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EAACI Biologicals Guidelines – Recommendations for severe asthma

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Short title: EAACI Guidelines for biologicals in severe asthma

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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.

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

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

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

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 -

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

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

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

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

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

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.

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

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

* 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

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

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

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

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

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

* 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.

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

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)

- 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)

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

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

*** 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

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).

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)

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

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

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

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

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).

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

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

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

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,

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

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

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

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

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).

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.

Table 1_Agache et al.

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.

Table 2_Agache et al.

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

Table 3_Agache et al.

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?"

Table 4_Agache et al.

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

Table 5_Agache et al.

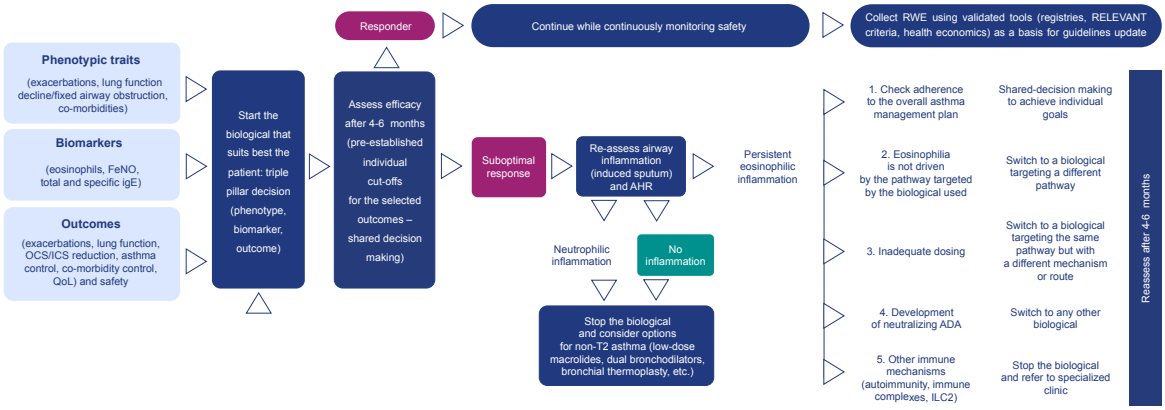
Table 6: Clinical questions not covered by the systematic reviews

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

Table 6_Agache et al.

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.

Table 7_Agache et al.



Agache et al._ Figure 1