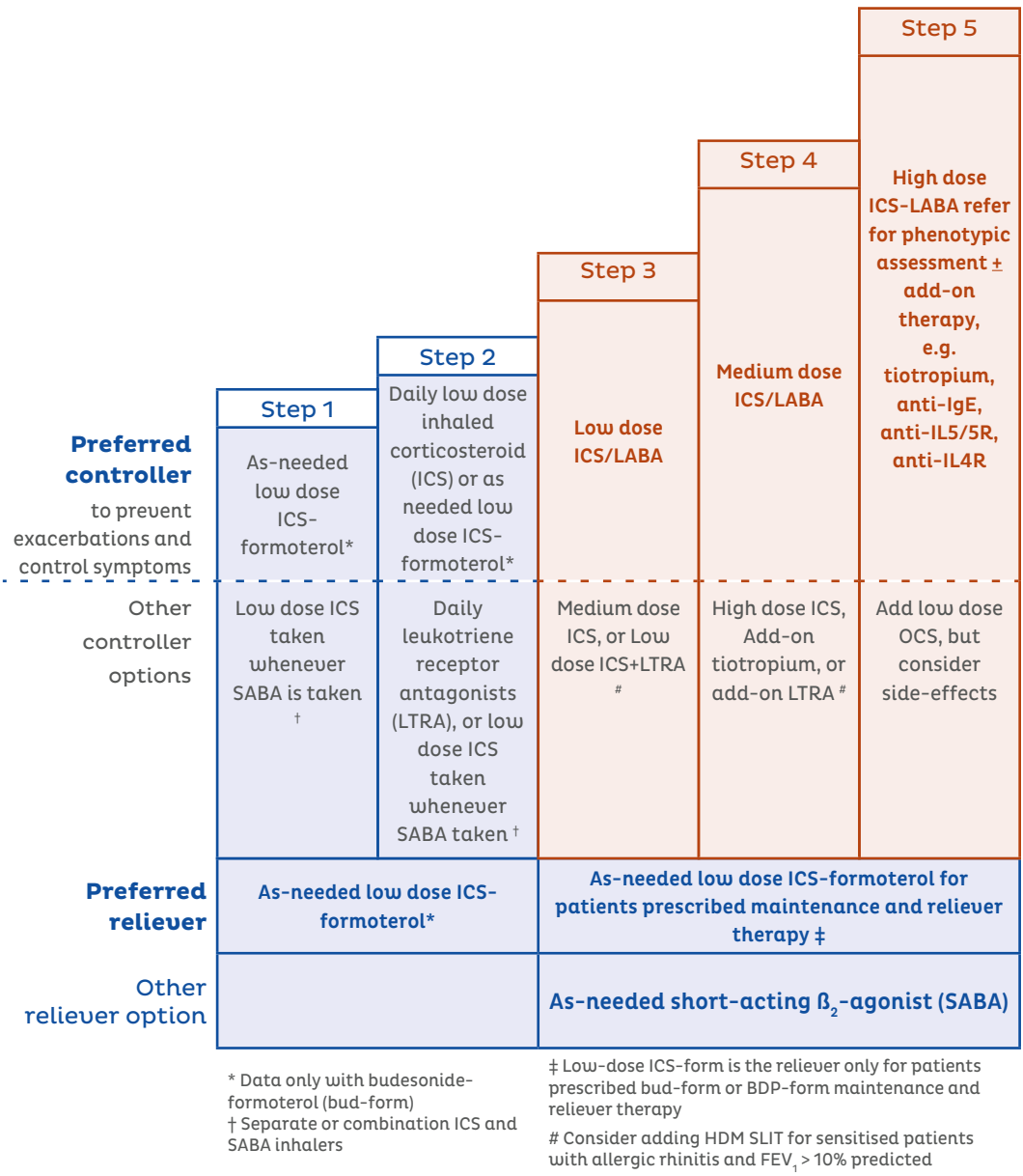
CONCLUSION

- Characterization studies show that the biosimilar Emzumab (omalizumab) is similar to Innovator Omalizumab.
- Emzumab is clinically comparable to Innovator Omalizumab based on the results of various efficacy parameters
- It is also similar in pharmacokinetic and pharmacodynamic parameters
- No new safety concerns were seen and similar immunogenicity and SAES were observed in both the groups

Data on File

CHAPTER 7
EMZUMAB
PLACE IN THERAPY

The new GINA 2020[9] strategy recommends omalizumab as the preferred Step 5 add-on treatment choice, before initiation of long-term OCS use.



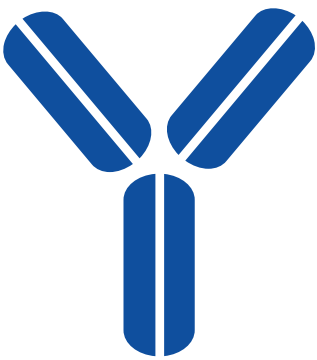
* Data only with budesonide-formoterol (bud-form)
† Separate or combination ICS and SABA inhalers

‡ Low-dose ICS-form is the reliever only for patients prescribed bud-form or BDP-form maintenance and reliever therapy

Consider adding HDM SLIT for sensitised patients with allergic rhinitis and FEV_1 > 10% predicted

CHAPTER 8

HOW TO USE EMZUMAB®



QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of Emzumab (omalizumab) upon reconstitution contains following constituents:

Table 1: Composition

Ingredient / parameter	Product strength - 150 mg
Omalizumab (mg)	202.5 mg
L-Histidine (mg)	1.8 mg
L-Histidine HCl (mg)	2.8 mg
Sucrose (mg)	145.5 mg
Polysorbate-20 (mg)	0.5 mg
Reconstitution volume (mL)	1.4 mL
Injecting volume to be taken from vial for 150 mg dose	1.2 mL
Injecting volume to be taken from vial for 75 mg dose	0.6 mL
pH	5.5-6.5

DOSAGE FORM AND STRENGTH

For Injection: 150 mg Lyophilized powder in a single use vial for reconstitution. The supplied Emzumab (omalizumab) lyophilized powder must be reconstituted with Sterile Water for Injection (SWFI) supplied in combikit.

THERAPEUTIC INDICATION

ASTHMA

Emzumab (omalizumab) is indicated for adult patients 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.

Limitations of Use:

Emzumab (omalizumab) is not indicated for the relief of acute bronchospasm or status asthmaticus.

Emzumab (omalizumab) is not indicated for treatment of other allergic conditions.

CHRONIC IDIOPATHIC URTICARIA (CIU)

Emzumab (omalizumab) is indicated for the treatment of adult patients with chronic idiopathic urticaria who remain symptomatic despite H1 antihistamine treatment.

Limitation of Use:

Emzumab (omalizumab) is not indicated for treatment of other forms of urticaria.

POSOLOGY AND METHOD OF ADMINISTRATION

DOSAGE FOR ASTHMA

Adults: (Subcutaneous)

Administer Emzumab (omalizumab) 75 mg to 375 mg by subcutaneous injection every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL) measured before the start of treatment and by body weight (kg).

Adjust doses for significant changes in body weight during treatment (see Table 2).

Total IgE levels are elevated during treatment and remain elevated for up to one year after the discontinuation of treatment. Therefore, re-testing of IgE levels during Emzumab (omalizumab) treatment cannot be used as a guide for dose determination.

- Interruptions lasting less than one year: Dose based on serum IgE levels obtained at the initial dose determination
- Interruptions lasting one year or more: Re-test total serum IgE levels for dose determination using Table 2, based on the patient's age

Periodically reassess the need for continued therapy based upon the patient's disease severity and level of asthma control. For adult patients, initiate dosing according to Table 2.

Table 2: Subcutaneous doses every 2 or 4 weeks* for adults patients with asthma

Pretreatment serum IgE (IU/mL)	Dosing Frequency	Body weight (kg)			
		30-60 kg	>60-70 kg	>70-90 kg	>90-150 kg
		Dose (mg)			
≥ 30-100	Every 4 Weeks	150	150	150	300
> 100-200		300	300	300	225
> 200-300		300	225	225	300
> 300-400	Every 2 Weeks	225	225	300	
> 400-500		300	300	375	
> 500-600		300	375	Insufficient data to recommend a dose	
> 600-700		375			

*Dosing frequency:

- Subcutaneous doses to be administered every 4 weeks
- Subcutaneous doses to be administered every 2 weeks

DOSAGE FOR CHRONIC IDIOPATHIC URTICARIA (CIU)

Administer Emzumab (omalizumab) 150 or 300 mg by subcutaneous injection every 4 weeks.

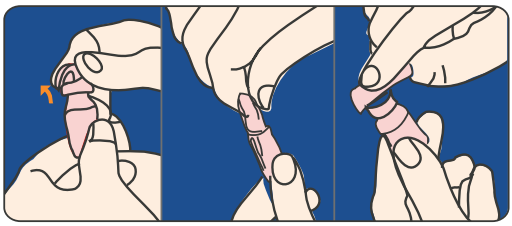
Dosing of Emzumab (omalizumab) in CIU patients is not dependent on serum IgE (free or total) level or body weight.

The appropriate duration of therapy for CIU has not been evaluated.

Periodically reassess the need for continued therapy.

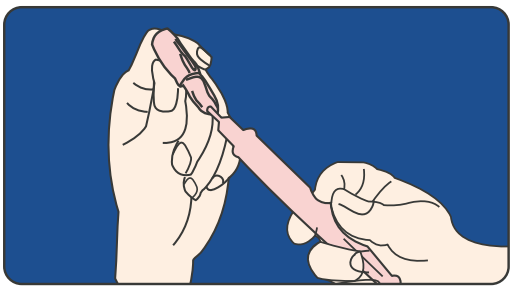
PREPARATION FOR ADMINISTRATION

PREPARING THE VIAL

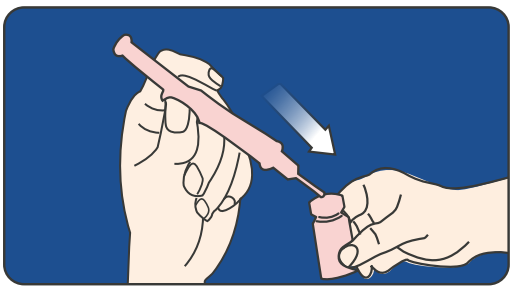


Remove the plastic cap from Emzumab vial. Open the vial of Sterile Water for Injection (SWFI). Using Alcohol swab, wipe the rubber stopper of the Emzumab vial.

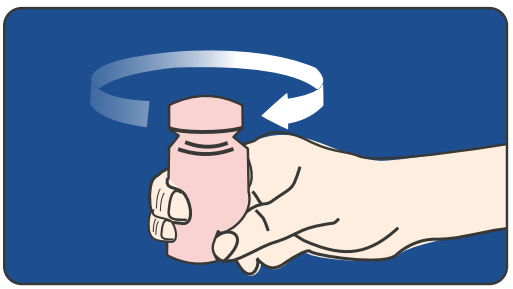
RECONSTITUTION



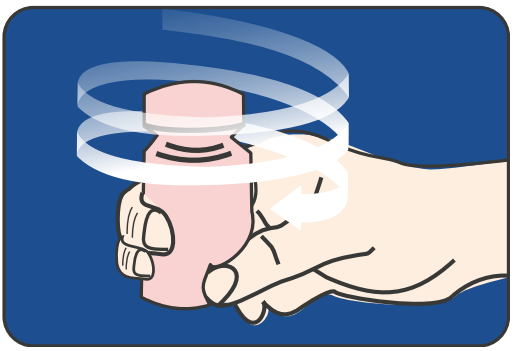
1. Draw 1.4 mL of Sterile Water for injection IP, into a 2 mL syringe equipped with a 1 inch 21G needle.



2. Place the vial upright on a flat surface and using standard aseptic technique, insert the needle and inject the Sterile Water for injection IP, directly onto the product.

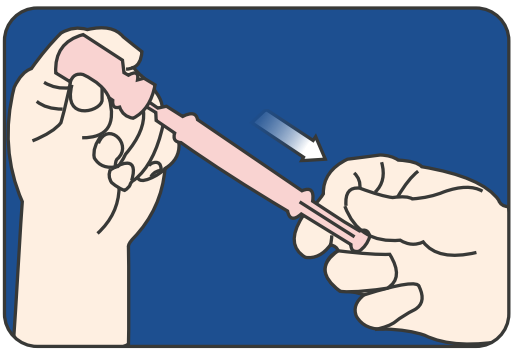


3. Keeping the vial upright, gently swirl the upright vial for approximately 1 minute to evenly wet the powder. Do not shake.

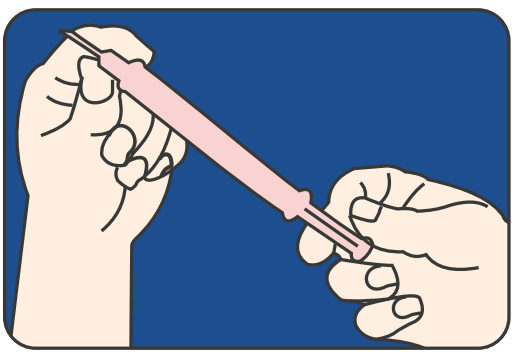


4. Gently swirl the vial for 5 to 10 seconds approximately every 5 minutes in order to dissolve any remaining solids. If it takes longer than 20 minutes to dissolve

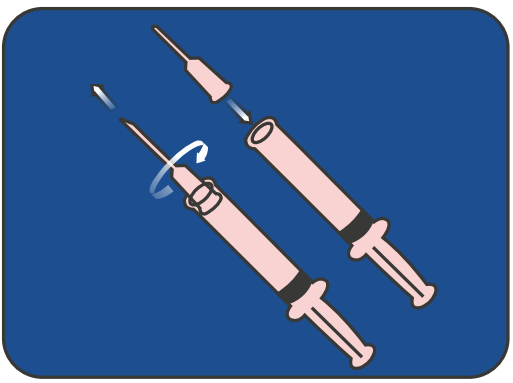
completely, gently swirl the vial for 5 to 10 seconds approximately every 5 minutes until there are no visible gel-like particles in the solution. Do not use if the contents of the vial do not dissolve by 40 minutes. After reconstitution, Emzumab (omalizumab) solution is somewhat viscous and will appear clear or slightly opalescent.



5. Invert the vial for 15 seconds in order to allow the solution to drain toward the stopper. Using a new 2 mL syringe equipped with a 1-inch 21-gauge needle, insert the needle into the inverted vial. Position the needle tip at the very bottom of the solution in the vial stopper when drawing the solution into the syringe.



6. In order to obtain 150 mg and 75 mg dose for injection, 1.2 mL and 0.6 mL volume must be withdrawn respectively from the vial before expelling any air or excess solution from the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove all of the solution from the inverted vial.



7. Replace the 21G needle with a 25G needle for subcutaneous injection.

ADMINISTRATION

- Administer Emzumab (omalizumab) by subcutaneous injection
- The injection may take 5-10 seconds to administer because the solution is slightly viscous
- Use the Emzumab (omalizumab) solution within 4 hours of reconstitution when stored at room temperature

REFERENCES:

1. Lancet Glob Health 2018; 6: e1363–74
2. Am J Respir Crit Care Med 2005; 172(2):149–160
3. Eur Respir J 2014; 43:343–373
4. Eur Respir Jr 2018 52: Suppl. 62, PA3918
5. Annu Rev Pathol Mech Dis 2015; 10:511–45
6. Am J Respir Crit Care Med 2000; 162:2341–2351
7. J Allergy Clin Immunol 2012; 130:332–42
8. Global Initiative for Asthma Management (GINA) guidelines: 2002
9. Eur Respir Rev 2013; 22:227–235
10. J Allergy Clin Immunol 2010; 126:926–38
11. J Allergy Clin Immunol 2007; 119:14–21
12. www.severeasthma.org (as accessed on 5th May 2020)
13. Am J Respir Crit Care Med 2012; 185 (4):356–362
14. J Allergy Clin Immunol 2007; 119:405–13
15. Clin Exp Allergy 2012; 42(5):650–8
16. Global Initiative for Asthma Management (GINA) guidelines: 2020
17. Thorax 2011; 66:910–917
18. Cochrane Database Syst Rev. 2014; 1:CD003559
19. Chest. 2014. doi:10.1378/chest. 14-1698. Online first (16th Oct 2014)
20. Lung India 2015; 32 (Supplement 1):S3–S42
21. Curr Opin Pulm Med 2014; 20:95–102
22. Int Arch Aller Imm 2003; 131:46-56
23. Am J Respir Crit Care Med 2004; 170:583-593
24. Allergy 2005: 60: 309-316
25. Respir Med 2008; 102: 1371-1378
26. Eur Respir J 2001;18(2):254–61.
27. Curr Med Res Opin 2011;27:2233–40
28. Resp Med 2013; 107:1141-51
29. Resp Med 2008;102:71–6
30. Allergy 2011;66:671–8
31. Resp Med 2009;103:1725–31
32. Curr Med Res Opin 2001;17:233–40
33. Emzumab prescribing information
34. ESMO Open 2017;2:e000180. doi:10.1136/esmoopen-2017-000180
35. https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products#biosimilar (as accessed on 5th May 2020)
36. Respiratory Medicine 2017; 124: 36-43
37. Eur Respir J 2018; 51: 702523[https://doi.org/10.1183/13993003.02523-2017].

NOTE

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