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EAACI Biologicals Guidelines – Recommendations for severe asthma

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Accepted Article

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Abstract

Severe asthma imposes a significant burden on patients, families and healthcare systems. Management is difficult, due to disease heterogeneity, comorbidities, complexity in care pathways and differences between national or regional healthcare systems. Better understanding of the mechanisms has enabled a stratified approach to the management of severe asthma, supporting the use of targeted treatments with biologicals. However, there are still many issues that require further clarification. These include selection of a certain biological (as they all target overlapping disease phenotypes), the definition of response, strategies to enhance the responder rate, the duration of treatment and its regimen (in the clinic or home-based) and its cost-effectiveness. The EAACI Guidelines on the use of biologicals in severe asthma follow the GRADE approach in formulating recommendations for each biological and each outcome. In addition, a management algorithm for the use of biologicals in the clinic is proposed, together with future approaches and research priorities.

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Key words: biologicals, cost-effectiveness, GRADE, guidelines, severe asthma

Abbreviations

ACQ = asthma control questionnaire
AQLQ = asthma quality of life questionnaire
ACT = asthma control test
AD = atopic dermatitis
ADA = anti-drug antibodies
AR = allergic rhinitis
ATS = American Thoracic Society
COI = conflict of interest
CRSwNP = chronic rhinosinusitis with nasal polyps
DCs = dendritic cells
EAACI = European Academy of Allergy and Clinical Immunology
ED = emergency department
EMA = European Medicines Agency
ERS = European Respiratory Society
EtD = evidence-to-decision
Fab = antigen-binding fragment
Fc = fragment crystallizable
FcεRI = IgE high affinity receptor
FDA = Food and Drug Administration
FeNO = fractional exhaled nitric oxide
FEV1 = Forced expiratory volume at the end of the first second of forced expiration
GDG = guidelines development group
GETE = global evaluation of treatment effectiveness
GINA = Global Initiative for Asthma
GRADE = Grading of Recommendations Assessment, Development, and Evaluation
HCP = healthcare professional
ICERs = incremental cost-effectiveness ratios
ICS = inhaled corticosteroids
Ig = immunoglobulin
IL = interleukin
IL-4Rα = the α subunit of the IL-4 receptor
IL-5Rα = the α subunit of the IL-5 receptor

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ISAR = International Severe Asthma Registry

IV = intravenous

JAK = Janus kinase

Mab = monoclonal antibody

NICE = National Institute for Health and Care Excellence

NK = natural killer

OCS = oral corticosteroids

PEF = peak expiratory flow

PICO (population, intervention, comparator, and outcomes)

PI3K = phosphoinositide 3 kinase

PROs = patient-reported outcomes

QALY = quality adjusted life-years

QoL = quality of life

ROB = risk of bias

SANI = Severe Asthma Network in Italy

SMART = Standardized Measure to Assess Response to Therapy

SMD = small molecule drug

SOF = summary of findings

SPACE = Severe Paediatric Asthma Collaborative in Europe

SRs = systematic literature reviews

STAT= signal transducer and activator of transcription

T2=type 2

TH = T helper

TNF = tumor necrosis factor

TSLP = Thymic stromal lymphopoietin

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I. Introduction

a. The current landscape of severe asthma

i. Definitions and burden

Asthma is a heterogeneous chronic inflammatory disease of the lower airways that affects nearly 400 million people worldwide (1). It is the most frequent chronic disease in children. The current estimate is that 3 to 10% of adult asthmatics suffer from severe asthma (2). The real prevalence might be lower, as these figures include cases with poor adherence, untreated co-morbidities or misdiagnosis (3,4,5,6,7). Although severe asthma comprises a small proportion of asthma cases, it is associated with increased mortality and hospitalisation, reduced quality of life (QoL), and increased healthcare costs (8,9,10,11,12,13). Extrapolating adult severity classifications to children is difficult for a number of reasons ranging from the clinical phenotypes to lung function parameters and response to treatment. Therefore, the incidence of paediatric severe asthma affecting up to 2.5% of all children with asthma (15) is not directly comparable with the incidence of severe asthma in adults. In children, severe asthma accounts approximately for half of all healthcare resources for paediatric asthma and it is associated with increased risk of mortality, and of development of chronic obstructive pulmonary disease in adulthood (15,16,17,18,19).

The European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines set out a framework for the diagnosis and management of severe asthma in adults and children (20,21). The Global Initiative for Asthma (GINA) has produced a useful guide for the diagnosis and management of “Difficult-to-treat” and Severe Asthma in adolescents and adults (22). Patients with a confirmed diagnosis of asthma who have had modifiable factors addressed, poorly controlled while receiving high dose inhaled corticosteroid (ICS) treatment, or with requirement of a high level of treatment to maintain control are classified as severe asthma (20).

ii. Severe asthma phenotypes and endotypes - practical implications for management

Following recent advances in our understanding of asthma mechanisms and therapeutic responsiveness, the concept of asthma as a single entity has been replaced with a model of a complex biological network with distinct, but interrelating immune - inflammatory pathways continuously modified by multiple external and internal factors (23,24,25,26,27,28). Several visible properties underpin the definition of severe adult asthma phenotypes: clinical, functional, morphological, inflammatory, molecular and microbiome-related (25, 29, 30,31). However, severe asthma phenotypes do not necessarily relate to or give insights into the underlying pathogenetic

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mechanisms; these are best described by disease endotypes. The major immune-inflammatory pathways for severe asthma include type-2 (T2) high, T2 low and mixed endotypes which may share certain genetic and epigenetic, metabolic, neurogenic and remodelling characteristics (24,31,32).

Severe paediatric asthma has been associated in most cases with severe and multiple aeroallergen sensitisation, allergic rhinitis, food allergy, eosinophilic airway inflammation, exposure to environmental tobacco smoke and airway remodelling (33, 34,35). Similar to adults it is quite heterogenous (36,37,38). Unfortunately, less is known about its endotypes and related biomarkers. Mechanisms of adult severe asthma cannot be extrapolated to children. Children with eosinophilic asthma may not have increases in other T2 markers (35). Unlike adults, intraepithelial neutrophils were associated with better lung function (39). The potential roles of the innate epithelial cytokine interleukin (IL)-33 and of lineage negative innate lymphoid cells (ILCs) are also described (40,41).

The advent of biologicals for asthma represents a giant leap forward for severe asthma management. Considering the availability of several specific targeted therapies for T2 asthma, the management approach to severe asthma currently includes a phenotyping step for the identification of allergic and eosinophilic and non-T2 phenotypes (2, 20, 21,42). This stratified approach is based on measurement of biomarkers such as eosinophils in blood or sputum, fractional exhaled nitric oxide (FeNO) and specific immunoglobulin (Ig) E of clinical relevance (42,43,44,45,46). Whether this stratified approach will improve the burden of severe asthma remains to be proven by real-life studies and registry data (43,44,47). While targeted treatment strategies and mathematical models such as multidimensional endotyping are currently being tested, they will ultimately require validated guidelines for optimal implementation (30, 43, 48, 49, 50). In addition, no specific investigation into tailored treatment for young children with severe asthma exists and the efficacy of biologicals is less frequently tested in children. The same holds true for treatment of T2-low severe asthma. Given the relatively high costs of biological therapies, cost-effectiveness analyses are a prerequisite for coverage and reimbursement. Carefully targeting biological therapy to specific populations, such as high-responders, or discounting the acquisition price in order to further improve value are currently advocated (51).

iii. Biologicals

Biologic products (biologicals) include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. They are isolated from a variety of natural sources - human, animal, or microorganism -

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and may be produced by biotechnology methods and other cutting-edge technologies. For the purpose of this guideline we refer to monoclonal antibodies (mAb) as biologicals. In contrast to chemical compounds and small-molecule agonists or antagonists, biologicals bind a specific determinant, for example, a cytokine or receptor. Owing to this selectivity, biologicals are ideal for 'personalized' or 'precision' medicine (52).

iv. Current management of severe asthma

The GINA 2020 asthma guideline (2) recommends a decision tree for the diagnosis and management of severe asthma with distinct tasks for primary and specialised care while reinforcing the value of the patient perspective and collaborative care by primary care physicians, specialists and other healthcare professionals (HCP). At the specialist level, assessment of the severe asthma phenotype during high dose ICS treatment or lowest possible dose of oral corticosteroids (OCS) and of the factors contributing to symptoms, QoL and exacerbations are advocated. T2 inflammation is defined by the presence of blood eosinophils ≥150/µl and/or FeNO ≥20 ppb and/or sputum eosinophils ≥2%, and/or asthma that is clinically allergen-driven and/or that require maintenance OCS. A tentative approach for first line biological targeting the T2 pathway is based on biomarkers and predictors of response, while taking into consideration local payer eligibility criteria, cost, dosing frequency, route (subcutaneous or intravenous) and patient preference. Response to the biological is evaluated after 4 months and if favourable the biological is continued with re-evaluation every 3-6 months. If the patient fails to respond to the initial agent but is still eligible for T2 targeted treatment, GINA 2020 recommends switching to another biological. GINA 2020 acknowledges that at present there are no well-defined criteria for a good response, but recommends considering exacerbation frequency, symptom control, lung function, medication side-effects, treatment intensity (including OCS dose), and patient satisfaction as important factors.

The 2014 ERS/ ATS guidelines on severe asthma in adults and school age children introduced the definition of severe asthma as it is used today, and highlighted the necessity of always confirming the diagnosis of asthma and excluding other conditions that may mimic asthma. This guideline also provided specific recommendations for the use of sputum eosinophil count and FeNO to guide the phenotypic driven approach (20). The 2019 revision of the ERS/ATS guidelines provided some specific recommendations for the use of biologicals targeting the IL-5, IgE and IL-4/IL-13 pathways based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology (21). Recommendations are formulated for all anti IL-5 interventions together, receiving a conditional recommendation for use as add-on treatment in severe eosinophilic asthma. Dupilumab received a conditional recommendation for

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adult patients with severe eosinophilic asthma, and for those with severe corticosteroid-dependent asthma regardless of blood eosinophil levels. A blood eosinophil cut-point of ≥ 150/μl received a conditional recommendation to guide anti-IL-5 initiation in adult patients with severe asthma and specific eosinophil (≥ 260 /μl) and FeNO (≥19.5 ppb) cut-offs are suggested to identify adolescents or adults with the greatest likelihood or response to anti-IgE therapy.

Currently five biologicals are approved for severe asthma (in alphabetical order): benralizumab (53,54); dupilumab, (55,56); mepolizumab (57, 58); omalizumab, (59,60); and reslizumab, (61,62) (tables 1, 2 and 3).

b. Purpose of the EAACI Guidelines for the use of biologicals in severe asthma

Delivering high-quality clinical care is a central priority for allergists, pneumologists, paediatricians and other specialities caring for patients with allergic diseases and asthma. The European Academy of Allergy and Clinical Immunology (EAACI) develops and updates each year resources to help HCP and researchers to design the best interventions, deliver high standard care and to assess their actions and decisions for purposes of quality improvement and/or reporting.

EAACI guidelines include recommendations for the management of patients with particular conditions or diseases. Guidelines are developed using a systematic process, and are based on available evidence and the clinical experience and expertise of all interested stakeholders.

EAACI developed a Position Paper on Biologicals in 2015 (52). Due to the rapid accrual of evidence and new therapies, advancement of guideline development methodologies, and the need to broaden the scope of the 2015 recommendations a new guideline was therefore needed.

The current guidelines address only treatment with biologicals of severe asthma and do not address any topics related to severe asthma correct diagnosis, background controller treatment, achieving asthma control, monitoring adherence or treating its co-morbidities.

The EAACI Guidelines for the use of biologicals in severe asthma are not intended to impose a standard of care. Instead, they provide the framework for rational decisions for the use of biologicals in severe asthma by HCPs, patients, third-party payers, institutional review committees and other stakeholders. Statements regarding the underlying values and preferences as well as qualifying remarks accompanying each recommendation are an integral part of the Guidelines and aim to facilitate more accurate interpretation. They should never be omitted or ignored when quoting Guidelines recommendations.

i. Target audience

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The target audience includes all HCPs involved in the management of severe asthma, patients and caregivers, basic scientists involved in biologicals development, regulatory authorities and policy makers.

ii. Biologicals included - rationale for choosing

The EAACI guidelines provide recommendations for the use of biologicals with current regulatory approval in patients with severe asthma: benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab (in alphabetical order).

Additional comments are provided for the biologicals currently tested and not yet approved and for doses/routes not approved by regulatory authorities.

II. Methods

The EAACI guidelines followed the GRADE methodology (available at www.gradeworkinggroup.org). Training was conducted with all members of the guidelines development group (GDG) to prepare them for their roles, including specific sessions on the GRADE methodology.

a. The Guidelines Development Group

A Core Leadership Team (table S1) supervised the project and was responsible for defining the project scope, drafting the clinical questions to be addressed by the guideline, coordinating the search, and drafting the manuscript together with the Voting Panel (table S1). It was led by three chairs with both content and methodologic expertise. The Core Leadership Team received support from a methodologist team, who advised on the process and provide input on the GRADE summary of findings (SOF) tables and from experts in guideline development.

The methodologist team conducted the systematic literature reviews (SRs) for each of the clinical questions, graded the quality of evidence, developed the SOF tables, and provided the evidence reports. Narrative reviews were conducted by different content specialist subgroups for each topic to be covered to complement the SRs.

The Voting Panel, composed of content experts, decided which clinical questions are to be asked and which outcomes are critical, important and of low importance, and voted for the final recommendations after reviewing the evidence provided by the methodology team and the narrative reviews. It included specialists with expertise and clinical experience in treating severe asthma, biologists and clinical immunology experts, as well as patient representatives.

In accordance with EAACI policy, everyone who was intellectually involved in the project (i.e., considered for guideline authorship) disclosed all potential conflict of interest (COIs) in writing at

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the beginning, middle, and end of the project. The Guideline Oversight Committee (table S1) was responsible for developing and implementing rules related to COIs.

b. Definitions

For the purpose of the three SRs (63,64,65) that informed the recommendations, severe asthma populations were defined as follows:

- Eosinophilic asthma: subjects with any of the following: a sputum eosinophil count of >1% or an asthma-related peripheral blood eosinophil count of ≥150 cells/ µL, or a fractional exhaled nitric oxide (FeNO) of ≥20 ppb (66)
- Allergic asthma: subjects diagnosed with moderate to severe allergic asthma with asthma symptoms due to exposure to a perennial aeroallergen and serum total IgE levels 30-1300 IU/mL not adequately controlled on ICS and/or other background controllers.
- For dupilumab SR the severe T2 asthma population was defined as subjects with confirmed diagnosis of asthma inadequately controlled on ICS and additional controllers

For the recommendations the population was defined as in the clinical trials that informed the regulatory approval.

c. TF questions and prioritisations of key outcomes

Clinically relevant interventions and comparators were developed balancing comprehensiveness with feasibility (table 4). The most challenging decision in framing the question was how broadly the patients and intervention should be defined. The underlying biology of asthma suggested that across the range of patients and interventions it is plausible that the magnitude of effect on the key outcomes is different, thus the GDG defined subpopulations based on age (6-11 years old, 12-18 years old, > 18 years old), co-morbidities (chronic rhinosinusitis with nasal polyps (CRSwNP) for anti IL-5 interventions and dupilumab; atopic dermatitis (AD) for dupilumab; chronic urticaria (CU), allergic rhinitis (AR) and food allergy for omalizumab, biomarkers (blood eosinophils, atopy, specific and total IgE, FeNO), dose, etc. The outcomes were evaluated per product and subgroup.

As required by the GRADE approach asthma-related outcomes were prioritised in a first step by the GDG using a 1 to 9 scale (7 to 9 critical; 4 to 6 important; 1 to 3 of limited importance). The critical outcomes were: severe asthma exacerbations, asthma control measured by the asthma control questionnaire (ACQ) and asthma control test (ACT), QoL measured by asthma quality of life questionnaire (AQLQ) and safety. The important outcomes were: lung function measured by the forced expiratory volume at first second (FEV_1), decrease in ICS and OCS dose, and in

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rescue medication use. FeNO, sputum and blood eosinophils were scored as low importance (table 5). After reviewing the evidence, the prioritisation of the outcomes was reassessed to ensure that important outcomes that were not initially considered are included and to reconsider the relative importance of outcomes in light of the available evidence. All asthma-related relevant outcomes were addresses simultaneously. As per GRADE methodology when surrogate outcomes were used (FeNO, FEV_1) the quality of the evidence was down-graded.

The GDG framed a separate cost-effectiveness question to assess the economic impact of the biologicals versus standard of care. The outcomes of interest were costs and resources use, the incremental cost-effectiveness ratios (ICERs) per both quality adjusted life-years (QALY), and asthma-related outcomes.

The GDG also defined and addressed clinical questions not covered by the systematic reviews (table 6).

d. The minimal important difference

To evaluate the imprecision for each outcome the minimal important difference (MID) thresholds were considered: St George's Respiratory Questionnaire (SGRQ) score change of 4 units, Asthma Control Questionnaire (ACQ-5, ACQ-6, and ACQ-7) score change of 0.5 units, Asthma Quality of Life Questionnaire (AQLQ) score change of 0.5 units (with disclaimer as calculated pre/post treatment), FEV_1 change in litres 0.20, OCS reduction by 50% , rescue medication reduction by 0.81 puff/day and a reduction of at least 20% in FeNO for values over 50 ppb or more than 10 ppb for values lower than 50 ppb (67,68, 69,70).

e. The GRADE approach (search, appraisal of the evidence)

Key principles and provisions, key terms, descriptions, drug categories, PICO (population, intervention, comparator, and outcomes) questions, search methodology and evidence reporting used in the guideline development process were predefined.

Separate systematic reviews on eosinophilic asthma (benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab), allergic asthma (benralizumab, dupilumab, omalizumab) and severe T2 asthma (dupilumab) were conducted to inform the recommendations (63,64,65). A GRADE SOF table was provided for each PICO question. The quality of evidence was evaluated based on GRADE quality assessment criteria by two independent reviewers and discordance resolved by consensus. Quality assessment includes the risk of bias (ROB) in included trials, the likelihood of publication bias, inconsistency between trial results, indirectness of the evidence (e.g., differences between populations, interventions, or outcomes of interest in the group to whom the recommendation applies versus those who were included in the studies referenced), and

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imprecision (wide confidence intervals, usually due to a small number of patients or events, or those situations where clinical decision-making would differ at the extremes of the confidence interval) (71,72). The quality of evidence for each outcome was rated as high, moderate, low, or very low. In the absence of any data, the level of evidence was rated as very low, based on clinical experience only. Search results were pooled in an evidence report as SOF tables and accompanied by a qualitative summary of the evidence for each PICO question. The Content Panel reviewed the drafted evidence report to address evidence gaps prior to presentation to the Voting Panel.

f. Additional evidence

In support of formulated recommendations, the GDG performed narrative reviews collecting evidence on phase IV, observational and real-world trials and on clinical questions not addressed by the SRs (table S2).

g. *Consensus building and formulating recommendations*

After reviewing the evidence report and the additional evidence, the Voting Panel decided in a face-to-face meeting followed by subsequent emails regarding the final recommendations. For each PICO question, the Voting Panel heard an oral summary of the evidence and provided votes on the direction and strength of the related recommendation. A 70% consensus threshold was reached for all recommendation presented below. The recommendations follow the data included in the evidence-to-decision (EtD) tables and take into consideration the balance of desirable and undesirable consequences, quality of evidence, patients' values and preferences, feasibility, and acceptability of various interventions, use of resources paid for by third parties, equity considerations, impacts on those who care for patients, and public health impact (71,72). A strong recommendation was made in favour of an intervention when the GDG was certain that the desirable consequences outweighed the undesirable consequences. A conditional recommendation was provided if there were reasons for uncertainty on the benefit-risk profile, especially for low or very low quality of evidence. The underlying values and preferences played a key role in formulating recommendations. As the key target audience of the EAACI Guidelines are HCPs and the patients they treat, the perspective chosen when formulating recommendation was mainly that of the HCPs and of the patient, although the health systems perspective was also evaluated (73). Recommendation are provided per product, per subgroups and per outcomes. The recommendations formulated in these guidelines should be used following the GRADE interpretation (table 7). These recommendations should be reconsidered when new evidence becomes available and an update of these guidelines is planned for 2024.

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Where no evidence was available the GDG formulated expert-based recommendations.
The Guidelines were available on the EAACI website for two weeks (20 April- 4 May) for public comment and were external peer-reviewed. All comments received were carefully revised by the GDG and where applicable incorporated.

h. Final review and approval of the guideline by EAACI

In addition to journal and external peer review, the EAACI Scientific Committee and Executive Committee reviewed the manuscript. These EAACI over-sight groups did not mandate that certain recommendations be made within the guideline, but rather serve as peer reviewers.

III. Key recommendations (biologicals are mentioned in alphabetical order)

III.A. Benralizumab – severe eosinophilic asthma – adults and paediatric population 12-17 years old

IL-5 is one of the major cytokines responsible for the growth, differentiation, recruitment, activation and survival of eosinophils. Benralizumab is a humanised Mab that binds to the α subunit of the IL-5 receptor (IL-5Rα) via its antigen-binding fragment (Fab) domain, blocking the binding of IL-5 to its receptor and resulting in inhibition of eosinophil differentiation and maturation in bone marrow. In addition, this antibody is able to bind through its afucosylated fragment crystallizable (Fc) domain of the IgG receptor FcyRIIIa on natural killer (NK) cells, macrophages, and neutrophils, thus strongly inducing antibody-dependent, cell-mediated cytotoxicity in both circulating and tissue-resident eosinophils (74). This double function of benralizumab rapidly induces and maintains depletion of eosinophils that is much greater than that induced by other monoclonal antibodies targeting the IL-5 pathway (75,76). This effect translates clinically into a rapid and significant improvement of patient reported outcomes (PROs) and of lung function (peak expiratory flow (PEF), together with a significant decrease in asthma exacerbations and OCS use (77,78,79, 80, 81).
The summary of the supportive evidence is presented in tables S3 and S4. Recommendations are based on the evidence-to-decision tables S5,S6,S7.
Recommendations are formulated separately for the adult population (Box 1) and the 12-17 years old population (Box 2)

Box 1: Recommendations for benralizumab as add-on treatment in adults with uncontrolled severe eosinophilic asthma

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1. Benralizumab is recommended in adults with uncontrolled severe eosinophilic asthma* in spite of optimal controller treatment to:	Decrease severe asthma exacerbations	Strong recommendation
	Decrease or withdraw oral corticosteroids for blood eosinophils > 150/ μL	Strong recommendation
	Improve quality of life	Conditional recommendation
	Improve asthma control	Conditional recommendation
	Improve lung function	Conditional recommendation**
2. Benralizumab demonstrated a good safety profile however patients should be regularly screened for parasitic infections in endemic areas		Conditional recommendation

* population: severe asthma uncontrolled by high-dosage ICS +LABA with baseline blood eosinophil cell counts > 300 cells/μL or >150 cells/μL for OCS-dependent patients

** although the effect size is small it might be beneficial in patients with very low lung function

Box 2: Recommendations for benralizumab as add-on treatment in the paediatric population 12-17 years old with uncontrolled severe eosinophilic asthma

1. Benralizumab is recommended in in the paediatric population 12-17 years old with uncontrolled severe eosinophilic asthma* in spite of optimal controller treatment to:	Decrease severe asthma exacerbations	Conditional recommendation
	Improve quality of life	Conditional recommendation
	Improve asthma control	Conditional recommendation
	Improve lung function	Conditional recommendation**
2. Benralizumab demonstrated a good safety profile however patients should be regularly screened for parasitic infections in endemic areas		Conditional recommendation

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* population: severe asthma uncontrolled by high-dosage ICS +LABA with baseline blood eosinophil cell counts > 300 cells/μL or >150 cells/μL for OCS-dependent patients

** although the effect size is small it might be beneficial in patients with very low lung function

Justification

There is high certainty for adults for decreasing asthma exacerbations in the overall group and for OCS decrease in the subgroup with > 150 eosinophils/ μL. Although there is high certainty for improving asthma control and QoL the effect of benralizumab did not reach the MID, thus a conditional recommendation was formulated.

The GDG formulated conditional recommendations for the paediatric population due to the low numbers of subjects 12-17 years old included in clinical trials.

Subgroups: stratified by biomarkers and co-morbidities

The higher the blood eosinophils the higher the expected impact of benralizumab on exacerbations, asthma control, QoL and lung function (table S8) (conditional recommendation)

Neither the atopic status or total IgE predict the magnitude of effect of benralizumab (conditional recommendation) (table S9)

Benralizumab can be recommended in patients with severe eosinophilic asthma and CRSwNP uncontrolled despite optimal treatment to:

1. Decrease asthma exacerbations (conditional recommendation)
2. Improve lung function (conditional recommendation) (table S10)

III.B. Benralizumab – severe allergic asthma - adults

In humans, IL-5 is often co-expressed with other T2 cytokines including IL-4 and IL-13 and associated in atopic individuals with increased IgE production (28, 30, 31, 82, 83). Thus, targeting the IL-5 pathway might be beneficial in allergic asthma.

From all anti IL-5 biologicals only benralizumab was evaluated in the regulatory approved dose in a post-hoc analysis of a subpopulation of adults with severe allergic asthma (84).

The summary of the supportive evidence is presented in tables S11 and S12. Recommendations are based on the evidence-to-decision tables S13, S14, S15 and are presented in box 3

Box 3: Recommendations for benralizumab as add-on treatment in adults with uncontrolled severe allergic asthma

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1. Benralizumab is recommended in adults with uncontrolled severe allergic asthma* in spite of optimal controller treatment to:	Decrease severe asthma exacerbations	Conditional recommendation
	Improve quality of life	Conditional recommendation
	Improve asthma control	Conditional recommendation
	Improve lung function	Conditional recommendation**
2. Benralizumab demonstrated a good safety profile however patients should be regularly screened for parasitic infections in endemic areas		Conditional recommendation

* population: severe asthma uncontrolled by high-dosage ICS +LABA with baseline blood eosinophil Cell counts >300 cells/μL or > 150 cells/μL meeting the criteria for atopy (by Phadiatrop test) and serum IgE concentration of 30 to 700 kU/L (US) and 30 to 1500 kU/L (EU)

** although the effect size is small it might be beneficial in patients with very low lung function

Justification

There is high certainty for adults for decreasing asthma exacerbations, however, data are derived from a post-hoc analysis. Although there is high certainty for improving asthma control and QoL the effect of benralizumab did not reach the MID, thus a conditional recommendation was formulated.

III.C. Dupilumab – severe eosinophilic asthma - adults and paediatric population 12-17 years old

IL-4 and IL-13 are key cytokines in driving the initiation and the chronicity of T2 inflammation, where IL-4 is considered an initiator of T2 immune responses and IL-13 an effector molecule (85 86, 87,88,89). Dupilumab is a human IgG4 Mab that targets the IL-4 receptor alpha chain (IL-4Rα), common to both IL-4R complexes: type 1 (IL-4Rα/γc; IL-4 specific) and type 2 (IL-4Rα/IL-13Rα1; IL-4 and IL-13 specific) (90,91). In mice models dual IL-4/IL-13 blockade prevents eosinophil infiltration into lung tissue without affecting circulating eosinophils (90). Supported by a strategic mechanism of action inhibiting T2 mediated inflammation dupilumab's efficacy has been assessed across a range of atopic diseases, such as AD, asthma, and chronic rhinosinusitis with nasal polyps (CRSwNP) which often occur together as co-morbidities (91). Previous to being approved for T2 asthma dupilumab has been approved in the USA for the treatment of atopic

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dermatitis (AD) and CRSwNP and in Europe for AD. Convincing clinical results were recently published for severe uncontrolled asthma (92,93,94) and for CRSwNP (95).

The summary of the supportive evidence is presented in tables S16 and S17. Recommendations follow the evidence-to-decision tables S18 and S19.

Recommendations are formulated for the adult and adolescent population altogether (Box 4) as we did not perform a separate analysis for the 12-17 years old subgroup

Box 4: Recommendations for dupilumab as add-on treatment in adults and paediatric population 12-17 years old with uncontrolled severe eosinophilic asthma

1. Dupilumab is recommended in adults and paediatric population 12-17 years old with uncontrolled severe eosinophilic asthma* in spite of optimal controller treatment to:	Decrease severe asthma exacerbations	Strong recommendation
	Improve quality of life	Conditional recommendation
	Improve asthma control	Conditional recommendation
	Improve lung function**	Strong recommendation
	Decrease rescue medication use***	Conditional recommendation
2. Dupilumab demonstrated a good safety profile, however longer-term data (up to 2 years) are extrapolated from atopic dermatitis studies and careful reporting of all drug-related adverse events is recommended		Conditional recommendation

* population: severe asthma uncontrolled by medium/high-dose ICS plus up to 2 additional controllers including OCS; T2 inflammation (EMA requirements) characterised by raised blood eosinophils (> 150) and/or raised FeNO >20

** population: adult subgroup with blood eosinophils > 300 cells/μL or with FeNO levels > 50 ppb (64)

*** although the effect size is small it might be beneficial in patients with increased risk due due to excessive use of rescue medication

Justification

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There is high certainty for adults for decreasing asthma exacerbations and moderate certainty for improving asthma control and QoL and the decrease in rescue medication use, thus a conditional recommendation was formulated. The increase in FEV_1 is significant (above the MID) for the adult subgroup with blood eosinophils > 300 cells/μL or with FeNO levels > 50 ppb (64). More efficacy and safety data are needed in the paediatric population.

Subgroups: stratified by biomarkers and co-morbidities

The higher the blood eosinophils and FeNO the higher the clinical efficacy of dupilumab, both in reduced exacerbations and in improving lung function (conditional recommendation) (tables S20 and S21).

Dupilumab can be recommended in adults and adolescents with severe eosinophilic asthma with chronic rhinosinusitis with nasal polyps who are uncontrolled despite optimal treatment to:

1. Decrease exacerbations (conditional recommendation)
2. Improve asthma control (conditional recommendation)
3. Improve quality of life (conditional recommendation)
4. Improve lung function (conditional recommendation)

III.D. Dupilumab –severe allergic asthma – adults and paediatric population 12-17 years old

Ligand binding of the type 1 (IL-4Rα/γc; IL-4 specific) and type 2 (IL-4Rα/IL-13Rα1; IL-4 and IL-13 specific) receptors activates a signal transduction cascade that mainly leads to the modulation of expression of genes involved in IgE class switching, T helper (TH) 2 cell differentiation, and M2 macrophage polarization (31, 82, 86, 87, 88). IL-4 has been shown to stimulate IgE production from B cells. In asthma, IL-4 plays a major role in TH2 cell proliferation, cytokine production, and IgE synthesis. Combined analyses of genetic alterations in the IL-4/IL-13 pathway showed a profound influence on serum IgE levels and the risk of childhood asthma (96). Dupilumab was specifically evaluated in a post-hoc analysis of patients with moderate to severe allergic asthma enrolled in QUEST trial. Allergic asthma was defined by total serum IgE ≥30 IU/mL and ≥1 perennial aeroallergen-specific IgE ≥0.35 kU/L at baseline (97).

The summary of the supportive evidence is presented in tables S22 and S23. Recommendations follow the evidence-to-decision tables S24 and S25.

Recommendations are formulated for the adult and adolescent population altogether (Box 5) as we did not perform a separate analysis for the 12-17 years old subgroup

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Box 5: Recommendations for dupilumab as add-on treatment in adults and in the paediatric population 12-17 years old with uncontrolled severe allergic asthma

1. Dupilumab is recommended in adults and in the paediatric population 12-17 years old with uncontrolled severe allergic asthma* in spite of optimal controller treatment to:	Decrease severe asthma exacerbations	Conditional recommendation
	Improve asthma control	Conditional recommendation
	Improve lung function**	Conditional recommendation
2. Dupilumab demonstrated a good safety profile, however longer term data (up to 2 years) are extrapolated from atopic dermatitis studies and careful reporting of all drug-related adverse events is recommended		Conditional recommendation

* population: severe asthma uncontrolled by medium/high-dose ICS plus up to 2 additional controllers including OCS; T2 inflammation (EMA requirements) characterised by raised blood eosinophils (> 150) and/or raised FeNO >20

** population: adults subgroup with blood eosinophils > 300 cells/μL or with FeNO levels > 50 ppb (64)

Justification

There is high certainty for adults for decreasing asthma exacerbations and for improving asthma control. However, because the improvement in asthma control did not reach the MID a conditional recommendation was formulated. The increase in FEV_1 is significant (above the MID) for the adults subgroup with blood eosinophils > 300 cells/μL or with FeNO levels > 50 ppb (64). More efficacy and safety data are needed in the paediatric population. As data are derived from a post-hoc analysis a conditional recommendation was formulated.

III.E. Dupilumab –severe T2 asthma – adults and paediatric population 12-17 years old

T2 asthma encompasses several pathways that are concomitantly activated, including cells of the innate immune system such innate lymphoid cells, macrophages, neutrophils, and natural killer T

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cells which are effective producers of a variety of cytokines and seem to play important roles in the development of non-allergic asthma (27,30,32). IL-13 cytokine serum levels were significantly high in atopic and non-atopic asthma patients compared to healthy controls. IL-4 and IL-13 can curtail chemotaxis and several effector functions of neutrophils in humans (98,99). In a recent analysis of the QUEST trial dupilumab reduced severe exacerbation rates, improved FEV_1 and asthma control, and suppressed T2 inflammatory biomarkers in patients with uncontrolled, moderate-to-severe asthma with or without evidence of allergic asthma (97). Following this rationale, the GDG decided to perform a SR on the efficacy and safety of dupilumab without using the criteria for eosinophilic or allergic asthma (65). This SR is the basis for the recommendations for dupilumab as add-on treatment in patients with T2 asthma uncontrolled under medium to high dose ICS plus up to two additional controllers.

The summary of the supportive evidence is presented in tables S26 and S27. Recommendations follow the evidence-to-decision tables S28, S29, S30.

Recommendations are formulated for the adult and adolescent population altogether (Box 6) as there were no differences between the adults and the 12-17 years old subgroup

Box 6: Recommendations for dupilumab as add-on treatment in adults and paediatric population 12-17 years old with uncontrolled severe T2 asthma

1. Dupilumab is recommended in adults and paediatric population 12-17 years old with uncontrolled severe T2 asthma* in spite of optimal controller treatment to:	Decrease severe asthma exacerbations	Strong recommendation
	Decrease or withdraw oral corticosteroids**	Strong recommendation
	Improve quality of life	Conditional recommendation
	Improve asthma control	Conditional recommendation
	Improve lung function***	Strong recommendation
	Decrease rescue medication****	Conditional recommendation
2. Dupilumab demonstrated a good safety profile, however longer term data (up to 2 years) are extrapolated from atopic dermatitis studies and careful reporting of all drug-related adverse events is recommended		Conditional recommendation

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* population: severe asthma uncontrolled by medium/high-dose ICS plus up to 2 additional controllers including OCS; T2 inflammation (EMA requirements) characterised by raised blood eosinophils (> 150) and/or raised FeNO >20

**population: Patients with severe asthma on maintenance OCS and high dose ICS in combination with a second controller

***population: adult subgroup with blood eosinophils > 300 cells/μL or with FeNO levels > 50 ppb (65) or OCS dependent patients (94)

**** although the effect size is small it might be beneficial in patients with increased risk due to excessive use of rescue medication

Justification

There is high certainty for adults for decreasing asthma exacerbations and for OCS reduction. Although there is high certainty for improving asthma control and QoL the effect does not reach above the MID, thus a conditional recommendation was formulated. The increase in FEV_1 is significant (above the MID) for the adult subgroup with blood eosinophils > 300 cells/μL and/or with FeNO levels > 50 ppb (65) and for OCS dependent patients (94). More efficacy and safety data are needed in the paediatric population.

Subgroups:

Dupilumab is effective both in allergic* and nonallergic asthma in a T2 asthma context (conditional recommendation)

*a total serum IgE ≥30 IU/mL and ≥1 positive perennial aeroallergen-specific IgE value (≥0.35 kU/L) at baseline (table S31 A and B)

III.F. Mepolizumab – eosinophilic severe asthma – adults and paediatric population 12-17 years old

Mepolizumab is humanised Mab of IgG1 κ type, which targets human IL-5 with high affinity and specificity. Mepolizumab inhibits the bioactivity of IL-5 with nanomolar potency by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signalling and reducing the production and survival of eosinophils (100). It was approved for severe asthma with peripheral eosinophilia. Good control of peripheral eosinophilia has been readily demonstrated together with translation into a significant reduction in asthma exacerbations and an OCS sparing effect (101,102,103). Its effect on asthma control, QoL and lung function are less clear.

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The summary of the supportive evidence is presented in tables S32 and S33. Recommendations follow the evidence-to-decision tables S34, S35, S36, S37.
Recommendations are formulated separate for the adult population (Box 7) and the 12-17 years old population (Box 8)

Box 7: Recommendations for mepolizumab as add-on treatment in adults with uncontrolled severe eosinophilic asthma

1. Mepolizumab is recommended in adults with uncontrolled severe eosinophilic asthma* in spite of optimal controller treatment to:	Decrease severe asthma exacerbations	Strong recommendation
	Decrease or withdraw oral corticosteroids	Strong recommendation
	Improve quality of life	Conditional recommendation
	Improve asthma control	Conditional recommendation
	Improve lung function	Conditional recommendation**
2. No recommendation can be made for reducing rescue medication use as the effect size is small		
3. Mepolizumab demonstrated a good safety profile (long term safety data up to 5 years), however patients should be regularly screened for parasitic infections in endemic areas		Conditional recommendation

* population: Severe eosinophilic asthma defined as presence of eosinophilic inflammation determined by a blood eosinophil level of either 300 cells or more per µL in the past 12 months or 150 cells or more per µL at initiation.
** although the effect size is small the improvement might be relevant in severe asthma with very low lung function

Box 8: Recommendations for mepolizumab as add-on treatment in paediatric population 12-17 years old with uncontrolled severe eosinophilic asthma

1. Mepolizumab is recommended in children 12-17 with	Decrease severe asthma exacerbations	Conditional recommendation
	Decrease or withdraw oral	Conditional

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uncontrolled severe eosinophilic asthma* in spite of optimal controller treatment to:	corticosteroids	recommendation
	Improve quality of life	Conditional recommendation
	Improve asthma control	Conditional recommendation
	Improve lung function	Conditional recommendation
2. Mepolizumab demonstrated a good safety profile (long term safety data up to 5 years), however patients should be regularly screened for parasitic infections in endemic areas		Conditional recommendation

* population: Severe eosinophilic asthma defined as presence of eosinophilic inflammation determined by a blood eosinophil level of either 300 cells or more per µL in the past 12 months or 150 cells or more per µL at initiation.

No recommendations can be formulated for children 6 -11 years old as per extrapolated data from mepolizumab 12-17 population.

Justification

There is high certainty for the decrease of moderate and severe asthma exacerbations and for the decrease in OCS and moderate or low certainty for improving asthma control, quality of life and lung function and for monitoring for parasitic infections. Only conditional recommendations can be formulated for the paediatric group 12-17 years old as there were low numbers enrolled in clinical trials.

Subgroups: stratified by biomarkers and co-morbidities

The higher the blood eosinophils the higher the expected impact of mepolizumab on exacerbations (table S38) (conditional recommendation).

Mepolizumab can be recommended in adult patients with severe eosinophilic asthma and CRSwNP uncontrolled despite optimal treatment to:

- decrease asthma exacerbations (conditional recommendation)
- decrease or withdraw OCS (conditional recommendation)
- Improve lung function (conditional recommendation)

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- Improve quality of life (conditional recommendation)

For the use of mepolizumab in allergic asthma in a licensed dose an open multicenter, open-label, single-arm study showed clinically significant improvements in asthma control, health status, and exacerbation rate (104). The post hoc meta-analysis of two phase 3 studies showed efficacy of mepolizumab regardless of allergic characteristics or omalizumab eligibility (105). Recent reports show that both mepolizumab and reslizumab can control severe asthma patients that failed to respond to omalizumab (106). The GDG considered that there are not enough data to conduct a SR on the licenced dose of mepolizumab in severe allergic asthma and a recommendation cannot be currently formulated.

III.G. Omalizumab – severe eosinophilic asthma - adults

While immunoglobulin E is a prominent biomarker for early-onset asthma, its serum levels is often also elevated in non-allergic late-onset asthma. The pattern of IgE expression in the latter is mostly polyclonal and frequently associated with high blood eosinophils (107, 108). The innate immune response also significantly contributes to this asthma phenotype. Release of IL-33 and TSLP from respiratory epithelium and activation of ILC2s via its receptor ST2 followed by T2 cytokine release from ILC2s and TH 2 cells drives further massive local B-cell activation and IgE formation, mast cell degranulation, and finally eosinophil attraction (99, 109, 110). Omalizumab indirectly downregulates the IgE high affinity receptor (FcεRI) expression on basophils, mast cells, and dendritic cells (DCs), decreasing T2 cytokine production and inhibiting the eosinophilic inflammation (111,112,113,114,115,116,117). Through a different mechanism, long-term omalizumab treatment dampens T2 inflammation acting on different cell types that play a pivotal role in the pathogenesis of asthma such as plasmacytoid DCs (pDCs) and CD-4 T helper cells (118). Several publications of case reports or short series describe the use of omalizumab adults and children suffering from severe non-allergic asthma, sometimes reporting the successful withdrawal of systemic corticosteroids under treatment (119,120,121). Better response to omalizumab for eosinophil counts >300 cells/μL were shown in a prospective trial and in a recent pooled analysis of the two pivotal trials of omalizumab in allergic asthma (122,123,124). However, in two real life studies omalizumab proved its efficacy regardless of the blood eosinophils status (125,126).

The summary of the supportive evidence is presented in table S39. Recommendations follow the evidence-to-decision tables S40, S41. Recommendations are formulated only for the adult population (Box 9)

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Box 9: Recommendations for omalizumab as add-on treatment in adults with uncontrolled severe eosinophilic asthma (both allergic and non-allergic)

1. Omalizumab is recommended in adults with uncontrolled severe eosinophilic asthma* in spite of optimal controller treatment to:	Decrease severe asthma exacerbations	Strong recommendation
	Improve quality of life	Conditional recommendation
	Improve lung function	Conditional recommendation**
	Decrease the use of rescue medication	Conditional recommendation***
2. Omalizumab has demonstrated a long-term (> 10 years) good safety profile, however 60 minutes monitoring for anaphylaxis is recommended for the first 3 administrations****		Conditional recommendation

* population: adults with uncontrolled severe persistent allergic asthma with FENO ≥24ppb, and blood eosinophil counts ≥260/µl

** although the effect size is small the improvement might be relevant in severe asthma with very low lung function

*** although the effect size is small it might be beneficial in patients with increased risk due to excessive use of rescue medication

**** the recommendations on the duration of monitoring after omalizumab injection and for the first 3 administrations are expert opinion-based following the data reported in the literature (127); of note anaphylaxis has also been documented two hours after administration and beyond 1 year after beginning regularly administered treatment, thus it is up to the clinician to decide based on the personal history of the patient

III.H. Omalizumab – moderate to severe allergic asthma – adults and paediatric population 12-17 years old

The first in a new class of biological therapies for allergic asthma, omalizumab works by binding to free IgE thereby, reducing the amount available to bind the IgE high affinity receptor (FcεRI) on mast cells, basophils and antigen presenting cells (80). The ability to detach IgE from its receptor following omalizumab was recently described (128). The pDCs act at the crossroads between innate and adaptive immunity. IgE receptor cross-linking on pDCs suppresses their anti-viral activity. Thus, a reduced expression of IgE receptors on pDCs and a reduced amount of

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circulating IgE might generally strengthen anti-viral immune responses following omalizumab administration (129,130). Pre-clinical and clinical evidence supports the existence of a close counter-regulation of the high-affinity IgE receptor and interferon (IFN) pathways, and a potential dual mechanism of action and therapeutic benefit for omalizumab, which may enhance the prevention and treatment of virally induced asthma exacerbations (131,132,133,134). Extensive experience with omalizumab treatment for severe allergic asthma confirmed its effectiveness and safety, reducing symptoms, frequency of reliever use, and severe exacerbations (135,136, 137,138,139,140,141).

The summary of the supportive evidence is presented in tables S42 and S43. Recommendations follow the evidence-to-decision tables S44 and S45. As we did not perform a separate analysis for the 12-17 population recommendations are formulated altogether for the adult and adolescent (12-17 years old) population (Box 10)

Box 10: Recommendations for omalizumab as add-on treatment in adults and the paediatric population 12-17 years old with uncontrolled moderate-to-severe allergic asthma

1. Omalizumab is recommended in adults and the paediatric population 12-17 years old with uncontrolled severe allergic asthma* in spite of optimal controller treatment to:	Decrease severe asthma exacerbations	Strong recommendation
	Improve asthma control	Conditional recommendation
	Improve quality of life	Conditional recommendation
	Decrease in the use of ICS	Conditional recommendation**
	Decrease the use of rescue medication	Conditional recommendation***
2. Omalizumab has demonstrated a long-term (> 10 years) good safety profile, however 60 minutes monitoring for anaphylaxis is recommended for the first 3 administrations ****		Conditional recommendation

* population: Moderate-to-severe asthma, total IgE level of 30–700 IU/ml (US) and 30 -1500 IU/ml (EU) ± one perennial aeroallergen

**of particular importance for the paediatric population

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*** although the effect size is small it might be beneficial in patients with increased risk due to excessive use of rescue medication

**** the recommendations on the duration of monitoring after omalizumab injection and for the first 3 administrations are expert opinion-based (127); of note anaphylaxis has also been documented two hours after administration and beyond 1 year after beginning regularly administered treatment, thus it is up to the clinician to decide based on the personal history of the patient

Justification

There is high certainty for the decrease in asthma exacerbations. Although there is high certainty for improving quality of life and for decreasing ICS and rescue medication use the GDG formulated conditional recommendations as the effect size did not reach the MID (where applicable) or was very small or there was a large confidence interval. There was moderate certainty for improving asthma control, not reaching the MID, however there was high certainty for the improvement in the global evaluation of treatment effectiveness (GETE).

Subgroups: stratified by biomarkers and co-morbidities

Serum IgE thresholds (within regulatory limits) do not influence response (conditional recommendation)

The effect of omalizumab on exacerbations does not depend on blood eosinophils (conditional recommendation) (table S46).

Omalizumab may control associated co-morbidities such as allergic rhinitis, chronic urticaria food allergy, CRSwNP but asthma-related recommendations and posology should be primarily used (conditional recommendation, expert opinion based).

III.I. Omalizumab – moderate to severe allergic asthma – paediatric population 6 -11 years old

As there is good evidence with omalizumab for the paediatric asthma subgroup 6-11 years old a separate analysis was performed (see evidence to decision table S47) and the GDG formulated separate recommendations (box 11).

Box 11: Recommendations for omalizumab as add-on treatment for children 6-11 years old with uncontrolled moderate-to-severe allergic asthma

1. Omalizumab is	Decrease severe asthma	Conditional

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recommended for children 6-11 years old with uncontrolled allergic asthma* in spite of optimal controller treatment to:	exacerbations	recommendation
	Improve asthma control	Conditional recommendation
	Improve quality of life	Conditional recommendation
	Decrease in the use of ICS	Conditional recommendation**
2. Omalizumab has demonstrated a long-term (> 10 years) good safety profile, however 60 minutes monitoring for anaphylaxis is recommended for the first 3 administrations***		Conditional recommendation
3. Serum IgE thresholds (within regulatory limits) do not influence response		Conditional recommendation
4. Omalizumab might reduce viral-induced exacerbations in this particular population		Conditional recommendation

* population: Moderate-to-severe asthma, total IgE level of 30–700 IU/ml (US) 30–1500 IU/ml (EU) ± one perennial aeroallergen

**of particular importance for the paediatric population

*** the recommendations on the duration of monitoring after omalizumab injection and for the first 3 administrations are expert opinion-based (127); of note anaphylaxis has also been documented two hours after administration and beyond 1 year after beginning regularly administered treatment, thus it is up to the clinician to decide based on the personal history of the patient

III.J. Reslizumab – severe eosinophilic asthma - adults

Reslizumab is an IL-5 antagonist (IgG4-kappa) binding to the IL-5 using a different epitope as compared to mepolizumab and in vitro with greater potency (142). It is administered via intravenous (iv) infusion and dosing is based on patients' weight (143). Administration is recommended immediately after preparation. In clinical trials, rare cases of anaphylaxis were observed within 20 minutes of infusion and was reported as early as the second dose. The pooled analysis of six clinical trials reports only three cases of anaphylaxis related to reslizumab, successfully managed with standard therapies (144). By week 52 patients receiving reslizumab showed a 92% reduction in mean blood eosinophil counts, and this effect translates into a significant decrease in asthma exacerbations (145,146,147,148).

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The summary of the supportive evidence is presented in tables S48 and S49. Recommendations (box 12) follow the evidence-to-decision tables S50, S51 and S52.

Box 12: Recommendations for reslizumab as add-on treatment in adults with uncontrolled severe eosinophilic asthma

1. Reslizumab is recommended in adults with uncontrolled severe eosinophilic asthma* in spite of optimal controller treatment to:	Decrease severe asthma exacerbations	Strong recommendation
	Improve quality of life	Conditional Recommendation
	Improve asthma control	Conditional recommendation
	Improve lung function	Conditional recommendation**
2. No recommendation can be made for reducing rescue medication use as the effect size is small; OCS reduction is not reported		
3. Reslizumab demonstrated a good safety profile however: a. patients should be regularly screened for parasitic infections in endemic areas b. patients should be carefully monitored 30 minutes after the iv administration for the risk of anaphylaxis		Conditional recommendation

* population: at least one blood eosinophil count of 400 cells per µL or higher during a 2–4 weeks screening period and inadequately controlled asthma, receiving at least a medium dose of ICS with or without another controller drug including OCS

** although the effect size is small the improvement might be relevant in severe asthma with very low lung function

Justification: Although there is high certainty for improving asthma control and QoL the effect does not reach the minimal important difference; thus, a conditional recommendation was formulated. There is moderate certainty for improving lung function and low certainty for monitoring for parasitic infections and the iv administration.

Subgroups: stratified by biomarkers and co-morbidities

The higher the blood eosinophils the higher the expected impact of reslizumab on lung function and on asthma control (conditional recommendation) (table S53)

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Reslizumab can be recommended in patients with severe eosinophilic asthma with CRSwNP uncontrolled despite optimal treatment to:

1. decrease moderate and severe asthma exacerbations (conditional recommendation)
2. Improve asthma control (conditional recommendation) (table S54)

Additional considerations: Reslizumab's flexibility in dosage based on body weight might benefit patients with uncontrolled severe eosinophilic asthma not responding to other anti IL-5 interventions (conditional recommendation, expert opinion based)

As there are no paediatric data available no recommendations can be formulated for the use of reslizumab in children with uncontrolled severe asthma.

III.K. Comparison between biologicals

No comparison can be made between the efficacy and safety of different biologics (strong recommendation, expert opinion based). Baseline asthma severity, atopic status definition, lung function, eosinophil cut-offs or exacerbation history and asthma duration are all important modulators of treatment efficacy. The rate of background exacerbations (in year prior to trial) or the placebo exacerbations rate (during the trial) should also be considered. These differ across trials because of different inclusion or exclusion criteria, thus the indirect treatment comparisons may be erroneous or biased.

III.L. Implementation consideration (for all biologicals)

The GDG formulated strong recommendations for the reduction in asthma exacerbations and for the reduction in OCS dose and conditional recommendations for the other asthma-related outcomes. According to GRADE for strong recommendations most individuals should receive the intervention and the recommendation can be adapted as policy or performance measure in most situations (table 6). However, the GDG cautions on several unsolved key pillars supporting the implementation of these recommendations, such as independent high-quality cost-effectiveness studies, selection of responders, documentation of the disease modifying effect together with long-term safety data, studies addressing a priori severe asthma together with its co-morbidities. Additional considerations are acceptability of the iv administration for reslizumab or the possibility of self-administration of biologicals at home and at longer intervals (149). The cost-effectiveness of biologicals based on real-world treatment patterns is unknown. Including broader evidence on treatment discontinuation, caregiver burden, and OCS reduction from real-world studies and severe asthma registries may better reflect the effects and value of biologicals for all healthcare

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stakeholders (48). Last but not least the value of the recommendations depends also on the setting in which the current guideline will be implemented, as recommendation suitable for resource-rich environments might change from strong to conditional in resource-poor environments.

IV. Other biologicals currently tested for severe asthma

Thymic stromal lymphopoietin (TSLP) is a critical upstream epithelial derived cytokine inducing T2 inflammation. TSLP activates distinct immune cell cascades in the context of innate and adaptive immune-mediated T2 inflammation (150). TSLP's importance in human asthma has been repeatedly documented (151,152,153). Targeting of TSLP-mediated signalling is a potential therapeutic strategy for severe asthma.

Tezepelumab, which is the first-in-class anti-TSLP mAb, is a fully human IgG2λ mAb that binds human TSLP and prevents interaction with its receptor. Because of the excellent results in the phase II trial which showed a notable reduction in the annual asthma exacerbation rate in a large population of severe asthma patients (154), FDA granted tezepelumab a 'breakthrough therapy designation' for the treatment of severe asthma without an eosinophilic phenotype (155). The drug is currently in Phase III clinical trials. In order to formulate a preliminary opinion a SR was performed for tezepelumab following the same methodology as for the currently approved biologicals for asthma (table S55). There was moderate certainty that tezepelumab decreases asthma exacerbations, low certainty for improving asthma control and QoL and very low certainty for improving FEV_1 and for decreasing FeNO. There was low certainty for an increase in treatment related AEs and SAEs. The subgroup analysis by eosinophil and FeNO levels found no difference for the exacerbation rate and FEV_1. For FEV_1 another subgroup analysis by IgE levels found no difference either.

MSTT1041A, an anti-ST2 (IgG2) human monoclonal antibody has recently been tested in a phase IIb trial and results are soon to be published (151). Several other anti IL-33 Mabs are currently being tested (156). The anti-IL-33 antibody REGN3500 (SAR440340) met the primary endpoint of improvement in loss of asthma control when comparing REGN3500 monotherapy to placebo. The greatest improvement was observed in patients with blood eosinophil levels ≥300 cells/microliter (157). Other anti-IL-33 antibodies, GSK3772847 (NCT03207243) and etokimab, are currently being tested in phase II trials.

V. Biologicals evaluated for severe asthma currently discontinued

Despite promising findings in several experimental models of allergic inflammation, the results of multicenter studies evaluating the efficacy of anti-IL4 and anti-IL-13 mAbs in patients with asthma

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were negative (table S56). It appears that individual blockade of IL-4 or IL-13 alone is insufficient to inhibit the complex allergic inflammation. For example, blocking IL-13 does not impact significantly tissue eosinophilia. Other explanations could be that the biomarkers used to identify responders to anti-IL-13 therapy (e.g., periostin, DPP-4, peripheral eosinophil count) were not optimal or non T2 asthma patients were included in phase III trials. Finally, systemic administration could not achieve optimal lung concentrations. The preliminary efficacy of a nebulized inhaled anti-IL-13 mAb antigen-binding fragment in macaque model of asthma was recently reported (158).

Targeting the IgE pathway via depletion of IgE-switched and memory B cells was not sufficient for a clinically meaningful benefit for adults with allergic asthma uncontrolled by standard therapy (table S56), indicating that there are major pathological mechanisms that extend beyond the new, local production of IgE in the lung (159).

The results of clinical trials of biological agents targeting mediators associated with non-eosinophilic inflammation, such as IL-17 and tumour necrosis factor (TNF)-α were disappointing (table S56). A better understanding of the mechanisms of non-eosinophilic inflammation in asthma should lead to improved therapies, with potential targeted treatment for (29,30,31).

VI. Clinical decision algorithm for the initiation and follow-up of biologicals for the treatment of patients with uncontrolled severe asthma

The algorithm developed by the GDG assumes that the diagnosis of severe asthma was correctly performed according to the current guidelines (GINA 2020, ERS/ATS), all co-morbidities and factors influencing asthma control were correctly addressed and patients are still symptomatic on high-intensity controller medication or deteriorate upon step-down (2,20,21).

The GDG developed a three-pillar decision tree aiming to help the clinician in reaching the decision to start on a particular biological (figure 1) based on the combination between phenotypic traits, biomarkers and clinically relevant asthma-related end-points (exacerbations, symptoms, lung function, QoL, etc.), including safety (conditional recommendation, expert opinion based). Cost-related and regulatory aspects should also be considered in reaching the decision to start with a particular biological.

The GDG recommends re-evaluation of response after 4-6 months (conditional recommendation, expert opinion based). Of note, in some patients, exacerbations might not decrease significantly in this short period of time and a composite end-point should be used to define response (160,161). The definition of a suboptimal response relies on individualised predefined cut-offs of

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the selected outcomes (conditional recommendation, expert opinion based). As there is no consensus or validated criteria to define response the GDG recommends individualised predefined targets established by informed shared decision focused on the patient's goals to control their asthma, in alignment with the principles of personalised treatment. Cost-related, administration at home or in the clinic and regulatory aspects should also be considered in establishing the predefined goals.

For suboptimal response the GDG recommends to re-assess airway inflammation and airway hyperresponsiveness (conditional recommendation, expert opinion based). Induced sputum is the preferred option to re-assess airway inflammation (conditional recommendation, expert opinion based) as a non-invasive validated tool. The GDG strongly recommends joint efforts from academia, industry and healthcare systems to develop both educational tools and resources supporting a wider use of induced sputum evaluation in severe asthma.

If airway eosinophilia is not controlled the clinician is advised to address the following possibilities:

1. Patient is not adherent to the background controller treatment or to the general management plan installed to ensure optimal asthma control. The GDG considers this as the first step to be considered in case of suboptimal response. Many patients stop their background controller treatment following the first 3-4 administrations of the biological (table S2) without consulting with their HCP (162). In this case the management plan should be re-discussed with the patient. Adherence could be monitored more closely by medication refills or by using smart inhalers with dose counting. The GDG considers that the shared decision process at the start of the treatment and establishment of common goals following the administration of the biological might mitigate the non-adherence to the overall management plan.
2. Airway eosinophilia is not driven by the pathway targeted by the biological used (106, 162,163). In this case consider switching to biologicals targeting a different pathway
3. Inadequate dosing. In this case consider switching to a biological targeting the same pathway but with different mechanism of action or route of administration (165)
4. Development of neutralising anti-drug antibodies (ADA). Following the ABIRISK consortium recommendations the titre, affinity, isotype and epitope mapping are important steps in characterising ADA (166). In this case consider switching to biologicals targeting a different pathway or to a biological targeting the same pathway but with different mechanism of action or route of administration
5. Other immune dysfunctions such as predominant ILC2 activation, autoimmune mechanisms (e.g. driven by Charcot-Leyden crystals) or IL-5-anti-IL-5 complement

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activating immune complexes are driving the treatment-resistant lung eosinophilia (167,168,169). As these cases are very rare referral to a specialised centre after all other caused were excluded is recommended.

If at re-evaluation for sub-optimal response there is no airway eosinophilia and neutrophilic inflammation is present the biological should be interrupted and measures addressing non-T2 asthma such as macrolides (170), should be considered (conditional recommendation, expert opinion based). In cases with no airway inflammation addressing airway hyperresponsiveness (LABA/LAMA combinations or bifunctional drugs) (172) or airway remodelling (bronchial thermoplasty (172) in selected cases) is recommended (conditional recommendation, expert opinion based).

For the duration of a biological treatment in a patient with good response according to the individualised predefined targets the GDG recommends continuing treatment, pending on the cost-efficacy evaluation and local regulatory status, while continuously monitoring for efficacy and safety (conditional recommendation, expert opinion based). The rationale behind this recommendation is the evidence that upon interruption of the biological, as for any other background controller of asthma, all the beneficial effect is lost. The longer-term administration informs as well on the long-term safety profile and might facilitate a disease-modifying effect.

VII. Discussion

a. Relevance of the EAACI Guidelines compared to GINA and ERS/ATS recommendations

The EAACI Guidelines recommendations for the use of currently regulatory approved biologicals in uncontrolled severe asthma are formulated per product and with a careful description of the population where the recommendation is applicable. In comparison with the current guidelines (GINA 2020 and ERS/ATS) the EAACI GDG considered this approach pertinent with the precision medicine framework, where an exact characterisation of the target population is advocated. Until real world evidence accumulates the only detailed description of the phenotype for each biological are the inclusion/exclusion criteria for the pivotal trials that allowed the regulatory approval. Although not immediately very helpful for the clinician the GDG considered important to acknowledge in the recommendations the heterogeneity of the patients with severe asthma and tried to be as precise as possible in the description of the phenotype. Another key difference is the formulation of recommendations per product as there is no proven “class effect” of the biologicals even if they target the same pathway (e.g. IL-5) or the same cell (eosinophils).

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This aspect is evident in the case of response to biologicals from the same "class" after switching for lack of response.

The National Institute for Health and Care Excellence (NICE) in the United Kingdom suggests re-evaluating patients on mepolizumab-based therapy after 12 months to verify if the frequency of asthmatic exacerbations has been reduced by at least 50% (173). Similar to GINA 2019 and ERS/ATS guidelines the clinical decision algorithm proposed by the EAACI Guidelines proposes re-evaluation after 4-6 months. This arbitrary cut-off was chosen based on the high-cost of these drugs with the assumption that the duration is long enough to select responders from suboptimal response. In addition, as no validated criteria exist for defining optimal response, the EAACI Guidelines advocate for individual predefined targets established by informed shared decision focused on the patient's goals to control their asthma (43).

b. Future perspectives: barriers and facilitators

i. Precision medicine using multiple or upstream targets

Focusing on antagonising one cytokine alone (anti IL-4, anti IL-13 interventions) were either unsuccessful on major clinical end-point or provided a dissociated effect (26, 63,64,65, 174), with impact mainly on exacerbations and less on lung function or asthma symptoms (anti-IL-5, anti IgE interventions). This dissociated effect seems to be less pronounced for dupilumab, which binds to IL-4Rα and consequently blocks both IL-4 and IL-13 signalling. These observations suggest that only the effective simultaneous blockade of two or more main pathogenic pathways in asthma (IL-5, IL-4/IL-13, IgE) would be more effective in the treatment of severe T2 asthma (28). The combined blockade of the IL-13 and IL-33 pathways leads to a greater inhibition of T2 inflammation over inhibition of either pathway alone (175). Similarly, co-blockade of IL-13 and IL-25 attenuated airway hyperreactivity, eosinophil infiltration in the lung, and mucus hyperproduction in a mouse model of allergic asthma (176). A novel dual antagonist anti-TSLP/IL-13 bispecific antibody has entered preclinical testing (177).

Small molecule drug (SMD)-based therapies represent an active field in pharmaceutical research and development. SMDs expand biologicals' therapeutic targets by reaching the intracellular compartment by delivery as either an oral or topically based formulation, offering both convenience and lower costs (178). A randomized, double-blind, placebo-controlled, crossover study investigating the efficacy, safety, tolerability, and pharmacokinetics of a phosphoinositide 3 kinase (PI3K) δ inhibitor, nemiralisib, in patients with persistent, uncontrolled asthma did not translate into meaningful clinical improvement in spite of local inhibition of PI3K δ. Further studies will investigate its potential efficacy in more specific phenotypes, including those colonised with

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bacteria or frequent exacerbators (179). Being pivotal for signalling for multiple asthma-relevant cytokines, including IL-4, IL-5, IL-13, and TSLP, Janus kinase (JAK)/ signal transducer and activator of transcription (STAT) inhibition, especially delivered through the inhaled route, might be a novel intervention strategy for severe asthma (180,181).

ii. Targeted treatment of non T2 asthma

No targeted therapies exist at present for the non-T2 severe asthma. It remains to be seen if such an endotype really exists as many data derive from cross-sectional studies or are confounded by the concomitant use of high dose ICS or OCS or by the co-existence of infection (182). Nevertheless, the identification of a non T2 profile is essential as it excludes treatment with the current biologicals available for severe asthma. The NHLBI PrecISE network is currently exploring therapeutic approaches for non-T2 asthma.

iii. Multidimensional endotyping

Current understanding of the heterogeneity of severe asthma requires a shift in the methodological approach from investigator-imposed hypothesis driven clusters to the unbiased approach of data-driven models leading to the discovery of new pathogenetic pathways. At present, large amount of multi-omics, imaging, information from medical devices, Apps and electronic health records data are available and require effective analytic tools. Advanced machine learning methods such as deep learning and platforms for cognitive computing represent the future toolbox for the data-driven analysis of big data (31, 44, 49, 50).

iv. The disease modifying effect

The “holy Grail” for the use of biologicals in severe asthma is to validate their disease modifying potential (183). If this proves to be true we might consider a future potential role for biologicals in mild asthma to prevent the evolution towards severe cases or for the primary prevention of asthma in high risk individuals. Several pathways for immune modulation in T2-driven inflammatory diseases are described, from trained immunity, epigenetic reprogramming, B and T regulatory cells, to microbiome, and novel metabolic pathways (109, 184,185,186,187,188,189). The induction of immune tolerance involves molecular mechanisms of anergy, deletion, suppression, immune privilege, and ignorance. Most of the knowledge accumulated of T2 immune modulation followed the application of allergen immunotherapy (AIT) in asthma (190,191,192). Currently none of the biologicals approved for the treatment of severe asthma demonstrated any disease modifying effect, as the efficacy is lost a few weeks or months after

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the treatment is stopped. Data from mechanistic studies on biologicals are very scarce and frequently contradictory.

v. Long term safety

In healthy individuals, eosinophils contribute to protective immune responses directed against parasites, viral, bacterial, and fungal pathogens, are crucial for the survival of long-lived plasma cells and are critical regulators of local immunity and remodelling/repair in both health and disease (193,194). Homeostatic eosinophils present in healthy individuals in various tissues are related to the control of glucose homeostasis, protection against obesity, regulation of mammary gland development, preparation of the uterus for pregnancy, and the maintenance of the intestinal homeostasis in collaboration with the local microbiota (195,196,197,198). In the lung homeostatic eosinophils have been shown to suppress T2-driven airway responses (199).

Besides its role against parasites IgE can exert anti-neoplastic surveillance via mast cell and eosinophil-mediated cytotoxicity or by engaging and re-educating alternatively-activated macrophages towards pro-inflammatory phenotypes and by priming all subsets to mediate anti-tumour functions (200,201,202). IgE deficiency was associated with a higher rate of prior diagnosis of malignancies compared with individuals with high or very high IgE levels (203). However, prospective studies are essential to better evaluate the association between IgE levels and risk of cancer.

The T2 cytokines IL-4 and IL-13, which signal through IL-4Rα, trigger a specialized macrophage phenotype (M(IL-4)) that promotes control of helminth infection and tissue repair in the lung and in the liver (204,205,206). IL-4 drives the production of defence collagens, SP-A and C1q, and the expression of their receptor, myosin 18A (206). By controlling complement activation, IL-4 regulates the induction of IL-6, thereby influencing a key pathway involved in regenerating liver cell proliferation and survival (207).

Omalizumab and mepolizumab have evidence for long-term safety above 5 years. For all the other biologicals there is evidence for long-term safety up until 2 years (table S2). Thus, post-marketing surveillance, especially collected through structured registries such as International Severe Asthma Registry (ISAR) or Severe Asthma Network in Italy (SANI), is of utmost importance (208, 209).

vi. Efficacy versus effectiveness in a real-world setting

Several reports show that a considerable proportion of patients with severe asthma remain uncontrolled and are not eligible for any of the available biological treatments (201). Of note patient selection for biologicals in real life might not be optimal: many omalizumab users have low

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or very low adherence rates for ICSs and/or ICS-LABA in the 12 months before omalizumab initiation compared the matched cohort of nonusers (210). In addition, there might be a selection bias as patients prescribed mepolizumab had a different prevalence of certain comorbidities such as CRSwNP, higher disease burden, higher healthcare resource utilization and costs compared with patients prescribed omalizumab (211,212). There is inequity in access to biologicals, as higher likelihood of use was related with middle age, higher income, commercial insurance, and access to a specialist (213).

A validated assessment tool is needed to adequately evaluate response to biologicals in real-world settings. The Real-life Effectiveness of Omalizumab Therapy study evaluated The Standardized Measure to Assess Response to Therapy (SMART), a tool designed to define response by physician's subjective assessment of asthma symptoms and control and objective assessment of 6 parameters (exacerbations, steroid bursts, emergency department visits, and hospitalizations; lung function; ACT score). True responders are defined as meeting both subjective and objective criteria (214).

vii. Efficacy and safety in the paediatric population with severe asthma

Omalizumab has good evidence for both for the 6-11- and the 12-17-years old subgroups. Data on the efficacy and safety of benralizumab, dupilumab and mepolizumab in the 12-17 years old patients with severe asthma subgroup are limited. Reslizumab has no paediatric data reported (table S2). Data are frequently extrapolated from adult trials and evidence for long-term use is lacking (215). The development of new drugs for the treatment of paediatric severe asthma proves difficult as: 1) criteria to diagnose severe asthma in children are ambiguous and require extensive step-by-step assessment; 2) there is a limited availability of a very heterogenous population to enter randomised placebo-controlled trials; 3) the requirements of the Paediatric Investigational Plan (EMA) or Paediatric Study Plan (FDA) are quite stringent. Registries like "Severe Paediatric Asthma Collaborative in Europe" (SPACE), the Severe asthma registry of the German Asthma Net or the Children's Health Foundation Paediatric Asthma Registry might prove of help. Large-scale international consortia evaluating severe paediatric asthma using unbiased methods such as multidimensional endotyping could help to overcome this major unmet need in the field of biologicals for asthma.

viii. Overall efficacy on asthma and its co-morbidities

There is high incidence of T2-driven co-morbidity in severe asthma cases such as chronic rhinosinusitis with nasal polyps (CRSwNP), allergic rhinitis, atopic dermatitis, food allergy,

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anaphylaxis, allergic conjunctivitis (216). A retrospective, observational study that assessed the efficacy of omalizumab in patients with asthma and other concomitant allergic diseases such as rhinosinusitis, atopic dermatitis, and allergic broncho-pulmonary aspergillosis showed improvement in symptoms of these allergic diseases (217). As all regulatory approved T2 biologicals are systemically bio available improving the overall patient wellbeing by acting on the non-airway targets should be further explored, both in RCTs and in real life studies. Currently dupilumab is approved for asthma, atopic dermatitis and chronic rhinosinusitis with nasal polyps and omalizumab is approved for asthma and chronic urticaria and is being assessed in allergic rhinitis, CRSwNP and food allergies. For the EAACI guidelines subgroup analysis for reported co-existing co-morbidities were performed and where possible recommendations were formulated for the use of the biological for severe asthma and associated co-morbidities.

ix. Impact on small airways disease

Severe asthma almost always involves small airways where inhaled drugs have difficult access (218,219). For benralizumab, dupilumab and mepolizumab there is evidence of improving small airways obstruction (77, 220, 221).

c. Additional major unmet needs and research priorities

The GDG proposed several key areas of interest both for the clinician and the basic researcher and from the health-care point of view (box 13). Unmet needs have been assessed from the perspectives of different stakeholders and in most past, converged (222).

Box 13: Gaps in evidence for the use of biologicals in severe asthma and plan to address

Gaps in evidence	Plan to address	Priority
Standardising the use of biologicals in clinical practice 1. Criteria for responders and suboptimal response (early stopping rules) 2. Switching rules 3. Duration of treatment in responders (late stopping rules) 4. Long-term treatment regimen in responders: longer interval, down-dosing, possibility of stopping treatment during the summer months, switch to strategies like topical application, etc. 5. Identification of factors related to failure 6. Efficacy in cases of prior failure to other biologicals 7. Routine measurement of ADA	Prospective trials testing the clinical question followed by validation in independent population	High

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Implementation of guidelines for the use of biologicals in clinical practice	In-depth education of HCPs on T2 inflammation recognising the involvement of both the innate and the adaptive immune system.	High
Long-term safety data	Well-structured post-marketing surveillance using severe asthma registries	High
Assess the long-term efficacy/disease modifying effect of biologicals in severe asthma (after treatment cessation)	Identify biomarkers related to the course of asthma (223) Well-designed RCT and real-life studies focusing on long-term efficacy Mechanistic studies at a single cell level	High
Efficacy and safety data in the paediatric population	RCT and RWE trials/registries focused primarily on the paediatric population	High
Cost-effectiveness of biologicals in severe asthma	Sectoral and generalised cost-effectiveness analysis, including the real-word perspective Long-term perspective as disease modifying intervention and thereby influence long-term cost	High
Identification of clinically relevant biomarkers in order to select responders to the current available biologicals	Proof of concept studies evaluating patient selection based on biomarkers	High
Impact of multi- morbidities (allergic rhinitis, atopic dermatitis, CRSwNP, food allergy, etc)	Studies evaluating the global effect of biologicals on multi- morbidities	High
Fair accessibility to severe asthma correct diagnosis and optimal targeted treatment	Reorganisation of severe asthma care Implementation of the patients' perspective from research to models of care Implementation of management pathways/clinical decision systems	High
Comparison between biologicals	Independent head-to-head comparison between biologicals, ideally with cross-over design	High
Alignment of studies (including RWE) with guidance from regulatory bodies.	Work in partnership with regulatory bodies to continuously review trial methodology and outcomes.	Medium
Correlation between biological and clinical response to biologicals	Well-designed RCT, example for personalised medicine	Medium
The impact of age on the short and the long-term effects (efficacy and safety) of treatment with biologics?	Well-designed RCT, example for personalised medicine	Medium
Does 'resistance' occur as in antibiotic or anti-cancer therapy and what are the underlying molecular mechanisms?	Well-designed RCT, example for personalised medicine	Medium

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Validation of different regimens: shorter or longer intervals ('pulse-wise') rather than as a chronic ('maintenance') therapy (e.g. to prevent resistance)?	RCTs and real-life studies testing different approaches in terms of dose, duration and route	Medium
Seasonal approach with other biologicals following the model of omalizumab	RCTs and real-life studies	Medium

VIII. Conclusion

The addition of targeted treatment for severe asthma based on phenotyping has proved of real value as is recommended by all contemporary guidelines on the management of severe asthma. This significant change in the management of severe asthma was supported by improved understanding of the contribution of immune-inflammatory mechanisms, followed by a relative fast development of biologicals and small molecules specifically targeting the innate and adaptive immune response. There are several critical points impacting the efficacy of this stratified approach, from the complexity of disease endotypes to the effectiveness in real-world settings. The EAACI Guidelines on the use of biologicals for uncontrolled severe asthma offers a desk reference tool for the healthcare providers, patients, regulators and healthcare systems based on a critical appraisal of the current evidence and a structured approach in formulating recommendations in alignment with the key principles of personalised medicine and implementation science.

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Figures and tables

Table 1. Monoclonal antibodies approved for severe asthma – targets and mechanism of action

Table 2. Summary of regulatory approvals for biologicals in severe asthma – European Medical Agency

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Table 4. Structured questions for the systematic reviews

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Table 6. Clinical questions not covered by the systematic reviews

Table 7. Interpretation of GRADE recommendations

Figure 1. Decision tree guiding biologicals use for patients with uncontrolled T2 severe asthma at the point of care

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This algorithm is based on a precise diagnosis of severe asthma uncontrolled under high intensity treatment after all other measures for reaching asthma control were implemented, as described in the GINA 2020 and the ERS/ATS guidelines

A three-pillar decision tree supports the clinician in reaching the decision to start on a particular biological based on the combination between **phenotypic traits**, **biomarkers** and clinically relevant **asthma-related end-points**, including safety (conditional recommendation, expert opinion based). Cost-related and regulatory aspects should also be considered in reaching the decision to start with a particular biological.

Re-evaluation of response should be done after 4-6 months (conditional recommendation, expert opinion based). As there is no consensus or validated criteria to define response the **definition of a suboptimal response relies on individualised predefined cut-offs of the selected outcomes established by informed shared decision** focused on the patient's goals to control its asthma, in alignment with the principles of personalised treatment (conditional recommendation, expert opinion based). Cost-related and regulatory aspects should also be considered in establishing the predefined goals.

I. For suboptimal response re-assessment of airway inflammation using induced sputum and airway hyperresponsiveness are recommended (conditional recommendation, expert opinion based).

A. If lung eosinophilia is not controlled the clinician is advised to address the following possibilities:

1. Patient is not adherent to the background controller treatment or to the general management plan installed to ensure optimal asthma control. The asthma management plan should be re-discussed with the patient.
2. Eosinophilia is not driven by the pathway targeted by the biological used. In this case consider switching to biologicals targeting a different pathway
3. Inadequate dosing. In this case consider switching to a biological targeting the same pathway but with different mechanism of action or route of administration

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4. Development of neutralising anti-drug antibodies (ADA). The titre, affinity, isotype and epitope mapping are important steps in characterising ADA. In this case consider switching to biologicals targeting a different pathway or to a biological targeting the same pathway but with different mechanism of action or route of administration

5. Other immune dysfunctions such as predominant ILC2 activation, autoimmune mechanisms or IL-5-anti-IL-5 complement activating immune complexes are driving the treatment-resistant lung eosinophilia. As these cases are very rare referral to a specialised centre after all other caused were excluded is recommended.

B. If at re-evaluation for suboptimal response there is no lung eosinophilia and neutrophilic inflammation is present the biological should be interrupted and measures addressing non-T2 asthma should be considered (conditional recommendation, expert opinion based). In case of no inflammation addressing airway hyperresponsiveness (LABA/LAMA combinations or bifunctional drugs) or airway remodelling (bronchial thermoplasty in selected cases) is recommended (conditional recommendation, expert opinion based).

II. In a patient with good response according to the individualised predefined targets **treatment should be continued**, pending on the cost-efficacy evaluation and local regulatory status, while continuously monitoring for efficacy and safety (conditional recommendation, expert opinion based).

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Table 1: Description of the biologicals included in the EAACI Guidelines	
Biological	Target and mechanism of action
Benralizumab	IgG1 kappa humanised monoclonal antibody. Binds to the α subunit of the IL-5 receptor (IL-5Rα) with inhibition of the hetero-oligomerization of α and β subunits and thus no signal transduction occurs. The afucosylated site of benralizumab enhances its binding to FcγRIIIa leading to antibody-dependent cell-mediated cytotoxicity by NK cells and macrophages. Depletes the eosinophils and reduces basophil levels.
Dupilumab	IgG4 human monoclonal antibody. Binds to the α subunit of the IL-4 receptor (IL-4Rα) shared by IL-4 and IL-13 receptor complexes, thus simultaneously inhibiting both IL-4- and IL-13-mediated signalling pathways. IL-4 and IL-13 are key cytokines for orchestration of type 2 immune responses. Simultaneous blocking of Type I receptor (IL-4Rα/γc) and Type 2 receptor (IL-4Rα/IL-13Rα) inhibit at the same time type 2 responses depending on IL-4 and IL-4/IL-13, respectively, in hematopoietic and non-hematopoietic cells.
Mepolizumab	IgG1 kappa humanised monoclonal antibody specific for IL-5. Binds to a specific epitope of IL-5 and prevents it from binding to IL-5Rα. Inhibits the maturation, activation, proliferation and recruitment of eosinophils.
Omalizumab	IgG1 kappa humanised monoclonal antibody. Binds to free IgE and inhibits the binding of IgE to both the high- and low-affinity IgE receptors (FcεRI and CD23, respectively). The reduction in surface bound IgE on FcεRI-bearing cells reduces the expression of this receptor in mast cells, basophils and dendritic cells, thus blocking the degree of release of cytokines and mediators of the allergic response and IgE-mediated presentation of Th2 cells. It also enhance the production of IFN-α by pDCs, thus reducing viral-induced exacerbations.
Reslizumab	IgG4 kappa humanised monoclonal antibody. Binds to a specific epitope IL-5 and prevents it from binding to IL-5Rα. The *in vitro* affinity of reslizumab for IL-5 is higher than mepolizumab and the capacity to suppress IL-5-dependent proliferation in vitro is also superior. Inhibits the maturation, activation, proliferation and recruitment of eosinophils.

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Table 2: EMA recommendations for the use of biologicals in severe asthma			
Product	Population	Posology	Remarks
Benralizumab (Fasenra®)	Add-on maintenance treatment in adult and adolescent patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS corticosteroids plus LABA.	30mg SC every 4 weeks for the first 3 doses, and then every 8 weeks thereafter.	Intended for long-term treatment. The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's disease severity and level of control of exacerbations. Special caution for helminth infections.
Dupilumab (Dupixent®)	Adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils (> 150) and/or raised FeNO >20), inadequately controlled with high dose ICS plus another maintenance treatment.	On OCS or with co-morbid AD, initial dose of 600 mg followed by 300 mg every other week SC. For all other patients, initial dose of 400 mg followed by 200 mg every other week SC.	Intended for long-term treatment. The need for continued therapy should be considered at least on an annual basis based on level of asthma control.
Mepolizumab (Nucala®)	Severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older.	> 12 years old 100 mg SC (pre-filled pen) once every 4 weeks. Children 6-11 years old 40 mg SC (powder for solution) once every 4 weeks.	Intended for long-term treatment. The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's disease severity and level of control of exacerbations.
Omalizumab (Xolair®)	>12 years old: add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and who have reduced lung function (FEV1<80%) as well as frequent daytime symptoms or night-time awakenings, and who have had multiple documented severe asthma exacerbations despite daily high-dose ICS + LABA. 6-12 years old: add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings, and who have had multiple documented severe asthma exacerbations despite daily ICS+LABA.	SC every 2-4 weeks based on total IgE level and body weight.	Intended for long-term treatment. Assessed for effectiveness at 16 weeks (GETE) before further injections are administered.
Reslizumab (Cinqaero®)	Adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus another maintenance treatment.	iv per body weight (see table)	Intended for long-term treatment. The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's disease severity and level of control of exacerbations.

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Table 3: FDA recommendations for the use of biologicals in severe asthma			
Product	Population	Posology	Remarks
Benralizumab (Fasenra®)	Add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype (blood eosinophil counts greater than or equal to 150 cells/µL).	30 mg administered SC once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter.	Caution for: 1. Hypersensitivity reactions 2. Helminth infections 3. Abrupt discontinuation of OCS or ICS
Dupilumab (Dupixent®)	Add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.	1. An initial dose of 400 mg followed by 200 mg given every other week. 2. An initial dose of 600 mg followed by 300 mg given every other week for patients requiring concomitant oral corticosteroids or with co-morbid moderate-to-severe atopic dermatitis start with an initial dose of 600 mg followed by 300 mg given every other week.	Caution for: 1. Hypersensitivity reactions 2. Helminth infections 3. Abrupt discontinuation of OCS or ICS 4. Eosinophilic conditions
Mepolizumab (Nucala®)	Add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype (blood eosinophils of ≥ 150 cells/mcL at screening (within 6 weeks of dosing) or blood eosinophils of ≥ 300 cells/mcL within 12 months of enrollment).	100 mg administered subcutaneously once every 4 weeks.	Caution for: 1. Hypersensitivity reactions 2. Helminth infections 3. Herpes zoster infections 4. Abrupt discontinuation of OCS or ICS
Omalizumab (Xolair®)	Moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or *in vitro* reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids.	75 to 375 mg SC 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 body weight (kg). See the dose determination charts.	Black box warning for anaphylaxis Caution for: 1. Abrupt discontinuation of OCS or ICS 2. Eosinophilic conditions 3. Serum sickness
Reslizumab (Cinqair®)	Add-on maintenance treatment of patients with severe asthma aged 18 years and older with an eosinophilic phenotype (blood eosinophil count of at least 400 cells/mcL within 3 to 4 weeks of dosing).	3 mg/kg once every 4 weeks administered by intravenous infusion over 20-50 minutes.	Black-box warming for anaphylaxis Caution for: 1. Helminth infections 2. Abrupt discontinuation of OCS or ICS

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Table 4: Structured questions for the systematic reviews
"Is the treatment with biologicals (i.e., benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) efficacious and safe for patients with uncontrolled severe eosinophilic asthma?"
"Is treatment with benralizumab, dupilumab and omalizumab efficacious and safe for patients with allergic asthma?"
"Is the treatment with dupilumab efficacious and safe for patients with severe asthma?"

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Table 5: Asthma-related outcomes; grading importance for the systematic reviews	
Outcome	Importance
Severe asthma exacerbations Asthma control Quality of life Safety (adverse events)	Critical
Lung function (FEV_1) Decrease in ICS dose and OCS dose Rescue medication use	Important
FeNO, sputum and blood eosinophils	Low importance

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Table 6: Clinical questions not covered by the systematic reviews

1. Dose not approved by FDA/EMA
2. Route not approved by FDA/EMA
3. Biological not approved by EMA/FDA
4. Relevance of clinical trial population for real-world patients
5. Efficacy in the paediatric population, especially 6-11 years old
6. Safety long term (> 5 years)
7. Safety in the paediatric population
8. Immunogenicity
9. Best method to monitor anti-drug antibodies (ADA)
10. Joint treatment of co-morbidities (asthma and CRSwNP or AR or AD)
11. Biomarkers
12. Continuation/discontinuation criteria
13. Switching rules
14. Defining efficacy; definition of responder, partial responder (dissociated outcome), non-responder
15. Time to achieve efficacy
16. Treatment duration
17. Combinations between biologicals
18. Effects after administration in the emergency department
19. Health economics data not included in the SR

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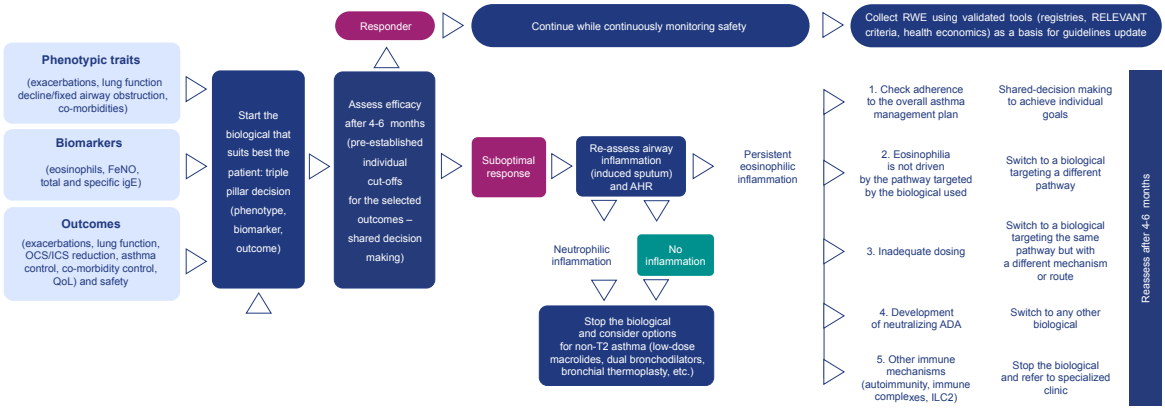
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Table 7: Interpretation of GRADE recommendations		
Implications	Strong recommendation	Conditional (weak) recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognise that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations	Policy making will require substantial debate and involvement of various stakeholders. Documentation of appropriate (e.g. shared) decision-making processes can serve as performance measure.

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Table S1: The EAACI Guidelines for Biologicals in Severe asthma – Guideline Development group

The Guideline Development Group is composed of the Core Leadership Team and the Voting Panel. The Methodology team provided support for the systematic reviews

Core Leadership Team	Voting Panel	Oversight Committee managing COI
Chairs: Ioana Agache (Romania), Oscar Palomares (Spain), Marek Jutel (Poland) Cezmi Akdis (Switzerland) Tomas Chivato (Spain) Stefano Del Giacco (Italy) Thomas Eiwegger (Canada) Liam O'Mahony (Ireland) Jurgen Schwarze (UK)	Mubeccel Akdis (Switzerland) Giorgio Walter Canonica (Italy) Thomas Casale (USA) Jonathan Corren (USA) Derek Chu (Canada) Breda Flood (Ireland) Davide Firinu (Italy) James E. Gern (USA) Eckard Hamelmann (Germany) Nicola Hanania (USA) Rebeca Knibb (UK) Mika Mäkelä (Finland) Irene Hernández Martín (Spain) Parameswaran Nair (Canada) Nikolaos G. Papadopoulos (Greece, UK) Alberto Papi (Italy) Hae-Sim Park (South Korea) Luis Pérez de Llano (Spain) Oliver Pfaar (Germany) Santiago Quirce (Spain) Joaquin Sastre (Spain) Mohamed Shamji (UK)	Chair: Barbara Rogala, Poland Joanna Gluck, Poland Maria Beatrice Bilo, Italy Glenis Scadding, UK Johannes Ring, Germany

Table S2: Additional evidence supporting recommendations not covered by the SR

	Benralizumab	Dupilumab	Omalizumab	Mepolizumab	Reslizumab
	References	References	References	References	References
Relevance of clinical trial population for real-world	No data	No data	See IDEAL study Busse NEJM 2011. The ICATA study screened 996 minority children in US urban centers and randomized	Bagnasco 2018 RWE population Older, less females, higher FEV1, NP, higher OCS and eos Plus see IDEAL study Llanos, J Asthma Allergy. 2019;12:43-58. In the 12 months prior to initiation of asthma-specific	Albers, J Asthma. 2018;55(2):152-160 The IDEAL study (cross-sectional, single-visit, observational study in six countries; 670 patients with severe asthma) Treatment eligibility defined according to the local prescribing information or protocol-defined inclusion/ exclusion criteria. Treatment eligibility for mepolizumab and omalizumab was higher than that

			419. The most common reason for exclusion was falling outside the omalizumab dosing table either due to excessive weight or serum IgE.	biologics, patients prescribed mepolizumab had a different prevalence of certain comorbidities, higher disease burden, higher HCRU, and higher healthcare costs compared with patients prescribed omalizumab. Jeimy, Allergy Asthma Clin Immunol. 2018 Nov 22;14:68. 128 patients with severe asthma from Canadian Allergist's practice : 1/3 qualified for all currently available biologics. 41-78% were eligible for at least one mAb. Patients were most likely to be eligible for mepolizumab.	for reslizumab. Although there was some overlap in treatment eligibility, the patient groups eligible for treatment with anti-IL-5 or anti-IgE therapies were often distinct
	Benralizumab	Dupilumab	Omalizumab	Mepolizumab	Reslizumab
Efficacy in the pediatric population	No data besides the 12-17 subgroup included in registration trials	No data besides the 12-17 subgroup included in registration trials	Rodrigo, Pediatr Allergy Immunol. 2015;26(6):551-6 SR of 3 RCTs; 1381 children and adolescents; ICS reduction protocol showed reduced number of exacerbations Folque 2019 RWE of efficacy Deschildre 2013 RWE benefit greater than that reported in clinical trials	Yancey 2019; subgroup analysis 12-18 years old Consistent with outcomes in the overall population, reduction in exacerbations Gupta JACI 2019, open-label, uncontrolled, repeat-dose extension study, 6-11 years, 52 weeks; reduced blood eosinophil counts and asthma exacerbations and improved asthma control across all treatment groups. Gupta, Pediatr Pulmonol. 2019;54(12):1957-1967 Mepo in 36 children 6 to 11 and eos ≥150 cells/μL at screening or ≥300 cells/μL last 12 months and ≥2 exacerbations in the prior year. Mepolizumab SC 40 or 100 mg provided bodyweight-adjusted drug exposure within twofold of target adult exposure as well as marked reductions to blood	No data

				eosinophil counts similar to adults	
	Benralizumab	Dupilumab	Omalizumab	Mepolizumab	Reslizumab
Safety long term (> 2 years) adult population	Busse 2019 Results from BORA up to 2 years	Data extrapolated from AD trials	Mansur 2017 RWE for safety for 60.7 ± 30.9 months (range 23-121) Singh, Ann Allergy Asthma Immunol. 2019;123(5):476-482 RWE for safety from the REALITY study (2004-2011); 198 patients	Results from COLUMBA up to 4.5 years Khurana, Clin Ther. 2019; 41(10):2041-2056 COSMEX: multicenter, open-label, long-term, Phase IIIb study enrolled 340 patients from COSMOS (52-week, open-label extension study that enrolled patients from MENSA and SIRIUS) To enter COSMEX, patients had to have life-threatening/seriously debilitating asthma before entering MENSA or SIRIUS and to demonstrate improvement with mepo. In COSMEX, patients received mepo as add-on therapy for up to 172 weeks (718 patient-years of additional exposure)	Virchow, J Allergy Clin Immunol Pract. 2019 Pooled analysis of 6 asthma clinical trials: 5 placebo-controlled (duration ≤52 weeks) and 1 open-label extension (up to 2 years of treatment). The incidence of AEs in patients on treatment for more than 12 months was no higher than in patients with shorter treatment durations.
	Benralizumab	Dupilumab	Omalizumab	Mepolizumab	Reslizumab
Safety in the pediatric population	No data	No data	Rodrigo, Pediatr Allergy Immunol. 2015;26(6):551-6 SR of 3 RCTs in 1381 children and adolescents The frequency of SAE similar to placebo; no evidence of increased risk of hypersensitivity reactions, nor malignant neoplasms. Folque 2019	Yancey 2019 Safety profile in adolescent patients was consistent with that seen in the overall population. Gupta JACI 2019, 6-11 years, 52 weeks; 90% on-treatment AEs; 23% SAEs. No SAEs treatment related. No fatal AEs. No specific patterns of AEs No ADA or neutralizing antibody responses were reported.	Virchow, J Allergy Clin Immunol Pract. 2019 Pooled analysis included 12-18 years old up to 2 years

			RWE of safety up to 6 years administra-tion Deschildre 2015 8% stopped omalizumab because of side-effects, 75% of which were fatigue following injection.		
	Benralizumab	Dupilumab	Omalizumab	Mepolizumab	Reslizumab
Immuno-genicity	Zeitlin 2018, ALIZE trial Benralizumab did not impair the antibody response to seasonal virus vaccination in asthma population 12-21 Pham 2016 Serum IL-5, eotaxin were decreased. No changes in TNF or IFN-γ Significant reductions in EDN and ECP concentrations, suggesting that cytotoxic granule proteins are not released following eosinophil depletiion. Sridhar 2019 Benralizumab is highly selective, modulating blood proteins or genes associated with eosinophils or basophils, especially in high eos patients (>	Blauvelt, J Am Acad Dermatol. 2019;80(1):158-167. Data from AD trials Dupilumab does not impact T-cell-dependent and T-cell-independent humoral immune responses to tetanus and meningococcal vaccines, IgE seroconversion to tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccination	Baker, AAPS J. 2016; 18(1):115-23. No correlation between either anaphylaxis or skin test reactivity and the presence of antibodies of IgE isotype to omalizumab. Sommerville, Curr Med Res Opin. 2014 Jan;30(1):59-66. Omalizumab in pre-filled syringes was not associated with immunogenicity . Mizuma 2015 Treatment with omalizumab increases tIgE and sIgE levels dependant on the baseline level; sIgE may be functional	Ortega 2019 data 3 RCTs (DREAM MENSA and SIRIUS and 2 open-label extension studies COSMOS and COLUMBA)	Mukherjee, Am J Respir Crit Care Med. 2018;197(1):38-46 Reduces anti-eosinophil peroxidase IgG

	300)				
	Benralizumab	Dupilumab	Omalizumab	Mepolizumab	Reslizumab
Best method to monitor ADA				Ortega 2019 screening, confirmation, and titration analysis	
Co-morbidities	No data	Bachert, J Allergy Clin Immunol Pract. 2019; 7(7):2447-2449. Subgroup analysis of patients with CRSwNP and comorbid asthma Dupilumab was associated with an improvement of both clinical and patient-reported NP-specific outcomes, and asthma-specific outcomes in patients with CRSwNP and comorbid asthma.	Bidder, Rhinology. 2018;56(1):42-45. Rapid improvement at 4 weeks and 16 weeks of treatment in both CRSwNP and asthma control. The improvement in CRSwNP similar to upper airway surgery. Gevaert 2013 Oma is effective in patient with asthma and NP, both allergic and non-allergic Gibson, Intern Med J. 2016;46(9):1054-62 Australian XOLAIR registry: Response in participants with comorbid obesity and CV disease was similar to those without these conditions. Hanania NA,	Albers 2019 Post hoc analysis of MENSA and MUSCA: Mepolizumab 100 mg SC has consistent clinical benefits across a range of BMIs: the fixed-dose regimen does not need weight-based dosing.	Weinstein J Allergy Clin Immunol Pract. 2019; 7(2):589-596 Post hoc analyses of pooled data from 2 BREATH phase 3 clinical trials Patients with self-reported CRSwNP, with and without aspirin sensitivity, are highly responsive to reslizumab for asthma-related outcomes.

			Chipps BE, Griffin NM, Yoo B, Iqbal A, Casale TB. Omalizumab effectiveness in asthma-COPD overlap: Post hoc analysis of PROSPERO. J Allergy Clin Immunol. 2019;143(4):1629-1633		
	Benralizumab	Dupilumab	Omalizumab	Mepolizumab	Reslizumab
Biomarkers		Corren, J Allergy Clin Immunol Pract. 2019 Greater efficacy observed in patients with elevated type 2 inflammatory biomarkers (Eos and FeNO) at baseline	Brooks 2019 Use of FeNO to identify omalizumab responders decreases the expected per-patient cost by nearly 50% Bhutani 2017 RWE (ASTERIX) FeNO predicts response Casale 2018 Baseline eos and severity criteria (exac, LF, ICS dose and LABA) predict response Casale 2019 RWE Prospero Omalizumab shows efficacy irrespective of the biomarker status	Albers 2019, Baseline blood eosinophil count as a predictor of treatment response, post-hoc analysis of MENSA and MUSCA: consistent clinical benefits in patients with baseline blood eosinophil counts ≥150 cells/μL Ayars 2013 Sputum hyaluronan values are reduced with mepolizumab and correlate with improved ACQ, FEV1 and decreased eos Harvey ES, et al. [published online ahead of print, 2020 Mar 5]. Eur Respir J. 2020;1902420. doi:10.1183/13993003.02420-2019 Format: Data from the Australian Mepolizumab Registry show that super-responders to mepolizumab had higher T2 inflammation and less co-morbidities	Mukherjee, Am J Respir Crit Care Med. 2018;197(1):38-46 Changes in sputum IL-5 and anti-eosinophil peroxidase IgG predicted response to reslizumab

			Hanania 2013 analysis of EXTRA; FeNO. Blood eos and periostin predict response Caminati 2019 RWE from NEONET Blood eosinophils predict responsiveness to omalizumab. Kawati Clin Ther. 2019; 41(10):1956-1971 RWE patients with allergic asthma could benefit from omalizumab regardless of pretreatment biomarker levels Brooks 2019 Use of FeNO to identify omalizumab responders decreases the expected per-patient cost by nearly 50% Bhutani 2017 RWE (ASTERIX) FeNO predicts response Casale 2018 Baseline eos		

			and severity criteria (exac, LF, ICS dose and LABA) predict response Casale 2019 RWE Prospero Omalizumab shows efficacy irrespective of the biomarker status Hanania 2013 analysis of EXTRA; FeNO. Blood eos and periostin predict response Caminati 2019 RWE from NEONET Blood eosinophils predict responsiveness to omalizumab. Kawati Clin Ther. 2019; 41(10):1956-1971 RWE patients with allergic asthma could benefit from omalizumab regardless of pretreatment biomarker levels, Sorkness JACI Pract 2013 Predictors of		

			omalizumab response in urban minority children included high exhaled nitric oxide, blood eosinophils and BMI.		
	Benralizumab	Dupilumab	Omalizumab	Mepolizumab	Reslizumab
The influence of background therapy (number and type)				Albers 2019 Posthoc analysis of Mensa; benefit across a wide range	
Patient selection on a biological	Chipps, Ann Allergy Asthma Immunol. 2019 post hoc analysis of pooled SIROCCO and CALIMA; benralizumab improved asthma related outocmes in patients with fixed airway obstruction		Mukherjee 2019 omalizumab is possibly inadequate to control sputum eosinophilia, and therefore may not have a steroid-sparing effect, especially in those maintained on OCS daily. Casale Allergy 2018 Baseline blood eos ≥300/μL and markers of asthma severity (emergency asthma treatment in prior year, asthma hospitalization in prior year, FEV1 <65% inhaled beclomethasone dipropionate	Humbert 2019: posthoc analysis of MENSA and MUSCA according to according to omalizumab eligibility and associated allergic characteristics shows mepolizumab efficacy regardless of the above criteria Comberiati, J Allergy Clin Immunol Pract. 2019;7(8):2689-2696. A smaller percentage of children with severe asthma were eligible for mepolizumab compared with their adult peers. Severe adult onset asthma has distinct phenotypic features that favor treatment with mepolizumab, including greater eosinophilia and NP	Nair J Allergy Clin Immunol Pract. 2019 Numerically greater improvements in OCS -dependent patients than the overall population. Having 2 or more versus 1 clinical asthma exacerbation in the previous 12 months was the strongest positive predictor of reduced exacerbation risk with reslizumab Carr, Allergy Asthma Proc. 2019;40(4):240-249 Post hoc analysis of two randomized, double-blind, placebo-controlled trials Reslizumab reduced lung-age deficit by 5 years Improvement in lung age correlated with improved quality of life. Brussselle, Pulm Pharmacol Ther. 2017; 43:39-45. Larger reductions in asthma exacerbations and larger improvements in lung function in patients with late versus early-onset asthma.

			dose ≥600 µg/day, and LABA use predict response to omalizumab Sposato, Eur J Intern Med. 2018;52:78-85; retrospective analysis of 340 patients Age, obesity, comorbidities, smoking habits, nasal polyps, allergic poly-sensitization might reduce Omalizumab effectiveness independently to other asthma-influencing factors.		
	Benralizumab	Dupilumab	Omalizumab	Mepolizumab	Reslizumab
Continuation/ discontinua-tion criteria			Bousquet 2014 GETE Sposato 2019 Higher blood eosinophil levels after omalizumab treatment associated with poorer asthma outcomes. Caminati 2016 RWE from NEO-NET: 32% drop-out rate due to patient decision or lack of efficacy	Lombardi 2019 4.2 % discontinuation rate in RWE, only 1 case for AE Cormier 2019; 2 case reports of loss of efficacy after several months or years of effective treatment. Loss of response is associated with recurrence of airway eosinophilia.	ACQ and FEV1

	Benralizumab	Dupilumab	Omalizumab	Mepolizumab	Reslizumab
Switching rules	Matsuno, Respir Med Case Rep. 2019 Jul 9;28:100899. three case reports whose asthma symptoms were rapidly improved by benralizumab following favorable response to mepolizumab. Benralizumab-induced eosinophil depletion contributed to clinical improvement of severe asthma after mepolizumab-induced eosinophil reduction; thus, prior favorable responses to mepolizumab may predict benralizumab efficacy.			Chapman 2019: non-responders to oma- switched to mepo -: 62% reduction in exacerbation rate and improvement in ACQ and SGRQ Bagnasco 2019, non-responders to oma switched to mepo: -81% decrease in exac rate and improve in FEV1, ACT, decrease in OCS	Mukherjee, Am J Respir Crit Care Med. 2018;197(1):38-46 Weight-adjusted IV reslizumab was superior to fixed-dose SC mepo- in attenuating airway eosinophilia in prednisone-dependent patients with asthma, with associated improvement in asthma control. Pérez de Llano 2019 weight-based intravenous reslizumab in patients who have previously failed therapy with omalizumab: improved ACT, decreased exacerbations and OCS
	Benralizumab	Dupilumab	Omalizumab	Mepolizumab	Reslizumab
Defining efficacy			Bousquet 2014 GETE Paganin 2017 FEV1, RV and RV/TLC improved at 6 months in responders patients and then remained stable for 2 years. Singh, Ann Allergy Asthma Immunol. 2019;123(5):476-482 The Standardized	Gunsoy 2029 Predefined reduction in: long-term (previous year) exacerbation frequency OCS and ICS dose. ACQ ?blood eos Predefined improvement in: FEV1 versus baseline QoL Drick 2018: FEV1 improvement, patient subjective evaluation, decrease in eos Farah 2019; early improvement in small airway function (Sacin) was associated with asthma control and may be a significant contributor to the therapeutic response.	Bateman 2016 ACQ and FEV1

			Measure to Assess Response to Therapy (SMART) tool; assessed in the REALITY study; real-life setting, long term (2004-2011); Response evaluated 1 year before to after treatment by 3 modules: (1) physician's subjective assessment of symptoms and control; (2) objective assessment of 6 parameters: improvement by 50% or more for asthma exacerbation, steroid bursts, emergency department visits, and hospitalizations; increase in FEV1 of 200 mL or greater; and improved Asthma Control Test score of 3 or higher; -and (3) true responders (patient meeting both module 1 and 2 criteria).	Antonicelli, Allergy 2019 Forced oscillation technique changes showed to correlate with both eosinophil counts and asthma control scores.	
	Benralizumab	Dupilumab	Omalizumab	Mepolizumab	Reslizumab

Time to achieve efficacy	Pelaia 2019 RWE Within 4 weeks improvement in LF and ACT, OCS stopped	Corren, J Allergy Clin Immunol Pract. 2019 Improvements evident by the first evaluation at week 2	Sorkness JACI Pract 2013. In urban minority children, the time of onset of omalizumab effect was <30 days.	Ortega 2018 Posthoc analysis of MUSCA and MENSA: > 150 fast effect (1st week) on morning PEF Pertzov 2019 within 6 months (composite end-point) Pelaia 2018 Within 4 weeks for LF, Eos, ACT and 24 weeks for exacerbations and OCS reduction Caminati 2019, RWE from RINOVA The greatest clinical change (ACT and FEV1) was observed within the first month.	No data
Treatment duration	No data	No data	Molimard 2014 A treatment of longer than 3.5 years was associated with no loss of control during the following 6 months. Pace 2011 marked improvement in clinical parameters and lung function in seven severe asthmatic patients after a 7-year course of omalizumab Ledford 2017, X- PORT: discontinuation after a 5- year course of oma-in adults. A higher blood eosinophil count at baseline and a	Ortega; Allergy Asthma Clin Immunol. 2019 ;15:37. Follow up of COSMOS; Cessation of mepolizumab was associated with a rise in the blood eosinophil count and loss of asthma control 12 weeks after stopping therapy. 4.5 years extension of DREAM shows NO evidence that any continuation rule adds value to established initiation criteria for mepolizumab	No data

			significant increase in FeNO from baseline to week 12 after discontinuation were associated with clinical deterioration Deschildre 2019 RWE for discontinuation of omalizumab in children allergic multimorbidity and decreased lung function argue for treatment continuation. Discontinuation could be safely proposed after long- term use (>2 years) in children with nonactive allergic disease, prolonged controlled asthma, and no severe exacerbations for at least one year. Deschildre 2015 After 2 years, pediatric population persistent positive effect on the severe exacerbation rate, and a		

			modest effect on asthma control in the children who continued omalizumab but lack of further lung function improvement 20.7% cessation during the second year due to treatment failure, patients' own decisions and loss to follow-up Colombo 2019 AQLQ showed a clear increase over time, following 9 years of observation Singh, Ann Allergy Asthma Immunol. 2019;123(5):476-482 RWE for long-term efficacy from the REALITY study (2004-2011); 198 patients OMADORE STUDY (A step-down protocol for omalizumab treatment in oral		

			corticosteroid-dependent allergic asthma patients Domingo et al. Br J Clin Pharmacol 2917). The OMADORE study found that in more than 50% of Severe Allergic Asthma patients on Oral Corticosteroids, OMALIZUMAB dose can be safely reduced or withdrawn based on a progressive dose reduction protocol. Exacerbations did not occur during the 18-30 month follow-up after drug withdrawn.		
	Benralizumab	Dupilumab	Omalizumab	Mepolizumab	Reslizumab
Combinations between biologicals				Altman MC, JACI -P 2017: mepolizumab as an additional and effective treatment option for severe ABPA resistant to corticosteroids, antifungal therapy, and omalizumab. The case-report demonstrates a potentially synergistic effect of using mepolizumab with omalizumab	
	Benralizumab	Dupilumab	Omalizumab	Mepolizumab	Reslizumab

Other potential indications	Nowak 2015 1 dose of benralizumab reduced the rate and severity of exacerbations experienced over 12 weeks by subjects who presented to the ED with acute asthma Ferguson 2017 BISE trial in mild to moderate asthma Some effect on lung function although did not reach the MID				
effects after administration in ED	Nowak RM, et al. Am J Emerg Med. 2015;33(1):14-20. Randomized, double-blind, placebo-controlled study; subjects presented to the ED with an asthma exacerbation, had partial response to treatment, and greater than or equal to 1 additional exacerbation within the previous year. 1 iv infusion of benralizumab added to outpatient management reduced the rate and severity of exacerbations over the next 12 weeks				
RWE			Brusselle 2009, PERSIST study: greater efficacy compared to RCTs Pelaia 2019: 5 years reduce exac, eos and OCS, improves	Caminati 2019, RINOVA data, significant improvement in exacerbation rate and decrease in OCS + safety + ACT, FeNO, LF Bagnasco; Pulm Pharmacol Ther. 2019 ;58:101836. retrospective analysis was performed on 138 patients,	

			ACT and LF Bhutani 2017 ASTERIX study: reduce exac and OCS, improves control and QoL Adachi 2018 post-marketing surveillance for oma 52 weeks, safety and efficacy proved, including elderly population Brodlie 2012 OCS-sparing effect equal in children <12 and >12 Rottem 2012 RWE for reducing OCS	treated with mepolizumab for at least 12 months, and referred to eleven severe asthma clinics in Italy. exacerbation rate, systemic steroids intake and safety similar to clinical trials Pertzov, J Asthma. 2019 Sep 3:1-6 Prospective observational trial in 61 patients >18 years treated with mepolizumab between March 2016 to March 2019; well tolerated and significantly lowered the exacerbation rate and OCS Harvey ES, et al. [published online ahead of print, 2020 Mar 5]. Eur Respir J. 2020;1902420. doi:10.1183/13993003.02420-2019 Format: Data from the Australian Mepolizumab Registry show that mepolizumab therapy effectively reduces the significant and long-standing disease burden faced by patients with severe eosinophilic asthma in a real-world setting	
	Benralizumab	Dupilumab	Omalizumab	Mepolizumab	Reslizumab
Health economics			Shaker, J Allergy Clin Immunol Pract. 2019, at-home administration of omalizumab may be a cost-effective strategy. Sullivan, Curr Med Res Opin. 2019 Based on RW	García-Mochón, Farm Hosp. 2019;43(6):187-193. Prioritizing mepo use for non Ig E-mediated severe refractory eosinophilic asthma with ≥ 500 eosinophils/µL improve its efficiency as well as reduces its budgetary impact. Shaker, J Allergy Clin Immunol Pract. 2019, at-home administration of mepolizumab may be a cost-effective strategy.	

			outcomes omalizumab may be cost-effective for uncontrolled asthma from the US payer perspective. Entrenas, Pharmacoecon Open. 2019 ; 3(3):333-342 RWE, 220 patients Omalizumab effective add-on therapy for patients with persistent severe asthma allowing reducing key drivers of asthma-related costs.		

Table S3: Summary of findings for benralizumab compared to standard of care for eosinophilic asthma

Outcomes	№ of participants (studies) Follow-up (range)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with benralizumab
Exacerbations Assessed with annualised asthma exacerbation rate	1373 (3 RCTs) [39,40,,41] 28 to 56 weeks	⊕⊕⊕⊕ HIGH [3,a,b]	Incidence r**ate ratio 0.53** (0.39 to 0.72) [c,d]	1500 exacerbations per 1000 patients per year	**705 fewer exacerbations per 1.000 patients per year** (915 fewer to 420 fewer)
Asthma Control Assessed with ACQ-6 score between-group-difference at the end of the study	1373 (3 RCTs) [39,40,,41] 28 to 56 weeks	⊕⊕⊕⊕ HIGH [3,4,b,e,f]	-		mean difference **– 0.26** (- 0.46 to - 0.07) [c,g]

Table S3: Summary of findings for benralizumab compared to standard of care for eosinophilic asthma

Outcomes	№ of participants (studies) Follow-up (range)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with benralizumab
Quality of life Assessed with Asthma Quality of Life Questionnaire for 12 years and older	1333 (3 RCTs) [39,40,,41] 28 to 52 weeks	⊕⊕⊕⊕ HIGH [3,6,b,j,k]	-		mean difference+ **0.23** (+0.11 to +0.36) [c]
Any drug related adverse event (AE) Assessed with number of events	478 (1 RCT) [40] 56 weeks	⊕⊕⊕◯ MODERATE [3,b,l]	**Risk ratio 1.41** (0.87 to 2.27)	105 per 1.000	**43 more per 1.000** (14 fewer to 133 more)
Any serious adverse event (SAE) unrelated to asthma exacerbation Assessed with number of events	148 (1 RCT) [41] 28 weeks	⊕⊕◯◯ LOW [3,b,l]	**Risk ratio 0.56** (0.22 to 1.44)	147 per 1.000	**65 fewer per 1.000** (114 fewer to 65 more)
Decrease in OCS use Assessed with reduction in daily OCS dose of ≥50%	148 (1 RCT) [41] 28 weeks	⊕⊕⊕⊕ HIGH [3,b]	**Risk ratio 1.76** (1.26 to 2.47)	373 per 1.000	**284 more per 1.000** (97 more to 549 more)
Lung function Assessed with pre-bronchodilator FEV1 (mL) between-group-difference at the end of the study	1370 (3 RCTs) [39,40,,41] 28 to 56 weeks	⊕⊕⊕◯ MODERATE [3,4,5,b,h,i]	-		mean difference +**140 mL** (+90 to +190) [c]
Rescue medication use Assessed with puffs/day	0 studies	-	not estimable		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: High confidence that the true effect lies close to that of the estimate of the effect
Moderate certainty: Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
Very low certainty: Little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Statistically significant (I2=65%) but probably unimportant heterogeneity.

b. All included studies were funded by industry, and all showed positive results. No industry-independent observational or randomized studies were identified to contrast results. Therefore, the quality of the evidence was downgraded for potential publication bias
c. The pooled data were assessed at 28 weeks (41) and at 48-52 weeks (71). Goldman 2017 included patients aged 12-17 years old.
d. In the current systematic review 2 studies reporting the effect on exacerbation leading to emergency room visits or hospitalizations were also included. The pooled risk ratio was 0.24 (95% CI 0.03-1.72)
e. Statistically significant (I^2=61%) but probably unimportant heterogeneity.
f. The minimal important difference (MID) for ACQ-6 is 0.5 points
g. In the current systematic review 3 studies reporting the effect on total asthma control score change were also included. The pooled mean difference was -0.19 (95CI% -0.31 to -0.08), see full text report.
h. Quality of the evidence was downgraded because FEV_1 is considered a surrogate outcome for asthma control, with a variable correlation with asthma symptoms.
i. The GDG agreed that minimal important difference for FEV_1 is 0.20 L.
j. Statistically significant (I2=55%) but probably unimportant heterogeneity.
k. For AQLQ(S)+12 the MID is 0.5
l. The effect may both be harmful or beneficial. Small sample size and number of events.

Table S4: Economic evaluation of benralizumab added to standard therapy vs. standard therapy – adults with eosinophilic asthma

Quality assessment							Summary of resources and costs			Quality
Nº. of studies	**Study design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Incremental cost per patient***	**Incremental effect per patient***	**ICER**	
ICER per QALY (high quality study - not funded by Industry)										
1[a]	Cost-utility, Markov model	Not serious[1]	Not serious	Serious[2]	Serious[3]	Not serious	581,000 $ (lifetime horizon)	1.41 QALYs (lifetime horizon)	412,000 $ / QALY[4]	⊕⊕⊕◯ MODERATE
ICER per QALY (high quality study - funded by Industry)										
1[b]	Cost-utility, Markov model	Not serious[5]	Not serious	Serious[6]	Serious[7]	Not serious	NR £ (lifetime horizon)	NR QALYs (lifetime horizon)	39,135 £ / QALY[4]	⊕⊕◯◯ LOW

*Incremental cost and effect due to the addition of benralizumab.
ICER: Incremental cost-effectiveness ratio. QALY: Quality adjusted life years. $: US Dollar. £: British pounds. NR: Not reported.

1. Markov model study with low risk of bias (CHEC score 13 or higher).
2. One single study performed in the USA. The results may not be applicable to other countries.
3. The deterministic sensitivity analysis showed large variations in the ICER value from 250,000 $ to 950,000 $ (0.85 to 0.81 utilities gained, respectively). Furthermore, at a threshold of 50,000, the probability for benralizumab to be cost-effective was 0%.
4. The incremental cost-effectiveness ratio drops substantially from ~400k/ QALY to ~200k/QALY when the responder definition is factored into the cost-effectiveness model.
5. One single study performed in the UK. The results may not be applicable to other countries.
6. The ICER varied from 34,270 £ reported by AstraZeneca to 73,560 £ found by the University of Exter in the deterministic sensitivity analysis (zero asthma related mortality).
7. AstraZeneca financed the original model critiqued by the University of Exeter. The University explored ICER sensitivity through changes in the age-stratified probabilities for hospitalised patients, oral corticosteroids use at baseline (42%), administration cost of benralizumab, and treatment discontinuation rate (0.0041/cycle).

References

a. ICER. Institute for Clinical and Economic Review. Biologic Therapies for Treatment of Asthma Associated with Type 2 inflammation: Effectiveness, Value, and Value-Based Price Benchmarks. Available at: https://icer-review.org/material/asthma-final-evidence-report/. Accessed Sept, 2019.
b. Tikhonova I, et al. Benralizumab for treating severe asthma: A Single Technology Appraisal. Peninsula Technology Assessment Group (PenTAG), 2018.

Table S5: Evidence to decision table supporting recommendations for benralizumab for severe eosinophilic asthma in adults (exacerbations and OCS reduction)

	Judgement						
Problem (importance)	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No studies included
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	no important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No studies included
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No studies included
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Table S6: Evidence to decision table supporting recommendations for benralizumab for severe eosinophilic asthma in adults (asthma control, QoL)

	Judgement						
Problem (importance)	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know

Certainty of evidence	**Very low**	**Low**	**Moderate**	**High**			**No studies included**
Values	**Important uncertainty or variability**	**Possibly important uncertainty or variability**	**Probably no important uncertainty or variability**	**no important uncertainty or variability**			
Balance of effects	**Favors the comparison**	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	**Favors the intervention**	**Varies**	**Don't know**
Resources required	**Large costs**	**Moderate costs**	**Negligible costs and savings**	**Moderate savings**	**Large savings**	**Varies**	**Don't know**
Certainty of evidence of required resources	**Very low**	**Low**	**Moderate**	**High**			**No studies included**
Cost effectiveness	**Favors the comparison**	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	**Favors the intervention**	**Varies**	**No studies included**
Equity	**Reduced**	**Probably reduced**	**Probably no impact**	**Probably increased**	**Increased**	**Varies**	**Don't know**
Acceptability	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Feasibility	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**

Table S7 Evidence to decision table supporting recommendations for benralizumab for severe eosinophilic asthma in adults (lung function)

	Judgement						
Problem (importance)	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Desirable Effects	**Trivial**	**Small**	**Moderate**	**Large**		**Varies**	**Don't know**
Undesirable Effects	**Large**	**Moderate**	**Small**	**Trivial**		**Varies**	**Don't know**
Certainty of evidence	**Very low**	**Low**	**Moderate**	**High**			**No studies included**
Values	**Important uncertainty or variability**	**Possibly important uncertainty or variability**	**Probably no important uncertainty or variability**	**no important uncertainty or variability**			
Balance of effects	**Favors the comparison**	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	**Favors the intervention**	**Varies**	**Don't know**
Resources required	**Large costs**	**Moderate costs**	**Negligible costs and savings**	**Moderate savings**	**Large savings**	**Varies**	**Don't know**

Certainty of evidence of required resources	Very low	Low	Moderate	High			No studies included
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Table S8 – benralizumab efficacy stratified according to blood eosinophils

Blood eosinophils	Exacerbations – Incidence rate ratio (95% CI)	FEV1 increase – MD (95% CI)	Asthma control (ACQ5) MD (95% CI)	QoL improvement MD (95% CI)
150-299	0.77 (0.55-1.08)	+ 0.06 (-0.04 to 0.16)	- 0.18 (-0.3 to -0.06)	+ 0.19 (0.07 - 0.31)
300 - 499	0.69 (0.51-0.93)	+ 0.03 (-0.05 to 0.12)	-0.29 (-0.43 to -0.15)	+ 0.30 (0.15 - 0.45)
>500	0.5 (0.39 -0.64)	+ 0.22 (0.15 to 0.29)	-0.31 (-0.53 to -0.17)	+ 0.35 (0.17 – 0.53)

Table S9 – benralizumab efficacy stratified according to atopic status and serum IgE

Atopic status	Exacerbations – Incidence rate ratio (95% CI)	FEV1 increase – MD (95%CI)
yes	0.66 (0.54 – 0.81)	+ 0.11 (0.03-0.19)
no	0.58 (0.45 – 0.75)	+ 0.18 (0.08-0.28)
IgE <150	0.58 (0.45 – 0.75)	+ 0.12 (0.04-0.2)
IgE >150	0.57 (0.41 – 0.79)	+ 0.14 (0.04-0.23)

Table S10 – benralizumab efficacy stratified according to co-morbidities (CRSwNP)

CRSwNP	Exacerbations – Incidence rate ratio (95% CI)	FEV1 increase – MD (95%CI)
With	0.45 (0.31-0.68)	0.27 (0.12-0.42)
Without	0.62 (0.49-0.78)	0.10 (0.03-0.17)

Table S11: Summary of findings for benralizumab efficacy and safety compared to standard of care for allergic asthma

Outcomes	№ of participants	Certainty of the	Relative effect	Anticipated absolute effects

	(studies) Follow-up	evidence (GRADE)	(95% CI)	Risk with standard of care	Risk difference with Benralizumab
Exacerbations assessed with annual asthma exacerbation rate	297 (2 RCTs) [34] 48 weeks to 56 weeks	⊕⊕⊕⊕ HIGH [2,a]	**Incidence rate ratio 0.63** (0.50 to 0.81)	13 per 1.000	**5 fewer per 1.000** (6 fewer to 2 fewer)
Asthma Control assessed with: ACQ-6 score between-group-difference at the end of treatment	414 (2 RCTs) [34] 48 weeks to 56 weeks	⊕⊕⊕⊕ HIGH [2,3,a,b]	-	The mean asthma Control was **0**	MD - **0.17** (-0.34 to 0)
Quality of Life assessed with: Quality of Life Questionnaire for 12 years and older [AQLQ(S)+12], between-group-difference at the end of treatment	404 (2 RCTs) [34] 48 weeks to 56 weeks	⊕⊕⊕⊕ HIGH [2,5,a,e]	-	The mean quality of Life was **0**	MD +**0.1** (-0.08 to +0.28)
Any drug related adverse event assessed with: Number of events- Urgent care visit, or admission to hospital	478 (1 RCT) [35] 56 weeks	⊕⊕◯◯ LOW [2,a,f,g]	**Risk ratio 1.41** (0.87 to 2.27)	105 per 1.000	**43 more per 1.000** (14 fewer to 133 more)
Any drug related serious adverse event assessed with: Number of SAE unrelated to asthma exacerbation	148 (1 RCT) [36] 28 weeks	⊕⊕◯◯ LOW [2,a,f,g]	**Risk ratio 0.56** (0.22 to 1.44)	147 per 1.000	**65 fewer per 1.000** (114 fewer to 65 more)
Lung function assessed with: Pre-bronchodilator FEV1 (mL) between-group-difference at the end of treatment)	490 (2 RCTs) [34] 48 weeks to 56 weeks	⊕⊕⊕◯ MODERATE [2,3,4,a,c,d]	-	The mean lung function was **0** L	MD + **0.055 L** (-0.025 to + 0.136)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: High confidence that the true effect lies close to that of the estimate of the effect
Moderate certainty: Moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect
Very low certainty: Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Explanations

a. Included studies were all funded by industry, and all showed positive results. No industry-independent observational or randomized studies were identified to contrast the results. Therefore, evidence was downgraded for potential publication bias (102).
b. For ACQ-6 the minimal important difference is 0.5 points (30)
c. Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a variable correlation with asthma symptoms (103).
d. The effect may both be harmful or beneficial. The minimal important difference (MID) for FEV1 is 0.20 L (Guidelines development group consensus).
e. For AQLQ(S) + 12 the minimal important difference is 0.5 (32)

f. Downgraded one level due to indirectness (data from severe asthma patients that may have or may have not allergic asthma)
g. The effect may both be harmful or beneficial. Estimations are based on less than 300 events, thus there is probably important imprecision.

Table S12: economic evaluation of benralizumab in addition to standard therapy vs. standard therapy for adults with severe allergic asthma

Quality assessment							Summary of resources and costs			Quality
Nº. of studies	**Study design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Incremental cost per patient***	**Incremental effect per patient***	**ICER**	
ICER per QALY (high quality study - not funded by Industry)										
1[a]	Cost-utility, Markov model	Not serious[1]	Not serious	Serious[2]	Serious[3]	Not serious	581,000 $ (lifetime horizon)	1.41 QALYs (lifetime horizon)	412,000 $ / QALY[4]	⊕⊕⊕◯ MODERATE
ICER per QALY (high quality study - funded by Industry)										
1[b]	Cost-utility, Markov model	Not serious[5]	Not serious	Serious[6]	Serious[6]	Not serious	NR £ (lifetime horizon)	NR QALYs (lifetime horizon)	39,135 £ / QALY[4]	⊕⊕◯◯ LOW

*Incremental cost and effect due to the addition of Benralizumab.
ICER: Incremental cost-effectiveness ratio. QALY: Quality adjusted life years. $: US Dollar. £: British pounds. NR: Not reported.

1. Markov model study with low risk of bias (CHEC score 13 or higher).
2. One single study performed in the USA. The results may not be applicable to other countries.
3. The deterministic sensitivity analysis showed large variations in the ICER value from 250,000 $ to 950,000 $ (0.85 to 0.81 utilities gained, respectively). Furthermore, at a threshold of 50,000, the probability for benralizumab to be cost-effective was 0%.
4. The incremental cost-effectiveness ratio drops substantially from ~400k/ QALY to ~200k/QALY when the responder definition is factored into the cost-effectiveness model.
5. One single study performed in the UK. The results may not be applicable to other countries.
6. The ICER varied from 34,270 £ reported by AstraZeneca to 73,560 £ found by the University of Exter in the deterministic sensitivity analysis (zero asthma related mortality).

AstraZeneca financed the original model critiqued by the University of Exeter. The University explored ICER sensitivity through changes in the age-stratified probabilities for hospitalised patients, oral corticosteroids use at baseline (42%), administration cost of benralizumab, and treatment discontinuation rate (0.0041/cycle

Table S13 Evidence to decision table supporting recommendations for benralizumab for severe allergic asthma in adults (exacerbations)

	Judgement						
Problem (importance)	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Desirable Effects	**Trivial**	**Small**	**Moderate**	**Large**		**Varies**	**Don't know**
Undesirable Effects	**Large**	**Moderate**	**Small**	**Trivial**		**Varies**	**Don't know**
Certainty of evidence	**Very low**	**Low**	**Moderate**	**High**			**No included studies**

Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	no important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Table S14 Evidence to decision table supporting recommendations for benralizumab for severe allergic asthma in adults (asthma control, QoL)

	Judgement						
Problem (importance)	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	no important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know

Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Table S15 Evidence to decision table supporting recommendations for benralizumab for severe allergic asthma in adults (lung function)

	Judgement						
Problem (importance)	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	no important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know

Acceptability	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Feasibility	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**

Table S16: Summary of findings of Dupilumab compared to standard of care for eosinophilic asthma

Outcomes	№ of participants (studies) Follow-up (range)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with dupilumab
Exacerbations Assessed with annualised asthma exacerbation rate	1712 (3 RCTs) [42,43,44] 24 to 52 weeks	⊕⊕⊕⊕ HIGH[4,a,b]	**Incidence rate ratio 0.44**(0.32 to 0.59)	1570 exacerbations per 1000 patients per year	**894 fewer exacerbations per 1000 patients per year** (1086 fewer to 655 fewer)[c]
Asthma control assessed with: Asthma Control Questionnaire -5 Scale from: 1 to 5	507 (1 RCT) [42] 24 weeks	⊕⊕⊕◯ MODERATE [4,8,a,b,g]	-		mean difference - **0.48** (-0.88 to - 0.09)
Quality of life Assessed with asthma Quality of Life Questionnaire Scale from: 1 to 7	958 (2 RCTs) [43,44] 24 to 52 weeks	⊕⊕⊕◯ MODERATE [4,9,a,b,h]	-		mean difference + **0.42** (+0.25 to +0.59)
Treatment-related adverse events (AE) Assessed with number of events	264 (1 RCT) [42] 24 weeks	⊕⊕⊕◯ MODERATE [4,a,b,m]	**Risk ratio 1.00** (0.88 to 1.13)	794 per 1.000	**0 fewer per 1.000** (95 fewer to 103 more)
Treatment-related serious adverse events (SAE) Assessed with number of events	264 (1 RCT) [42] 24 weeks	⊕⊕◯◯ LOW [4,a,b,m]	**Risk ratio 1.46** (0.60 to 3.54)	59 per 1.000	**27 more per 1.000** (24 fewer to 149 more)
Decrease in OCS dose Assessed with percentage of reduction compared to baseline	150 (1 RCT) [42] 24 weeks	⊕⊕⊕⊕ HIGH [4,a,b]	-		mean difference - **29.4 %** (-43.23 to -15.57)
Lung function Assessed with FEV1 in mL	1030 (3 RCTs) [42,43,44] 24 to 52 weeks	⊕⊕◯◯ LOW [4,5,6,7,a,b,d,e,f]	-		mean difference + **180 mL** (+110 to +250)
Fraction of exhaled nitric oxide Assessed with mean % change (ppb) from baseline	150 (1 RCT) [42] 24 weeks	⊕⊕◯◯ LOW [4,10,11,12,a,b,i,j]	-		mean difference - **40.11 %** (-78.68 to -1.55)

Table S16: Summary of findings of Dupilumab compared to standard of care for eosinophilic asthma					
Outcomes	**№ of participants (studies) Follow-up (range)**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with standard of care	**Risk difference with dupilumab**
Rescue medication use Assessed with puffs/day	143 (1 RCT) [42] 24 to 52 weeks	⊕⊕⊕◯ MODERATE [4,7,a,b,k,l]	-		mean difference - **0.56 puff/day** (-2.28 to +1.16)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: High confidence that the true effect lies close to that of the estimate of the effect
Moderate certainty: Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
Very low certainty: Little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. All included studies had a high risk of selective reporting bias (42,43,44). However, the evidence quality was not downgraded because most of the outcomes of interest for our analysis were reported.
b. All included studies were founded by industry and the same company (Sanofi and Regeneron Pharmaceuticals), and all showed positive results. No industry-independent observational or randomized trials were identified to contrast the results. Therefore, the quality of the evidence was downgraded for potential publication bias (70)
c. Two studies (Rabe 2018, Wenzel 2016) assessed exacerbations at 24 weeks, and Castro2018 at 52 weeks.
d. The quality of the evidence was downgraded because FEV1 is considered a surrogate outcome of asthma control, with a variable correlation with asthma symptoms (72).
e. The panel agreed that minimal important difference (MID) for FEV1 is 0.20 L and considered the effect as imprecise.
f. The panel agreed that minimal important difference (MID) for FEV1 is 0.20 L and thus the effect was considered as imprecise.
g. Downgraded because the effect of dupilumab is beneficial but the lower side of the CI is less than the MID(0.5 points). (37)
h. Downgraded because the effect of dupilumab is beneficial but the lower side of the CI is less than the MID(0.5 points). (37)
i. Downgraded because FeNO is not consistently considered a good surrogate of eosinophilic inflammation (73,74)
j. From one visit to the next a change greater than 20% for basal values over 50 ppb or more than 10 ppb for basal values lower than 50 ppb may indicate significant response (38).
k. Downgraded because the effect may both be beneficial and harmful.
l. The MID for rescue medication use is a reduction by 0.81 puffs/day (35).
m. The effect may both be harmful or beneficial. Small number of events.

Table S17: Health economic evaluation dupilumab in addition to standard therapy vs. standard therapy in adults with eosinophilic asthma

Quality assessment							Summary of resources and costs			Quality
Nº. of studies	**Study design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Incremental cost per patient***	**Incremental effect per patient***	**ICER**	
ICER per QALY (high quality study - not funded by Industry)										
1[a]	Cost-utility, Markov model	Not serious[1]	Not serious	Serious[2]	Serious[3]	Not serious	704,000 $ (lifetime horizon)	1.51 QALYs (lifetime horizon)	464,000 $ / QALY[4]	⊕⊕⊕◯ MODERATE

*Incremental cost and effect due to the addition of Dupilumab.
ICER: Incremental cost-effectiveness ratio. QALY: Quality adjusted life years. $: US Dollar.

1. Markov model study with low risk of bias (CHEC score 13 or higher).
2. One single study performed in the USA. The results may not be applicable to other countries.
3. The deterministic sensitivity analysis showed large variations in the ICER value from 300,000 $ to 1,000,000 $ (0.85 to 0.81 utilities gained, respectively). Furthermore, at a threshold of 50,000, the probability for Dupilumab to be cost-effective was 0%.
4. The incremental cost-effectiveness ratio drops substantially from ~400k/ QALY to ~200k/QALY when the responder definition is factored into the cost-effectiveness model.

References

c. ICER. Institute for Clinical and Economic Review. Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks. Available at: https://icer-review.org/material/asthma-final-evidence-report/. Accessed Sept, 2019.

Table S18: Evidence to decision table supporting recommendations for dupilumab for eosinophilic asthma in adults (exacerbations)

	Judgement						
Problem (importance)	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Desirable Effects	**Trivial**	**Small**	**Moderate**	**Large**		**Varies**	**Don't know**
Undesirable Effects	**Large**	**Moderate**	**Small**	**Trivial**		**Varies**	**Don't know**
Certainty of evidence	**Very low**	**Low**	**Moderate**	**High**			**No included studies**
Values	**Important uncertainty or variability**	**Possibly important uncertainty or variability**	**Probably no important uncertainty or variability**	**no important uncertainty or variability**			
Balance of effects	**Favors the comparison**	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	**Favors the intervention**	**Varies**	**Don't know**
Resources required	**Large costs**	**Moderate costs**	**Negligible costs and savings**	**Moderate savings**	**Large savings**	**Varies**	**Don't know**
Certainty of evidence of required resources	**Very low**	**Low**	**Moderate**	**High**			**No included studies**
Cost effectiveness	**Favors the comparison**	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	**Favors the intervention**	**Varies**	**No included studies**
Equity	**Reduced**	**Probably reduced**	**Probably no impact**	**Probably increased**	**Increased**	**Varies**	**Don't know**
Acceptability	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Feasibility	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**

Table S19: Evidence to decision table supporting recommendations for dupilumab for severe eosinophilic asthma in adults (asthma control, QoL, lung function, rescue medication reduction)

	Judgement						
Problem (importance)	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Desirable Effects	**Trivial**	**Small**	**Moderate**	**Large**		**Varies**	**Don't know**
Undesirable Effects	**Large**	**Moderate**	**Small**	**Trivial**		**Varies**	**Don't know**
Certainty of evidence	**Very low**	**Low**	**Moderate**	**High**			**No included studies**
Values	**Important uncertainty or variability**	**Possibly important uncertainty or variability**	**Probably no important uncertainty or variability**	**no important uncertainty or variability**			
Balance of effects	**Favors the comparison**	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	**Favors the intervention**	**Varies**	**Don't know**
Resources required	**Large costs**	**Moderate costs**	**Negligible costs and savings**	**Moderate savings**	**Large savings**	**Varies**	**Don't know**
Certainty of evidence of required resources	**Very low**	**Low**	**Moderate**	**High**			**No included studies**
Cost effectiveness	**Favors the comparison**	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	**Favors the intervention**	**Varies**	**No included studies**
Equity	**Reduced**	**Probably reduced**	**Probably no impact**	**Probably increased**	**Increased**	**Varies**	**Don't know**
Acceptability	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Feasibility	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**

Table S20: Clinical efficacy of dupilumab in asthma stratified by blood eosinophils

Blood eos	Exacerbations – incidence rate ratio (95% CI)	FEV1 increase (95% CI)
>300	0.35 (0.28-0.44)	+ 0.23 (+0.18 to +0.29)

<300	0.63 (0.48 -0.83)	+0.08 (+0.04 to +0.13)

Table S21: Clinical efficacy of dupilumab in asthma stratified by fractional exhaled NO

FeNO	Exacerbations – incidence rate ratio (95% CI)	FEV1 increase, MD (95% CI)
<25	0.76 (0.61-0.95)	+0.07 (-0.01 to +0.15)
25-50	0.38 (0.28 – 0.53)	+0.16 (+0.09 to +0.22)
>50	0.33 (0.24 – 0.46)	+0.34 (+0.25 to +0.43)

Table S22: Summary of findings for dupilumab compared to standard of care for allergic asthma

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with Dupilumab
Clinically significant exacerbations rate ratio assessed with: annual asthma exacerbations	1083 (1 RCT) [38] 52 weeks	⨁⨁⨁⨁ HIGH [2,a]	**Rate ratio 0.58** (0.47 to 0.73)	**Moderate** 10 per 1.000	**4 fewer per 1.000** (5 fewer to 3 fewer)
Asthma control assessed with: Asthma Control Questionnaire (ACQ-5) Scale from: 1 to 5	1013 (1 RCT) [38] 24 weeks	⨁⨁⨁⨁ HIGH [2,7,a,d]	-	The mean asthma control was **0**	MD - **0.27** (-0.4 to - 0.14)
Lung function assessed with: Forced expiratory volume in one second (FEV1 in L) change from baseline	1055 (1 RCT) [38] 12 weeks	⨁⨁◯◯ LOW [2,3,4,5,a,b,c]	-	The mean lung function change from baseline was **0** L	MD + **0.15 L** (+0.09 to + 0.2)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: High confidence that the true effect lies close to that of the estimate of the effect
Moderate certainty: Moderately confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect
Very low certainty: Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Explanations

a. The study included was funded by Sanofi and Regeneron Pharmaceuticals. No industry-independent observational or randomised trials were identified to compare the results. The GDG members considered that there were no major concerns about potential publication/sponsorship bias
b. Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a uncertain correlation with asthma symptoms (103).
c. The minimal important difference (MID) for FEV1 is 0.20 L (GDG consensus).
d. The effect of dupilumab is below the MID (0.5 points). (32)

Table S23: Health economic evaluation of dupilumab in addition to standard therapy vs. standard therapy for uncontrolled severe allergic asthma

Quality assessment							Summary of resources and costs			Quality
Nº. of studies	Study design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Incremental cost per patient*	Incremental effect per patient*	ICER	
ICER per QALY (high quality study - not funded by Industry)										
1[a]	Cost-utility, Markov model	Not serious[1]	Not serious	Serious[2]	Serious[3]	Not serious	704,000 $ (lifetime horizon)	1.51 QALYs (lifetime horizon)	464,000 $ / QALY[4]	⊕⊕⊕◯ MODERATE

*Incremental cost and effect due to the addition of Dupilumab.
ICER: Incremental cost-effectiveness ratio. QALY: Quality adjusted life years. $: US Dollar.

1. Markov model study with low risk of bias (CHEC score 13 or higher).
2. One single study performed in the USA. The results may not be applicable to other countries.
3. The deterministic sensitivity analysis showed large variations in the ICER value from 300,000 $ to 1,000,000 $ (0.85 to 0.81 utilities gained, respectively). Furthermore, at a threshold of 50,000, the probability for Dupilumab to be cost-effective was 0%.
4. The incremental cost-effectiveness ratio drops substantially from ~400k/ QALY to ~200k/QALY when the responder definition is factored into the cost-effectiveness model.

Table S24: Evidence to decision table supporting recommendations for dupilumab for severe allergic asthma in adults (exacerbations and asthma control)

	Judgement						
Problem (importance)	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Desirable Effects	**Trivial**	**Small**	**Moderate**	**Large**		**Varies**	**Don't know**
Undesirable Effects	**Large**	**Moderate**	**Small**	**Trivial**		**Varies**	**Don't know**
Certainty of evidence	**Very low**	**Low**	**Moderate**	**High**			**No included studies**
Values	**Important uncertainty or variability**	**Possibly important uncertainty or variability**	**Probably no important uncertainty or variability**	**no important uncertainty or variability**			

Balance of effects	**Favors the comparison**	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	**Favors the intervention**	**Varies**	**Don't know**
Resources required	**Large costs**	**Moderate costs**	**Negligible costs and savings**	**Moderate savings**	**Large savings**	**Varies**	**Don't know**
Certainty of evidence of required resources	**Very low**	**Low**	**Moderate**	**High**	**Favors the intervention**	**Varies**	**No included studies**
Cost effectiveness	**Favors the comparison**	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	**Favors the intervention**	**Varies**	**No included studies**
Equity	**Reduced**	**Probably reduced**	**Probably no impact**	**Probably increased**	**Increased**	**Varies**	**Don't know**
Acceptability	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Feasibility	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**

Table S25 Evidence to decision table supporting recommendations for dupilumab for severe allergic asthma in adults (lung function)

	Judgement						
Problem (importance)	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Desirable Effects	**Trivial**	**Small**	**Moderate**	**Large**		**Varies**	**Don't know**
Undesirable Effects	**Large**	**Moderate**	**Small**	**Trivial**		**Varies**	**Don't know**
Certainty of evidence	**Very low**	**Low**	**Moderate**	**High**			**No included studies**
Values	**Important uncertainty or variability**	**Possibly important uncertainty or variability**	**Probably no important uncertainty or variability**	**no important uncertainty or variability**			
Balance of effects	**Favors the comparison**	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	**Favors the intervention**	**Varies**	**Don't know**
Resources required	**Large costs**	**Moderate costs**	**Negligible costs and savings**	**Moderate savings**	**Large savings**	**Varies**	**Don't know**
Certainty of evidence of required resources	**Very low**	**Low**	**Moderate**	**High**			**No included studies**
Cost effectiveness	**Favors the**	**Probably favors the**	**Does not favor either the**	**Probably favors the**	**Favors the intervention**	**Varies**	**No included studies**

	comparison	comparison	intervention or the comparison	intervention			
Equity	**Reduced**	**Probably reduced**	**Probably no impact**	**Probably increased**	**Increased**	**Varies**	**Don't know**
Acceptability	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Feasibility	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**

Table S26 Summary of finding for dupilumab in severe T2 asthma

Dupilumab compared to standard of care for asthma

Population: patients with severe asthma uncontrolled under ICS/OSC and 1-2 additional controllers
Intervention: dupilumab
Comparison: standard of care

Outcomes	№ of participants evaluated for a particular outcome (no of studies pooled for the SR) Follow-up range	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with dupilumab
EXACERBATION RATE RATIO assessed with annualised asthma exacerbations rate	2735 (3 RCTs) [26, 27,28] 24 to 52 weeks	⊕⊕⊕⊕ HIGH [4,a]	**ıncidence risk ratio 0.51** (0.45 to 0.59) [b]	Moderate: 90 per 1,000	**757 fewer** per 1,000 (from 836 fewer to 655 fewer)
LUNG FUNCTION assessed with FEV1 in L	2577 (3 RCTs) [26,27,28] 24 to 52 weeks	⊕⊕⊕◯ MODERATE [4,a,c,d]	-	-	MD +**0.15** (+0.11 to +0.18)[b]
ASTHMA CONTROL assessed with Asthma Control Questionnaire-5 (ACQ-5) Scale from: 1 to 5	2516 (3 RCTs) [26,27,28] 24 to 52 weeks	⊕⊕⊕⊕ HIGH [4,a, e]	-	-	MD -**0.28** (-0.39 to -0.17) [b]
QUALITY OF LIFE assessed with Asthma Quality of Life Questionnaire (AQLQ) Scale from: 1 to 7	2046 (2 RCTs) [26,27] 24 to 52 weeks	⊕⊕⊕⊕ HIGH [4,a, f]	-	-	MD +**0.28** (+0.2 to +0.37) [b]

Dupilumab compared to standard of care for asthma

Population: patients with severe asthma uncontrolled under ICS/OSC and 1-2 additional controllers
Intervention: dupilumab
Comparison: standard of care

Outcomes	№ of participants evaluated for a particular outcome (no of studies pooled for the SR) Follow-up range	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with dupilumab
SAFETY Treatment-related adverse events (AE)	356 (1 RCT) [26] mean 24 weeks	⊕⊕⊕◯ MODERATE [4,a,j]	**Risk ratio 1.12** (0.98 to 1.28) k	711 per 1.000	**85 more per 1.000** (14 fewer to 199 more)
SAFETY Treatment-related serious adverse events (SAE)	356 (1 RCT) [26] mean 24 weeks	⊕⊕◯◯ LOW [4,a,k]	**Risk ratio 1.23** (0.54 to 2.77)	56 per 1,000	**13 more per 1.000** (26 fewer to 98 more)
REDUCTION IN RESCUE MEDICATION USE assessed with: puffs/day	568 (1 RCT) [26] 24 to 52 weeks	⊕⊕⊕⊕ HIGH [4,a]	**-**	-	MD -**0.35 lower** (-0.73 to -0.02)
REDUCTION OF ORAL CORTICOSTEROID USE assessed with mg/day decrease	210 (1 RCT) [28] mean 24 weeks	⊕⊕⊕⊕ HIGH [4,a]	-	-	MD - **28.2** (-40.7 to -15.7)
Fraction of exhaled nitric oxide (FeNO) assessed with mean % change (ppb)	2375 (2 RCTs)[26,27] mean 24 weeks	⊕⊕⊕◯ MODERATE [4,5,6,a,h]	-	-	MD - **38.57** (-48.83 to -28.31)[g]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: High confidence that the true effect lies close to that of the estimate of the effect
Moderate certainty: Moderately confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Limited confidence in the effect estimate : the true effect may be substantially different from the estimate of the effect
Very low certainty: Very limited confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. All three trials in our meta-analysis were industry-funded, all by the same company (Sanofi-Regeneron Pharmaceuticals), and all showed positive results. No observational or industry-independent randomized trials were identified to compare with the results derived from the included RCTs.
b. Testing for subgroup differences indicated that there was not relevant subgroup effect by dupilumab dose
c. Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a variable correlation with asthma symptoms (35).
d. Minimal important difference (MID) of 0.23 L (22).
e. The MID of ACQ-5 is 0.5 points (24)

f. The MID of AQLQ is 0.5 points (24)
g. The MID decrease of the FENO value is defined as a difference larger than 20% for values over 50ppb or more than 10ppb for values lower than 50ppb from one visit to the next (25).
h. Downgraded because FeNO is not consistently considered a good surrogate of inflammation (36,37)
i. For rescue medication use, the MID is a reduction by 0.81 puffs/day (22).
j. The effect may both be harmful or beneficial.
k. Few events reported in both intervention and control arm, and the effect may be both harmful and beneficial

Table S27 Health economic analysis of Dupilumab in addition to standard therapy vs. standard therapy in severe T2 asthma

Quality assessment							Summary of resources and costs			Quality
Nº. of studies	Study design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Incremental cost per patient*	Incremental effect per patient*	ICER	
ICER per QALY (high quality study - not funded by Industry)										
1	Cost-utility, Markov model	Not serious[1]	Not serious	Serious[2]	Serious[3]	Not serious	704,000 $ (lifetime horizon)	1.51 QALYs (lifetime horizon)	464,000 $ / QALY[4]	⊕⊕⊕◯ MODERATE

*Incremental cost and effect due to the addition of Dupilumab.
ICER: Incremental cost-effectiveness ratio. QALY: Quality adjusted life years. $: US Dollar.

1. Markov model study with low risk of bias (CHEC score 13 or higher).
2. One single study performed in the USA. The results may not be applicable to other countries.
3. The deterministic sensitivity analysis showed large variations in the ICER value from 300,000 $ to 1,000,000 $ (0.85 to 0.81 utilities gained, respectively). Furthermore, at a threshold of 50,000, the probability for Dupilumab to be cost-effective was 0%.
4. The incremental cost-effectiveness ratio drops substantially from ~400k/ QALY to ~200k/QALY when the responder definition is factored into the cost-effectiveness model.

Table S28 Evidence to decision table supporting recommendations for dupilumab for severe T2 asthma in adults (exacerbations and OCS reduction)

	Judgement						
Problem (importance)	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Desirable Effects	**Trivial**	**Small**	**Moderate**	**Large**		**Varies**	**Don't know**
Undesirable Effects	**Large**	**Moderate**	**Small**	**Trivial**		**Varies**	**Don't know**
Certainty of evidence	**Very low**	**Low**	**Moderate**	**High**			**No included studies**
Values	**Important uncertainty or variability**	**Possibly important uncertainty or variability**	**Probably no important uncertainty or variability**	**no important uncertainty or variability**			

Balance of effects	**Favors the comparison**	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	**Favors the intervention**	**Varies**	**Don't know**
Resources required	**Large costs**	**Moderate costs**	**Negligible costs and savings**	**Moderate savings**	**Large savings**	**Varies**	**Don't know**
Certainty of evidence of required resources	**Very low**	**Low**	**Moderate**	**High**			**No studies included**
Cost effectiveness	**Favors the comparison**	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	**Favors the intervention**	**Varies**	**No studies included**
Equity	**Reduced**	**Probably reduced**	**Probably no impact**	**Probably increased**	**Increased**	**Varies**	**Don't know**
Acceptability	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Feasibility	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**

Table S29 Evidence to decision table supporting recommendations for dupilumab for severe T2 asthma (asthma control, QoL,rescue medication reduction)

	Judgement						
Problem (importance)	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Desirable Effects	**Trivial**	**Small**	**Moderate**	**Large**		**Varies**	**Don't know**
Undesirable Effects	**Large**	**Moderate**	**Small**	**Trivial**		**Varies**	**Don't know**
Certainty of evidence	**Very low**	**Low**	**Moderate**	**High**			**No included studies**
Values	**Important uncertainty or variability**	**Possibly important uncertainty or variability**	**Probably no important uncertainty or variability**	**no important uncertainty or variability**			
Balance of effects	**Favors the comparison**	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	**Favors the intervention**	**Varies**	**Don't know**
Resources required	**Large costs**	**Moderate costs**	**Negligible costs and savings**	**Moderate savings**	**Large savings**	**Varies**	**Don't know**
Certainty of evidence of required resources	**Very low**	**Low**	**Moderate**	**High**			**No included studies**

Cost effectiveness	**Favors the comparison**	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	**Favors the intervention**	**Varies**	**No included studies**
Equity	**Reduced**	**Probably reduced**	**Probably no impact**	**Probably increased**	**Increased**	**Varies**	**Don't know**
Acceptability	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Feasibility	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**

Table S30 Evidence to decision table supporting recommendations for dupilumab for severe T2 asthma (lung function)

	Judgement						
Problem (importance)	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Desirable Effects	**Trivial**	**Small**	**Moderate**	**Large**		**Varies**	**Don't know**
Undesirable Effects	**Large**	**Moderate**	**Small**	**Trivial**		**Varies**	**Don't know**
Certainty of evidence	**Very low**	**Low**	**Moderate**	**High**			**No studies included**
Values	**Important uncertainty or variability**	**Possibly important uncertainty or variability**	**Probably no important uncertainty or variability**	**no important uncertainty or variability**			
Balance of effects	**Favors the comparison**	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	**Favors the intervention**	**Varies**	**Don't know**
Resources required	**Large costs**	**Moderate costs**	**Negligible costs and savings**	**Moderate savings**	**Large savings**	**Varies**	**Don't know**
Certainty of evidence of required resources	**Very low**	**Low**	**Moderate**	**High**			**No studies included**
Cost effectiveness	**Favors the comparison**	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	**Probably favors the intervention**	**Favors the intervention**	**Varies**	**No studies included**
Equity	**Reduced**	**Probably reduced**	**Probably no impact**	**Probably increased**	**Increased**	**Varies**	**Don't know**
Acceptability	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**
Feasibility	**No**	**Probably no**	**Probably yes**	**Yes**		**Varies**	**Don't know**

Table S31 A and B: Clinical efficacy of dupilumab in severe T2 asthma stratified by dose and atopic status

Dose 200 mg	Exacerbations reduction (95%CI)	FEV1 increase (95%CI)	Asthma control (ACQ5) (95%CI)
With allergic asthma	36.9 (13.4-54)	0.13 (0.05-0.2)	- 0.28 (-0.46 to -0.11)
Without allergic asthma	60 (42.7-72.1)	0.14 (0.07-0.22)	-0.44 (-0.65 to -0.22)

Dose 300 mg	Exacerbations reduction (95%CI)	FEV1 increase (95%CI)	Asthma control (ACQ5) (95%CI)
With allergic asthma	45.5 (26-59.9)	0.16 (0.09-0.23)	- 0.26 (-0.44 to – 0.08)
Without allergic asthma	44.6 (21.5-60.9)	0.09(0.01 -0.16)	-0.08 (-0,29 to 0.12)

Table S32: Summary of findings of mepolizumab compared to standard of care for eosinophilic asthma

Outcomes	№ of participants (studies) Follow-up (range)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with mepolizumab
Exacerbations Exacerbation rate ratio Assessed witt the annualized rates of asthma exacerbations	1071 (3 RCTs) [45,46,47] 24 to 32 weeks	⊕⊕⊕⊕ HIGH [4,5,a,b,c]	**Incidence rate ratio 0.49** (0.38 to 0.66)	1700 exacerbations per 1000 patients per year	**870 fewer exacerbations per 1000 patients per year** (592 fewer to 1079 fewer)
Exacerbations leading to hospitalisation Assessed with the annualized rate of asthma exacerbations leading to hospitalisation	(2 RCTs) [45,47] 24 to 32 weeks	⊕⊕⊕⊕ HIGH [4,5,a,c,d]	**Incidence rate ratio 0.30** (0.13 to 0.71)	100 exacerbations per 1000 patients per year	**70 fewer exacerbations per 1000 patients per year** (29 fewer to 87 fewer)
Asthma control Assessed with: ACQ-5 score between-group-difference at the end of the study Scale from: 0 to 6 [9,j]	912 (3 RCTs) [45,47]	⊕⊕⊕◯ MODERATE [4,5,a,c,i]	-		mean difference - **0.43** (- 0.56 to - 0.31)

Table S32: Summary of findings of mepolizumab compared to standard of care for eosinophilic asthma

Outcomes	№ of participants (studies) Follow-up (range)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with mepolizumab
Quality of life Assessed with St. George's Respiratory Questionnaire between-group-difference at the end of the study	1045 (3 RCTs) [45,46,47] 24 to 32 weeks [10,k]	⊕⊕⊕◯ MODERATE [4,5,a,c,l]	-		mean difference - **7.14** (- 9.07 to - 5.21)
Treatment-related adverse events (AE) Assessed with number of events	1071 (3 RCTs) [45,46,47]	⊕⊕⊕⊕ HIGH [4,5,c]	**Risk ratio 1.35** (1.01 to 1.80)	796 per 1.000	**279 more per 1.000** (8 more to 637 more)
Treatment-related serious adverse events (SAE) Assessed with number of events	385 (1 RCT) [47]	⊕◯◯◯ VERY LOW [4,5,c,m,n]	**Risk ratio 0.98** (0.06 to 15.63)	5 per 1.000	**0 fewer per 1.000** (-5 fewer to 77 more)
Lung function assessed with pre-bronchodilator FEV1 (mL) between-group-difference at the end of the study	1043 (3 RCTs) [45,46,47] 24 to 32 weeks [6,e]	⊕⊕⊕◯ MODERATE [4,5,7,a,c,f]	-		mean difference +**110.9 mL** (+58.91 to +162.89)
Lung function assessed with AM peak expiratory flow (PEF)	936 (2 RCTs) [77] 24 weeks [6,g]	⊕⊕◯◯ LOW [4,5,c,h,i]	-		mean difference +**22.46** (+13.98 to +30.94)
Rescue medication use assessed with puffs/day	(1 RCT) [45] 21 to 24 weeks [o]	⊕⊕⊕⊕ HIGH [4,5,c]	-		mean difference -**0.1** (-0.35 to +0.15)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: High confidence that the true effect lies close to that of the estimate of the effect
Moderate certainty: Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
Very low certainty: Little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Two of three studies had a high risk of attrition bias (45,47). Modified intention-to-treat analysis was conducted (i.e. patients were analysed as treated, not as randomized).
b. Probable unimportant heterogeneity
c. Included studies were all funded by industry, and all showed positive results. We identified two industry-independent observational trials that showed similar effects with our meta-analysis (76,77).
d. Mean rates of exacerbation requiring hospitalization across studies were very low (i.e. from 0.02 to 0.10 exacerbations requiring hospitalization per person-year), both in the placebo and intervention arms
e. The panel agreed that minimal important difference (MID) for FEV1 is 0.20 L

f. Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a variable correlation with asthma symptoms (72).
g. The MID of PEF is 18.8 L/min (35)
h. Potential attrition bias because PEF baseline values reported in the primary publication (47) differed from values reported in post-hoc analysis publication (77)
i. Downgraded because the lower CI boundary crosses the MID threshold
j. 0.5 points is the minimal important difference for the Asthma Control Questionnaire (ACQ-5 score) (37)
k. >-4.0 was considered the threshold for the MID for quality of life measured with the St.George's Respiratory Questionnaire (36)
l. The St.George's Respiratory Questionnaire SGRQ is not a disease-specific questionnaire for asthma
m. Findings from only 1 RCT available. Downgraded due to publication bias
n. Very few numbers of events per arm
o. The minimal important difference for rescue medication use is -0.81 puffs/day (35)

Table S33: Economic evaluation of mepolizumab in addition to standard therapy vs. standard therapy in adults with severe eosinophilic asthma

Quality assessment							Summary of resources and costs			Quality
Nº. of studies	**Study design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Incremental cost per patient***	**Incremental effect per patient***	**ICER**	
ICER per QALY (high quality study - not funded by Industry)										
1[a]	Cost-utility, Markov model	Not serious[1]	Not serious	Serious[2]	Serious[3]	Not serious	589,941 $ (Lifetime horizon)	1.53 QALY (Lifetime horizon)	385,546 $ / QALY[4]	⊕⊕◯◯ LOW

*Incremental cost and effect due to the addition of Mepolizumab.
ICER: Incremental cost-effectiveness ratio. QALY: Quality adjusted life years. $: US Dollar.

1. Markov model study with low risk of bias. CHEC (consensus on health economics criteria checklist) score 16 out of 20.
2. One single study performed in the USA[a]. The results might not be directly applicable to European countries.
3. The ICER varied from 385,546 $ to 160,000 $ in the group of responder patients. However, the ICERs obtained from the sensitivity analyses were not lower than 30,000 € (the willingness to pay threshold in most European countries).
4. The incremental cost-effectiveness ratio drops substantially from ~400k/ QALY to ~200k/QALY when the responder definition is factored into the cost-effectiveness model.

References

d. Whittington, M. D. et al. Assessing the value of mepolizumab for severe eosinophilic asthma: a cost-effectiveness analysis. Ann Allergy Asthma Immunol. 2017; 118 (2): 220-225.

Table S34- Evidence to decision table supporting recommendations for mepolizumab for severe asthma in adults (exacerbations)

	Judgement						
Problem (importance)	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know

Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	no important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No studies included
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No studies included
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Table S35: Evidence to decision table supporting recommendations for mepolizumab for severe asthma in adults (decrease or withdraw OCS)

	Judgement						
Problem (importance)	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	no important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Table S36: Evidence to decision table supporting recommendations for mepolizumab for severe asthma in adults (asthma control and QoL)

	Judgement						
Problem (importance)	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No studies included
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	no important uncertainty or variability			

Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No studies included
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No studies included
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Table S37: Evidence to decision table supporting recommendations for mepolizumab for severe asthma in adults (lung function – FEV1)

	Judgement						
Problem (importance)	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No studies included
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	no important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No studies included
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No studies included

Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Table S38: Reduction in asthma exacerbations following mepolizumab stratified by blood eosinophils

Blood eos	Incidence rate ratio (95% CI)
150-300	0.50 (0.38 to 0.66)
300-500	0.68 (0.47 to 0.98)
>500	0.44 (0.35 to 0.55)

Table S39: Summary of findings of Omalizumab compared to standard of care for eosinophilic asthma

Outcomes	№ of participants (studies) Follow-up (range)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with omalizumab
Exacerbations Assessed with annual asthma exacerbations rate	779 (3 RCTs) [48,50,51] 16 to 48 weeks	⊕⊕⊕⊕ HIGH [4,a,b]	**Incidence rate ratio 0.56** (0.40 to 0.77)	660 exacerbations per 1000 patients per year	**290 fewer exacerbations per 1.000 patients per year** (396 fewer to 152 fewer)
Asthma Control Assessed with Total Asthma Symptoms Score	414 (1 RCT) [48] 48 weeks	⊕⊕◯◯ LOW [4,a,b,c,d]	-		mean difference - **0.16** (- 0.51 to +0.19) [e,f]
Quality of Life Assessed with Asthma Quality of Life Questionnaire	414 (1 RCT) [48] 48 weeks	⊕⊕⊕◯ MODERATE [4,a,b,d]	-		mean difference + 0.13 (-0.11 to + 0.37) [l]
Any adverse event Assessed with number of events	414 (1 RCT) [48] 48 weeks	⊕⊕⊕◯ MODERATE [4,a,b,d]	**Risk ratio 1.01** (0.91 to 1.11)	794 per 1.000	**8 more per 1.000** (71 fewer to 87 more)

Table S39: Summary of findings of Omalizumab compared to standard of care for eosinophilic asthma

Outcomes	№ of participants (studies) Follow-up (range)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with omalizumab
Lung Function Assessed with % pre-bronchodilator FEV1 between-group-difference at the end of the study	(2 RCTs) [48,50] 24 weeks to 48 weeks	⊕⊕⊕◯ MODERATE [4,5,a,b,g,h,i]	-		mean difference + **3.7 %** (-2.1 to + 9.5) [j,k]
Rescue medication use Assessed with puffs/day change from baseline	414 (1 RCT) [48] 48 weeks	⊕⊕⊕◯ MODERATE [4,a,b,d]	-		mean difference - **0.34** (-0.83 to +0.15) [6,m,n]

GRADE Working Group grades of evidence
High certainty: High confidence that the true effect lies close to that of the estimate of the effect
Moderate certainty: Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
Very low certainty: Little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Information of included studies from non-predefined subgroup analysis.
b. Included studies were all funded by industry, and all showed positive results. We identified one industry-independent observational trial that showed similar effects with our meta-analysis (78).
c. The total asthma symptoms score is an unvalidated scale.
d. The effect may both be harmful or beneficial.
e. Data from subgroup of patients with blood eosinophil count ≥ 260/ul. This study also reported total asthma symptoms score for the subgroup of FeNO ≥ 24ppb, the mean difference is -0.25 (CI 95% -0.77 to 0.27).
f. In the current systematic review we also included one study (49) reporting the effect on the symptom days over the previous 2 weeks at 48 weeks follow up, the mean difference is -0.45 (p=0.05) (see full text report).
g. Statistically significant (I2=70%), but probably unimportant heterogeneity.
h. Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a variable correlation with asthma symptoms (72)
i. The panel agreed that minimal important difference (MID) for FEV1 is 0.20 L j. Population with different threshold of eosinophil counts across the studies: ≥ 200 cells/µl (51), ≥ 300 cells/µl (50) and ≥ 260 cells/µl (48).
k. One of the included studies (48) also reported the effect on FEV1 % change for a population with FeNO ≥ 24 ppb, the LS mean difference is 3.20 (CI 95% -0.74 to 0.27). The pooled effect evaluated at 48 weeks (48) and 24 weeks (50).
l. Data from subgroup of patients with blood eosinophil count ≥ 260/ul. This study also reported AQLQ for the subgroup of FeNO ≥ 24ppb , the mean difference is 0.37 (CI 95% 0.01 to 0.73).
m. This study also reported the effect on rescue medication use for the subgroup of FeNO ≥ 24 ppb, the mean difference is -0.49 (CI 95% -0.88 to -0.11).
n. The MID for rescue medication use is 0.81 puffs/day (35).

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Table S40- Evidence to decision table supporting recommendations for omalizumab for severe eosinophilic asthma in adults (exacerbations)

	Judgement						
Problem (importance)	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No studies included
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	no important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No studies included
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Table S41: Evidence to decision table supporting recommendations for omalizumab for severe eosinophilic asthma in adults (QoL, lung function, reduction in rescue medication)

	Judgement

Problem (importance)	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No studies included
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	no important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No studies included
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No studies included
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Table S42: Summary of findings of omalizumab efficacy and safety compared to standard of care for allergic asthma

Outcomes	№ of participants (studies) Follow-up range	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with Omalizumab
Annual rate of clinically significant asthma exacerbations assessed with annualised rate	2772 (6 RCTs) [42,44,51,54,55,68] 24 weeks to 52 weeks [a]	⨁⨁⨁⨁ HIGH [b,c,d]	**Rate ratio 0.56** (0.45 to 0.69) [e,f]	**Low**	
				14 per 1.000	**616 fewer per 1.000** (770 fewer to 378 fewer)

Outcomes	№ of participants (studies) Follow-up range	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with Omalizumab
Asthma control assessed with ACQ-6 score;	939 (3 RCTs) [44,56,59] 26 weeks to 52 weeks	⊕⊕⊕◯ MODERATE [9,b,d,g]	-	The mean asthma Control was **0** point	MD -**0.38** (-0.68 to -0.09) [h,i]
Global evaluation of treatment effectiveness assessed with: physicians/investigators' assessment	3783 (10 RCTs) [68, 54,59,62,66,40,48,47,43,63] 16 weeks to 52 weeks	⊕⊕⊕⊕ HIGH [b,d,j]	**Rate ratio 1.50** (1.32 to 1.70) [k]	418 per 1.000	**209 more per 1.000** (134 more to 292 more) [k]
Clinically significant improvement of Asthma Quality of Life (≥0.5 from baseline) assessed with: AQLQ Questionnaire (S)	3540 (9 RCTs) [40,47,51,52,54,55,62,63,67] 12 weeks to 52 weeks	⊕⊕⊕⊕ HIGH [b,d,l]	**Rate ratio 1.32** (1.16 to 1.51) [m]	563 per 1.000	**180 more per 1.000** (90 more to 287 more) [m]
Any drug-related AE	2341 (7 RCTs) 68,54,66, 43, 63, 67, 50 16 weeks to 52 weeks	⊕⊕⊕◯ MODERATE [ab,b,d]	**Rate ratio 1.27** (0.93 to 1.74)	127 per 1.000	**34 more per 1.000** (9 fewer to 94 more)
Any drug-related SAE)	1163 (2 RCTs) [51, 60] 16 weeks to 48 weeks	⊕⊕⊕◯ MODERATE [ab,b,d]	**Rate ratio 1.62** (0.76 to 3.45)	18 per 1.000	**11 more per 1.000** (4 fewer to 43 more)
Lung function (FEV1) assessed with absolute FEV1 (L) change versus baseline	1209 (6 RCTs) [55, 42,62, 43, 60, 61] range 12 weeks to 52 weeks [n,o]	⊕⊕◯◯ LOW [21,22,23,b,p,q,r]	-	The mean lung function was **0** L	MD +**0.17 L** (+0.02 to + 0.32) [s]
Lung function (PEF) assessed with morning PEF rate change (L/m) versus baseline	1735 (7 RCTs) 59, 48, 52,60, 41,58,49 12 weeks to 36 weeks [t]	⊕⊕⊕◯ MODERATE [21,22,23,b,p,r,u]	-	The mean lung function was **0**	MD +**10.04 higher** (+7.49 to +12.6)
Decrease in inhaled corticosteroid assessed as µg/day variation versus baseline	1861 (5 RCTs) [41, 42, 46, 52, 65] 24 weeks to 52 weeks	⊕⊕⊕⊕ HIGH [23,b,r,v]	-	-	SMD -**0.38 SD** (-0.48 to - 0.29)
Rescue medication use (puffs/day) assessed with change from baseline	3367 (7 RCTs) [68, 54, 42, 59, 66, 52, 41] 16 weeks to 52 weeks [22,w]	⊕⊕⊕⊕ HIGH [b,d,x]	-	The mean the change from baseline of Rescue medication use (puffs/day) was **0** puff/day	MD -**0.47 puff/day** (-0.68 to -0.27)

Outcomes	№ of participants (studies) Follow-up range	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with Omalizumab
FeNO level change from baseline [29,y]	495 (3 RCTs) [51, 65,41]	⨁⨁⨁◯ MODERATE [32,33,b,d,z]	-	The mean feNO leval change from baseline was **0** ppb	MD **4.65 ppb lower** (-7.39 to -1.92) [aa]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **SMD:** Standardised mean difference

GRADE Working Group grades of evidence
High certainty: High confidence that the true effect lies close to that of the estimate of the effect
Moderate certainty: Moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect
Very low certainty: Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Explanations

a. Clinical significant asthma exacerbation: episodes of asthma worsening requiring treatment with systemic corticosteroids.
b. Despite some studies being at high risk of bias for some of the domains, the effect observed in all of them is similar.
c. Lanier included patients aged 6-12 years old, all had allergic asthma (68).
d. Included studies were all funded by industry, and all showed positive results. No industry-independent observational or randomized studies were identified to compare the results. Therefore, evidence was downgraded for potential publication bias (102).
e. 9 studies included reported exacerbations as "patients who had ≥1 exacerbation", the pooled risk ratio was 0.59(95% CI 0.52-0.67). 3 studies included reported clinically significant severe asthma exacerbation, the pooled rate ration was 0.51 (95% CI 0.39-0.67)
f. The pooled effect of risk ratio evaluated at 24-28 weeks (44, 54, 68, 63) and at 48-52 weeks (42, 51, 68, 55). Lanier 2009 included patients aged 6-12 years old.
g. Downgraded because the effect of omalizumab is beneficial but the upper side of the CI is less than the minimal important difference (MID=0.5) (32).
h. Asthma control using asthma control test (ACT) was assessed by three studies (65, 43, 56), the pooled mean different was 0.57(95% CI 0.17-0.97). We also included the ACQ scores assessed by 5 studies (68, 51, 52, 59, 46), the pooled standard mean difference was -0.20 (95% CI -0.26 - -0.14)
i. The pooled effect of ACQ-6 evaluated at 16 weeks (44), 24-32 weeks (44, 59), and at 52 weeks (56).
j. Although there were a high I2 (67%.), this was influenced by only one study with low number of events.
k. The pooled data were assessed at 16 and 20 weeks (48, 62), and 52 weeks (68); Other studies evaluated at 24-28 weeks. GETE evaluated by patients show that omalizumab is more effective than placebo, the risk ratio was 1.49 (1.26-1.77), see full text report.
l. Statistically significant (I2=83%), but probably unimportant heterogeneity.
m. The mean change of AQLQ scores was assessed by 7 studies, the pooled standard mean difference was 0,34 (95% IC 0.18-0.49)
n. Milgrom reported FEV1 in children (6-12 years old) for 28 weeks follow up (64). The Mean change from baseline was 93.9 mL in the omalizumab group and 28.3 mL in the placebo group. Lanier reported between group differences in FEV1 at week 48 and 52 in 40 ml (p=0.28) and 52 ml (p=0.16) (41).
o. Lung function was also reported as ratio FEV1/FVCx100. Busse reported the ratio in 77.5±0.38 in the intervention group and 77.3±0.36 in the placebo group (63). Milgrom also reported mean FVC in children (6-12 years old) for 28 weeks follow up. Mean FVC change from baseline was 132.7 in the omalizumab group and 132.7 mL in the placebo group at week 28 (64). See full text report.
p. Downgraded because FEV1 and PEF are considered surrogate outcomes for asthma control, with an inconsistent correlation with asthma symptoms (101).

q. The minimal important difference (MID) for FEV1 is 0.20 L (Guidelines Development Group consensus).
r. Included studies were all funded by industry, and all showed positive results. One observational study showed similar results (102), therefore, we did not downgrade for potential publication bias.
s. The predicted value for pre-bronchodilator FEV1 was assessed by 6 studies, the pooled standard mean difference was 1.05 (95% CI 0.35-1.75), see full text report.
t. Milgrom 2001 reported PEFR in children (6-12 years old) with 28 weeks of follow up. Mean morning PEFR change from baseline was 8.5 L/min in the omalizumab group, and 1 L/min in the placebo group at week 28)
u. Average MID is 18.8L/min (30)
v. High heterogeneity (91%); Not downgraded as all effects favour intervention.
w. For rescue medication use MID is the reduction by 0.81 puffs/day (30)
x. Statistically significant (68% (p=0.004)) but probably unimportant heterogeneity.
y. The MID of FeNO change from baseline is more than 10ppb (33).
z. Downgraded because FeNO is not consistently considered a good surrogate of asthmatic inflammation (105, 106)
aa. FeNO change was reported according to IgE level by one study (64). The median percentage change was -7.2 (for IgE 30-300 IU/ml) and -16 (for IgE 700–2,000 IU/ml) in the Omalizumab group and 64 in the placebo group.
bb. The effect may both be harmful or beneficial

Table S 43: Economical evaluation of omalizumab in addition to standard therapy vs. standard therapy for severe allergic asthma

Quality assessment							**Summary of resources and costs**			**Quality**
Nº. of studies	**Study design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Incremental cost per patient (range)***	**Incremental effect per patient (range)***	**ICER (range)**	
ICER per QALY (high quality studies - not funded by Industry)										
7[a-g]	Cost-utility, Markov model	Not serious[1]	Not serious[2]	Not serious[3]	Serious[4]	Not serious	39,720 £ to 179,415 $ (5year to lifetime horizon)	0.18 to 0.67 QALYs (5year to lifetime horizon)	53,348 £ to 821,000 $ / QALY[5]	⊕⊕⊕◯ MODERATE
ICER per QALY (high quality studies - funded by Industry)										
5[h-l]	Cost-utility, Markov model	Not serious[1]	Not serious[2]	Not serious[6]	Serious[7]	Serious[8]	33,854 € to 91,100 $ (5year to lifetime horizon)	0.32 to 1.46 QALYs (5year to lifetime horizon)	31,209 € to 287,200 $ / QALY[5]	⊕⊕◯◯ LOW
ICER per QALY (low quality studies)										
3[m-o]	Cost-utility, pre-post study	Very serious[9]	Not serious[10]	Not serious[11]	Not serious[12]	Serious[13]	3,581 € to 5,169 € (10 months to 1 year horizon)	0.13 to 0.22 QALYs (10 months to 1 year horizon)	23,880 € to 26,865 € / QALY	⊕◯◯◯ VERY LOW
ICER per avoid exacerbation (low quality studies)										

Quality assessment							Summary of resources and costs			Quality
Nº. of studies	**Study design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Incremental cost per patient (range)***	**Incremental effect per patient (range)***	**ICER (range)**	
4[p-s]	Cost-effectiveness, pre-post study	Very serious[9]	Not serious[10]	Not serious[14]	Not serious[12]	Serious[15]	8,731 € to NR (1 year horizon)	NR to 7.72 avoided exacerbations (1 year horizon)	1,131 € to 17,721 € / avoided exacerbation	⊕◯◯◯ VERY LOW
ICER per increase in ACT (Asthma Control Test) score										
2[p,s]	Cost-effectiveness, pre-post study	Very serious[9]	Not serious[10]	Not serious[14]	Not serious[12]	Serious[16]	8,731 € to 9,979 € (1 year horizon)	6.35 to 8.4 mean increase in ACT score (1 year horizon)	3,555 € to 4,124 € / 3 points increase in ACT score	⊕◯◯◯ VERY LOW
ICER per increase in AQLQ (Juniper Asthma-Related Quality of Life Questionnaire) score										
1[t]	Cost-effectiveness, trial based study	Very serious[9]	Not serious	Not serious	Not serious	Serious[17]	NR	NR	378 $ / 0.5-point increase in AQLQ score	⊕◯◯◯ VERY LOW
ICER per controlled day										
1[t]	Cost-effectiveness, trial based study	Very serious[9]	Not serious	Not serious	Not serious	Serious[17]	NR	NR	523 $ / day	⊕◯◯◯ VERY LOW

*Incremental cost and effect due to the addition of omalizumab. Range (minor and maximum value) as reported by the studies.
ICER: Incremental cost-effectiveness ratio. QALY: Quality adjusted life years. ACT: Asthma Control Test. €: Euro. $: US Dollar. NR: Not clearly reported in the study. AQLQ: Juniper Asthma-Related Quality of Life Questionnaire.

1. Markov model studies with low risk of bias (CHEC score 13 or higher).
2. All studies reported an ICER higher than 30,000 €, which is the willingness to pay threshold in most European countries.
3. Six studies were performed in high-income countries (two in the UK[a,c], three in the USA[d,e,f], one in Japan[b]), and one in China[g]. Three studies[a,c,g] included children, whereas the rest only adults.
4. Reported ICERs varied from 53,348 £ to 821,000 $ per QALY.
5. The incremental cost-effectiveness ratio drops substantially from ~400k/ QALY to ~200k/QALY when the responder definition is factored into the cost-effectiveness model.
6. Four studies were performed in high-income countries (two in Europe[h,i], two in North America[j,l]), one in Brazil. All included adults.
7. Reported ICERs varied from 31,209 € to 287,200 $ per QALY.
8. All studies financed by Novartis (manufacturer of omalizumab) reported lower ICERs compared to those not financed by Industry.
9. CHEC score lower than 13 (see limitations and transferability assessment section). Cost-utility analysis based on a pre-post study has several limitations. The most important is the bias of not including all clinical health states and the potential exclusion of severe patients. Mortality was impossible to be measured (all included patients were alive). Utilities in post-omalizumab are conditioned by pre-omalizumab results.

10. All studies reported an ICER lower than 30,000 €, which is the willingness to pay threshold in most European countries.
11. All studies conducted in European countries (2 in Italy, 1 in Spain).
12. Reported ICERs showed scarce variation.
13. Two studies financed by Novartis, one by a research centre.
14. All studies conducted in European countries.
15. Three studies with ICER lower or equal than 2,273 € / avoided exacerbation were financed by Novartis. The higher ICER (17,721 €) was reported by a study non-Industry funded.
16. Novartis financed the studies.
17. Source of funding not reported.

Table S44- Evidence to decision table supporting recommendations for omalizumab for severe allergic asthma in adults and adolescents (12-17 years old) (exacerbations)

	Judgement						
Problem (importance)	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	no important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No studies included
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No studies included
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Table S45- Evidence to decision table supporting recommendations for omalizumab for severe allergic asthma in adults and adolescents (12-17 years old) (asthma control, QoL, ICS use, rescue use)

	Judgement						
Problem (importance)	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No studies included
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	no important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No studies included
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No studies included
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Table S46: Effect of omalizumab on asthma exacerbations stratified by blood eosinophils

Blood eos	Exacerbations – incidence rate ratio (95% CI)
>200	0.59 (0.40-0.86)
>300	0.37 (0.22 – 0.61)

>400	0.26 (0.12 – 0.56)

Table S47- Evidence to decision table supporting recommendations for omalizumab for severe allergic asthma in children 6-11 years old (asthma exacerbations, control, QoL, ICS use)

	Judgement						
Problem (importance)	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No studies included
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	no important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No studies included
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No studies included
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Table S48: Summary of findings of Reslizumab compared to standard of care for eosinophilic asthma

Outcomes	№ of participants (studies) Follow-up (mean or range)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with reslizumab
Exacerbations Assessed with annualised rate of asthma exacerbations[a]	1059 (3 RCTs) [1,2] 52 weeks	⊕⊕⊕⊕ HIGH [3,b]	**Incidence rate ratio 0.46** (0.37 to 0.58) [c]	1800 exacerbations per 1000 patients per year	**972 fewer exacerbations per 1000 patients per year** (1134 fewer to 756 fewer)
Exacerbations leading to ER visit or hospitalisation Assessed with annualised rate of asthma exacerbations	953 (2 RCTs) [1] 52 weeks	⊕⊕⊕◯ MODERATE [3,b,d]	**Incidence rate ratio 0.67** (0.39 to 1.17)	120 exacerbations per 1000 patients per year	**40 fewer exacerbations per 1000 patients per year** (73 fewer to 20 more)
Asthma control Assessed with Asthma Control Questionnaire-7 Scale from: 0 to 6	1359 (5 RCTs) [1,2,4,5] 15 weeks to 16 weeks	⊕⊕⊕⊕ HIGH [3,8,b,h]	-		mean difference - **0.25** (- 0.34 to - 0.16)
Quality of life assessed with Asthma Quality of Life Questionnaire Scale from: 1 to 7	1153 (3 RCTs) [1,4] 15 to 16 weeks	⊕⊕⊕⊕ HIGH [3,10,b,k]	-		mean difference + **0.17** (+0.08 to + 0.25) [l]
Treatment-related adverse events Assessed with number of events	1269 (4 RCTs) [1,2,4] 15 to 52 weeks	⊕⊕⊕◯ MODERATE [3,b,o]	**Risk ratio 1.18** (0.89 to 1.56) [p]	125 per 1.000	**22 more per 1.000** (14 fewer to 70 more) [p]
Treatment-related serious adverse events Assessed with number of events	1269 (4 RCTs) [1,2,4] 15 to 52 weeks [p]	⊕⊕◯◯ LOW [3,b,q]	**Risk ratio 4.71** (0.54 to 41.31)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
Decrease in inhaled corticosteroid (ICS) and oral corticosteroid (OCS) dose	0 studies	**-**	-	-	-
Lung function Assessed with: FEV_1 in mL	1360 (5 RCTs) [1,2,4,5] 15 to 16 weeks	⊕⊕⊕◯ MODERATE [3,6,7,b,e,f]	-		mean difference +**141.82 mL** (+89.23 to 194.41) [g+]

Table S48: Summary of findings of Reslizumab compared to standard of care for eosinophilic asthma

Outcomes	№ of participants (studies) Follow-up (mean or range)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard of care	Risk difference with reslizumab
Rescue medication use Assessed with puffs/day	1251 (4 RCTs) [1,4,5] 16 weeks	⊕⊕⊕⊕ HIGH [3,7,b,n]	-		mean difference **− 0.24** (-0.46 to - 0.02)
Asthma symptoms Assessed with: Asthma Symptom Utility Index Scale from: 0 to 1	1157 (3 RCTs) [1,4] 16 weeks to 16 weeks	⊕⊕⊕⊕ HIGH [3,9,b,j]	-		mean difference +**0.05** (+0.03 to +0.07 higher)
Changes in blood eosinophil counts Assessed with: cells/µL	1264 (4 RCTs) [1,2,4] 15 weeks to 16 weeks	⊕⊕⊕◯ MODERATE [3,11,b,m]	-		mean difference - **468.58** (-494.92 to - 442.24)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: High confidence that the true effect lies close to that of the estimate of the effect
Moderate certainty: Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
Very low certainty: Little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Clinically significant asthma exacerbations: episodes of asthma worsening with systemic corticosteroids for 3 or more days, a two-times increase in the dose of either inhaled corticosteroids or the need for asthma-related emergency treatment.
b. All included studies were funded by industry, and all showed positive results. No industry-independent observational or randomized studies were identified to contrast the results. Therefore, the quality of the evidence was downgraded for potential publication bias (70).
c. The pooled effect of risk ratio was assessed at 15 weeks (52) and the rate ratio was evaluated at 52 weeks (53)
d. Downgraded because the absolute effect includes both potential clinically meaningful benefits and harms.
e. Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a variable correlation with asthma symptoms (72).
f. The panel agreed that minimal important difference (MID) for FEV1 is 0.20 L g. Castro 2015 also assessed FEV1 at 52 weeks, the mean difference from baseline was 122.28 mL(45.54, 199.02). We also included 3 studies (52,54, 55) reporting FVC (mL), the pooled mean difference was 205.94 (88.69, 323.19); see full text report.
h. MID for ACQ-7 is 0.5 points (Juniper 2005).
i. Castro 2015 also assessed ACQ-7 at 52 weeks, the mean difference from baseline of ACQ-7 was -0.25 (-0.34, -0.16), see full text report.
j. MID for the Asthma symptoms utility index is an increase of 0.09 points (79).
k. MID of AQLQ is 0.5 points (37).
l. Castro 2015 also assessed AQLQ at 52 weeks, the mean difference from baseline was 0.29 (0.18, 0.41), see full text report.
m. Reduction of blood eosinophil counts is a surrogate endpoint and not validated as a valuable outcome for monitoring asthma therapy (80).
n. MID for rescue medication use is a reduction by 0.81 puffs/day (35).
o. The effect may both be harmful or beneficial.
p. Data regarding this outcome was extracted from www.clinicaltrials.gov for ref.52 and ref.53
q. Very few events in both arms, thus it is not possible to estimate precisely the effect size between arms

Table S49: Economic evaluation of reslizumab in addition to standard therapy vs. standard therapy -adults with eosinophilic asthma

Quality assessment							Summary of resources and costs			Quality
Nº. of studies	Study design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Incremental cost per patient*	Incremental effect per patient*	ICER	
ICER per QALY (high quality study - not funded by Industry)										
1[a]	Cost-utility, Markov model	Not serious[1]	Not serious	Serious[2]	Serious[3]	Not serious	24,404 $ (5-year horizon)	0.035 QALYs (5-year horizon)	697,403 $ / QALY[4]	⊕⊕⊕◯ MODERATE
ICER per QALY (high quality study - funded by Industry)										
1[b]	Cost-utility, Markov model	Not serious[1]	Not serious	Serious[5]	Not serious[6]	Serious[7]	119,394 $ (lifetime horizon)	5.17 QALYs (lifetime horizon)	23,081 $ / QALY	⊕⊕◯◯ LOW

*Incremental cost and effect due to the addition of Reslizumab.

ICER: Incremental cost-effectiveness ratio. QALY: Quality adjusted life years. $: US Dollar.

1. Markov model studies with low risk of bias (CHEC score 13 or higher).
2. One single study performed in the USA. The results may not be applicable to other countries.
3. The sensitivity analysis showed large variations in the ICER value. However, all of them were higher than 100,000 $, which is the willingness to pay threshold in most countries. Increasing 20% the quality of life with reslizumab would drop the ICER to 154,352 $, and it was 467,010 $ where non-responders had the same quality of life and exacerbations rates as the standard therapy group. Furthermore, in 95% of the iterations the ICER varied between 378,534 $ and 2,082,379 $.
4. The incremental cost-effectiveness ratio drops substantially from ~400k/ QALY to ~200k/QALY when the responder definition is factored into the cost-effectiveness model.
5. One single study performed in South Korea. The results may not be applicable to other countries.
6. The ICER varied from 18,465 $ to 30,005 $. In the deterministic sensitivity analysis. Also, the ICER had 99% probability of being cost-effective at a 38,275 $ threshold.
7. Teva-Handok Pharma financed the study.

References

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f. Han, S. et al. Cost–utility analysis of reslizumab for patients with severe eosinophilic asthma inadequately controlled with high-dose inhaled corticosteroids and long-acting β2-agonists in South Korea. Current medical research and opinion. 2019; 10.1080/03007995.2019.1605159.

Table S50: Evidence to decision table supporting recommendations for reslizumab for severe eosinophilic asthma in adults (exacerbations)

	Judgement						
Problem (importance)	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No studies included
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	no important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No studies included
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No studies included
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Table S51: Evidence to decision table supporting recommendations for reslizumab for severe eosinophilic asthma in adults (lung function)

	Judgement						
Problem (importance)	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know

Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	no important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Table S52: Evidence to decision table supporting recommendations for reslizumab for severe eosinophilic asthma in adults (asthma control and QoL)

	Judgement						
Problem (importance)	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No studies included
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	no important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No studies included
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No studies included
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Table S53: Efficacy of reslizumab stratified by blood eosinophils

Blood eos	Exacerbations – incidence risk ratio (95% CI)	FEV1 improvement (95% CI)	Asthma control (ACQ ((95% CI)
>400	0.46 (0.37 to 0.57)	142 (-334 to 618)	-0.14 (-0.77 to 0.5)
>500	0.49 (0.36 to 0.67)	105 (-326 to 536.19)	-0.43 (-1.7 to 0.83)
>600	0.41 (0.28 to 0.6)	250 (10-490)	-0.8 (-1.39 to – 0.21)

Table S54: Efficacy of reslizumab stratified by co-morbidities (CRSwNP)

CRSwNP	Exacerbations – indicence risk ratio (95% CI)	FEV1 improvement ((95% CI)	Asthma control (ACQ) ((95% CI)
With	0.17 (0.10 to 0.29)	220.0 (25.56 – 414.44)	-0.9 (-1.63 to -0.17)
Without	0.56 (0.44 to 0.71)	280.0 (71.86-488.14)	-0.1 (-0.53 to 0.33)

Table S55: Evidence profile for tezepelumab as add-on treatment in asthma

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tezepelumab	standard of care	Relative (95% CI)	Absolute (95% CI)		
Annual exacerbation rates (follow up: mean 52 weeks; assessed with: annual asthma exacerbations)[1a]												
1 [2]	randomised trial	not serious	not serious	not serious	not serious	publication bias strongly suspected [3,b]	0/412	0.7%	IRR **0.33** (0.21 to 0.51)	**757 fewer per 1000 patient(s) per years** (from 836 fewer to 655 fewer)	⨁⨁⨁◯ MODERATE	Critical
Lung function (follow up: mean 52 weeks; assessed with: Pre-bronchodilator Forced Expiratory Volume in One Second (FEV1 in L))[1a]												
1 [2]	randomised trial	not serious	not serious	serious [4,c]	serious [5,d]	publication bias strongly suspected [3,b]	0	0	-	MD **+0.15 SD** (-0.01 to + 0.3)	⨁◯◯◯ VERY LOW	Important
Asthma control (follow up: mean 52 weeks; assessed with: Asthma Control Questionnaire (ACQ-6); Scale from: 1 to 6)[1a]												
1 [2]	randomised trials	not serious	not serious	not serious	serious [6,e]	publication bias strongly suspected [3,b]	0	0	-	MD **-0.31** (-0.44 to -0.18)	⨁⨁◯◯ LOW	Critical
Quality of life (follow up: mean 52 weeks; assessed with: Asthma Quality of Life Questionnaire (AQLQ); Scale from: 1 to 7)[1a]												
1 [2]	randomised trials	not serious	not serious	not serious	serious [7,f]	publication bias strongly suspected [3,b]	0	0	-	MD **+0.04** (-0.4 to +0.48)	⨁⨁◯◯ LOW	Critical
Fraction of exhaled nitric oxide (FeNO) (follow up: mean 52 weeks; assessed with: mean change (ppb))[1a]												
1 [2]	randomised trials	not serious	not serious	serious [g]	serious [8,h]	publication bias strongly suspected [3,b]	0	0	-	MD **-7.74** (-21.79 to +7.2)	⨁◯◯◯ VERY LOW	Low
Treatment-related adverse events (AE) (follow up: mean 52 weeks)[1a]												
1 [2]	randomised trials	not serious	not serious	not serious	serious [i]	publication bias strongly suspected [3,b]	272/412 (66.0%)	91/138 (65.9%)	**Risk ratio 1.00** (0.87 to 1.15)	**0 fewer per 1.000** (from 86 fewer to 99 more)	⨁⨁◯◯ LOW	Critical
Treatment-related serious adverse events (SAE) (follow up: mean 52 weeks)[1a]												

Table S55: Evidence profile for tezepelumab as add-on treatment in asthma

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tezepelumab	standard of care	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1 [2]	randomised trials	not serious	not serious	not serious	serious [i]	publication bias strongly suspected [3,b]	48/412 (11.7%)	18/138 (13.0%)	**Risk ratio 0.90** (0.53 to 1.50)	**13 fewer per 1.000** (from 61 fewer to 65 more)	⨁⨁◯◯ LOW	Critical
Rescue medication use - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Reduction in corticosteroid use - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

CI: Confidence interval; IRR: incidence rate ration **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. As there were three intervention arms and one placebo arm, an adjusted standard error (SE) analysis was used for the calculation of the confidence interval (CI) for the overall effect (1).
b. The only study was funded by industry, and showed positive results. No industry-independent observational or randomized studies were identified to contrast the results. Therefore, evidence was downgraded for potential publication bias (3).
c. Evidence was downgraded because FEV_1 is considered a surrogate outcome for asthma control, with a variable correlation with asthma symptoms (4).
d. The effect may both be harmful or beneficial. The Minimal Important Difference (MID) is 0.23 L (5).
e. The MID is 0.5 points (6).
f. The effect may both be harmful or beneficial. The MID is 0.5 points (6).
g. Evidence was downgraded because FeNO is considered a surrogate outcome of T2 inflammation, with a variable correlation with asthma symptoms.
h. The effect may both be harmful or beneficial. The MID of FeNO change from baseline is more than 10ppb (8).
i. The effect may both be harmful or beneficial.

References

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Table S56: Previous targeted interventions in asthma, currently discontinued

Biological/small molecule	Target/mechanism of action/characteristics	Outcomes	References
Pascolizumab	Humanised Mab selective blocking the interaction of IL-4 with its receptor	Preclinical efficacy; clinical development programmed discontinued to lack of efficacy	Hart TK et al. Clin. Exp. Immunol. 2003; 130, 93–100.
Pitrakinra	IL-4 variant inhibiting the binding of interleukin 4 and interleukin 13 to IL-4R alpha receptor complexes	Modest efficacy in phase IIa trial	Wenzel S et al. Lancet. 2007; 370(9596):1422-31.
AMG317	Fully human Mab to IL-4Ralpha that blocks both IL-4 and IL-13 pathways	No clinical efficacy	Corren J et al. Am J Respir Crit Care Med. 2010;181(8):788–796
Lebrikizumab	Anti-IL-13 humanised Mab; binds to and blocks the activity of IL-13	In phase II trials reduced exacerbation rate in periostin-high patients Failed to reduce exacerbations in phase III trials	Corren J et al. N Engl J Med. 2011; 365(12):1088-98 Hanania N et al. Thorax. 2015; 70(8):748-56 Hanania N et al. Lancet Respir Med. 2016; 4(10):781-796
Tralokinumab	Human IL-13-neutralising immunoglobulin G4 Mab	Failed in both in phase II and phase III trials (asthma control, exacerbation rate, OCS sparing effect)	Piper E et al. Respir. J. 2013; 41, 330–338 Brightling C et al. Lancet Respir. Med. 2015; 3, 692–701 Panettieri R et al. Lancet Respir. Med. 2018; 6, 511–525. Russel J et al. Lancet Respir. Med. 2018; 6, 499–510 Busse WW et al. Eur Respir J. 2019; 53(2)
Quilizumab	Humanised IgG1 Mab targeting the M1-prime segment of membrane-expressed IgE, leading to depletion of IgE-switched and memory B cells	No impact on asthma exacerbations, lung function, or patient-reported symptom measures in phase II trial; biomarker subgroups (periostin, blood eosinophils, serum IgE, and exhaled nitric oxide) without meaningful efficacy benefits	Harris JM et al. Respir Res. 2016;17:29.
Ligelizumab	Mab with greater affinity for IgE than omalizumab	Failed to demonstrate superiority over placebo or omalizumab in treating asthma patients not adequately controlled with high-	https://www.novctrd.com/CtrdWeb/displaypdf.nov?trialresultid=15687

		dose inhaled corticosteroids (ICS) plus long-acting beta2-agonists (LABA) after 16 weeks of treatment	
Brodalumab	Human Mab anti-IL-17 receptor alpha	No treatment effect	Busse WW et al. Am J Respir Crit Care Med. 2013; 188(11):1294–1302
Golimumab	Human Mab against TNF-alpha	Unfavourable risk-benefit profile led to early discontinuation of the study	Wenzel SE, et al. Am J Respir Crit Care Med. 2009; 179(7):549–558
Etanercept	Fully soluble, human dimeric fusion protein, functions as a TNF inhibitor by competitively binding to TNF and preventing its activation of the inflammatory cascade	No clinical efficacy	Holgate ST et al. Eur Respir J. 2011;37(6):1352–1359
Etokimab (ANB020)	Mab inhibiting the activity of IL-33	Positive results in phase IIa study (25 severe adult eosinophilic asthma patients) Phase 2b trial in eosinophilic asthma, a multi-dose, randomized, double-blinded, placebo-controlled trial in 300-400 patients was postponed until results from the ECLIPSE trial (CRSwNP) are analysed	Londei et al., 2019 June. Presented at the 2019 European Academy of Allergy and Clinical Immunology (EAACI) Congress