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

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

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

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

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Benralizumab | Dupilumab | Omalizumab | Mepolizumab | Reslizumab |
|  | References | References | References | References | References |
| Relevance of clinical trial population for real-world | No data | No data | See IDEAL study  Busse NEJM 2011. The ICATA study screened 996 minority children in US urban centers and randomized 419. The most common reason for exclusion was falling outside the omalizumab dosing table either due to excessive weight or serum IgE. | Bagnasco 2018  RWE population Older, less females, higher FEV1, NP, higher OCS and eos  Plus see IDEAL study  Llanos, J Asthma Allergy. 2019;12:43-58.  In the 12 months prior to initiation of asthma-specific biologics, patients prescribed mepolizumab had a different prevalence of certain comorbidities, higher disease burden, higher HCRU, and higher healthcare costs compared with patients prescribed omalizumab.  Jeimy, Allergy Asthma Clin Immunol. 2018 Nov 22;14:68.  128 patients with severe asthma from Canadian Allergist's practice : 1/3 qualified for all currently available biologics. 41-78% were eligible for at least one mAb.  Patients were most likely to be eligible for mepolizumab. | Albers, J Asthma. 2018;55(2):152-160  The IDEAL study (cross-sectional, single-visit, observational study in six countries; 670 patients with severe asthma)  Treatment eligibility defined according to the local prescribing information or protocol-defined inclusion/  exclusion criteria.  Treatment eligibility for mepolizumab and omalizumab was higher than that for reslizumab.  Although there was some overlap in treatment eligibility, the patient groups eligible for treatment with anti-IL-5 or anti-IgE therapies were often distinct |
|  | Benralizumab | Dupilumab | Omalizumab | Mepolizumab | Reslizumab |
| Efficacy in the pediatric population | No data besides the 12-17 subgroup included in registration trials | No data besides the 12-17 subgroup included in registration trials | Rodrigo, Pediatr Allergy Immunol. 2015;26(6):551-6  SR of 3 RCTs; 1381 children and adolescents; ICS reduction protocol showed reduced number of exacerbations  Folque 2019 RWE of efficacy  Deschildre 2013  RWE benefit greater than that reported in clinical trials | Yancey 2019; subgroup analysis 12-18 years old  Consistent with outcomes in the overall population, reduction in exacerbations  Gupta JACI 2019, open-label, uncontrolled, repeat-dose extension study, 6-11 years, 52 weeks; reduced blood eosinophil counts and asthma exacerbations and improved asthma control across all treatment groups.  Gupta, Pediatr Pulmonol. 2019;54(12):1957-1967  Mepo in 36 children 6 to 11 and eos ≥150 cells/µL at screening or ≥300 cells/µL last 12 months and ≥2 exacerbations in the prior year.  Mepolizumab SC 40 or 100 mg provided bodyweight-adjusted drug exposure within twofold of target adult exposure as well as marked reductions to blood eosinophil counts similar to adults | No data |
|  | Benralizumab | Dupilumab | Omalizumab | Mepolizumab | Reslizumab |
| Safety long term (> 2 years) adult population | Busse 2019 Results from BORA up to 2 years | Data extrapolated from AD trials | Mansur 2017 RWE for safety for 60.7 ± 30.9 months (range 23-121)  Singh, Ann Allergy Asthma Immunol. 2019;123(5):476-482  RWE for safety from the REALITY study (2004-2011); 198 patients | Results from COLUMBA up to 4.5 years  Khurana, Clin Ther. 2019; 41(10):2041-2056  COSMEX: multicenter, open-label, long-term, Phase IIIb study enrolled 340 patients from COSMOS (52-week, open-label extension study that enrolled patients from MENSA and SIRIUS)  To enter COSMEX, patients had to have life-threatening/seriously debilitating asthma before entering MENSA or SIRIUS and to demonstrate improvement with mepo.  In COSMEX, patients received mepo as add-on therapy for up to 172 weeks (718 patient-years of additional exposure) | Virchow, J Allergy Clin Immunol Pract. 2019  Pooled analysis of 6 asthma clinical trials: 5 placebo-controlled (duration ≤52 weeks) and 1 open-label extension (up to 2 years of treatment).  The incidence of AEs in patients on treatment for more than 12 months was no higher than in patients with shorter treatment durations. |
|  | Benralizumab | Dupilumab | Omalizumab | Mepolizumab | Reslizumab |
| Safety in the pediatric population | No data | No data | Rodrigo, Pediatr Allergy Immunol. 2015;26(6):551-6  SR of 3 RCTs in 1381 children and adolescents The frequency of SAE similar to placebo; no evidence of increased risk of hypersensitivity reactions, nor malignant neoplasms.  Folque 2019 RWE of safety up to 6 years administra-tion  Deschildre 2015  8% stopped omalizumab because of side-effects, 75% of which were fatigue following injection. | Yancey 2019 Safety profile in adolescent patients was consistent with that seen in the overall population.  Gupta JACI 2019, 6-11 years, 52 weeks; 90% on-treatment AEs; 23% SAEs.  No SAEs treatment related.  No fatal AEs. No specific patterns of AEs  No ADA or neutralizing antibody responses were reported. | Virchow, J Allergy Clin Immunol Pract. 2019  Pooled analysis included 12-18 years old up to 2 years |
|  | Benralizumab | Dupilumab | Omalizumab | Mepolizumab | Reslizumab |
| Immuno-genicity | Zeitlin 2018, ALIZE trial  Benralizumab did not impair the antibody response to seasonal virus vaccination in asthma population 12-21  Pham 2016  Serum IL-5, eotaxin were decreased.  No changes in TNF or IFN-γ Significant reductions in EDN and ECP concentrations, suggesting that cytotoxic granule proteins are not released following eosinophil depletiion.  Sridhar 2019  Benralizumab is highly selective, modulating blood proteins or genes associated with eosinophils or basophils, especially in high eos patients (> 300) | Blauvelt, J Am Acad Dermatol. 2019;80(1):158-167.  Data from AD trials  Dupilumab does not impact T-cell-dependent and T-cell-independent humoral immune responses to tetanus and meningococcal vaccines, IgE seroconversion to tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccination | Baker, AAPS J. 2016; 18(1):115-23.  No correlation between either anaphylaxis or skin test reactivity and the presence of antibodies of IgE isotype to omalizumab.  Sommerville, Curr Med Res Opin. 2014 Jan;30(1):59-66.  Omalizumab in pre-filled syringes was not associated with immunogenicity.  Mizuma 2015  Treatment with omalizumab increases tIgE and sIgE levels dependant on the baseline level; sIgE may be functional | Ortega 2019  data 3 RCTs (DREAM  MENSA and SIRIUS  and 2 open-label extension studies COSMOS  and COLUMBA) | Mukherjee, Am J Respir Crit Care Med. 2018;197(1):38-46  Reduces anti-eosinophil peroxidase IgG |
|  | Benralizumab | Dupilumab | Omalizumab | Mepolizumab | Reslizumab |
| Best method to monitor ADA |  |  |  | Ortega 2019  screening,  confirmation, and titration analysis |  |
| Co-morbidities | No data | Bachert, J Allergy Clin Immunol Pract. 2019; 7(7):2447-2449. Subgroup analysis of patients with CRSwNP and comorbid asthma  Dupilumab was associated with an improvement of both clinical and patient-reported NP-specific outcomes, and asthma-specific outcomes in patients with CRSwNP and comorbid asthma. | Bidder, Rhinology. 2018;56(1):42-45.  Rapid improvement at 4 weeks and 16 weeks of treatment in both CRSwNP and asthma control.  The improvement in CRSwNP similar to upper airway surgery.  Gevaert 2013  Oma is effective in patient with asthma and NP, both allergic and non-allergic  Gibson, Intern Med J. 2016;46(9):1054-62  Australian XOLAIR registry: Response in participants with comorbid obesity and CV disease was similar to those without these conditions.  Hanania NA, Chipps BE, Griffin NM, Yoo B, Iqbal A, Casale TB. Omalizumab  effectiveness in asthma-COPD overlap: Post hoc analysis of PROSPERO. J Allergy  Clin Immunol. 2019;143(4):1629-1633 | Albers 2019  Post hoc analysis of MENSA and MUSCA: Mepolizumab 100 mg SC has consistent clinical benefits across a range of BMIs: the fixed-dose regimen does not need weight-based dosing. | Weinstein J Allergy Clin Immunol Pract. 2019; 7(2):589-596  Post hoc analyses of pooled data from 2 BREATH phase 3 clinical trials  Patients with self-reported CRSwNP, with and without aspirin sensitivity, are highly responsive to reslizumab for asthma-related outcomes. |
|  | Benralizumab | Dupilumab | Omalizumab | Mepolizumab | Reslizumab |
| Biomarkers |  | Corren, J Allergy Clin Immunol Pract. 2019  Greater efficacy observed in patients with elevated type 2 inflammatory biomarkers (Eos and FeNO) at baseline | Brooks 2019  Use of FeNO to identify omalizumab responders decreases the expected per-patient cost by nearly 50%  Bhutani 2017 RWE (ASTERIX) FeNO predicts response  Casale 2018  Baseline eos and severity criteria (exac, LF, ICS dose and LABA) predict response  Casale 2019 RWE Prospero  Omalizumab shows efficacy irrespective of the biomarker status  Hanania 2013 analysis of EXTRA; FeNO. Blood eos and periostin predict response  Caminati 2019 RWE from NEONET  Blood eosinophils predict responsiveness to omalizumab.  Kawati Clin Ther. 2019; 41(10):1956-1971  RWE patients with allergic asthma could benefit from omalizumab regardless of pretreatment biomarker levels  Brooks 2019  Use of FeNO to identify omalizumab responders decreases the expected per-patient cost by nearly 50%  Bhutani 2017 RWE (ASTERIX) FeNO predicts response  Casale 2018  Baseline eos and severity criteria (exac, LF, ICS dose and LABA) predict response  Casale 2019 RWE Prospero  Omalizumab shows efficacy irrespective of the biomarker status  Hanania 2013 analysis of EXTRA; FeNO. Blood eos and periostin predict response  Caminati 2019 RWE from NEONET  Blood eosinophils predict responsiveness to omalizumab.  Kawati Clin Ther. 2019; 41(10):1956-1971  RWE patients with allergic asthma could benefit from omalizumab regardless of pretreatment biomarker levels,  Sorkness JACI Pract 2013 Predictors of omalizumab response in urban minority children included high exhaled nitric oxide, blood eosinophils and BMI. | Albers 2019, Baseline blood eosinophil count as a predictor of treatment response, post-hoc analysis of MENSA and MUSCA: consistent clinical benefits in patients with baseline blood eosinophil counts ≥150 cells/μL  Ayars 2013  Sputum hyaluronan values are reduced with mepolizumab and correlate with improved ACQ, FEV1 and decreased eos  Harvey ES, et al. [published online ahead of print, 2020 Mar 5]. Eur Respir J. 2020;1902420. doi:10.1183/13993003.02420-2019  Format:  Data from the Australian Mepolizumab Registry show that super-responders to mepolizumab had higher T2 inflammation and less co-morbidities | Mukherjee, Am J Respir Crit Care Med. 2018;197(1):38-46  Changes in sputum IL-5 and anti-eosinophil peroxidase IgG predicted response to reslizumab |
|  | Benralizumab | Dupilumab | Omalizumab | Mepolizumab | Reslizumab |
| The influence of background therapy (number and type) |  |  |  | Albers 2019 Posthoc analysis of Mensa; benefit across a wide range |  |
| Patient selection on a biological | Chipps,  Ann Allergy Asthma Immunol. 2019  post hoc analysis of pooled SIROCCO and CALIMA; benralizumab improved asthma related outocmes in patients with fixed airway obstruction |  | Mukherjee 2019  omalizumab is possibly inadequate to control sputum eosinophilia, and therefore may not have a steroid-sparing effect, especially in those maintained on OCS daily.  Casale Allergy 2018  Baseline blood eos ≥300/μL and markers of asthma severity (emergency asthma treatment in prior year, asthma hospitalization in prior year, FEV1 <65% inhaled beclomethasone dipropionate dose ≥600 μg/day, and LABA use predict response to omalizumab  Sposato, Eur J Intern Med. 2018;52:78-85; retrospective analysis of 340 patients  Age, obesity, comorbidities, smoking habits, nasal polyps, allergic poly-sensitization might reduce Omalizumab effectiveness independently to other asthma-influencing factors. | Humbert 2019: posthoc analysis of MENSA and MUSCA according to according to omalizumab eligibility and associated allergic characteristics shows mepolizumab efficacy regardless of the above criteria  Comberiati, J Allergy Clin Immunol Pract. 2019;7(8):2689-2696.  A smaller percentage of children with severe asthma were eligible for mepolizumab compared with their adult peers. Severe adult onset asthma has distinct phenotypic features that favor treatment with mepolizumab, including greater eosinophilia and NP | Nair J Allergy Clin Immunol Pract. 2019  Numerically greater improvements in OCS -dependent patients than the overall population. Having 2 or more versus 1 clinical asthma exacerbation in the previous 12 months was the strongest positive predictor of reduced exacerbation risk with reslizumab  Carr, Allergy Asthma Proc. 2019;40(4):240-249  Post hoc analysis of two randomized, double-blind, placebo-controlled trials  Reslizumab reduced lung-age deficit by 5 years Improvement in lung age correlated with improved quality of life.  Brussselle, Pulm Pharmacol Ther. 2017; 43:39-45.  Larger reductions in asthma exacerbations and larger improvements in lung function in patients with late versus early-onset asthma. |
|  | Benralizumab | Dupilumab | Omalizumab | Mepolizumab | Reslizumab |
| Continuation/  discontinua-tion criteria |  |  | Bousquet 2014 GETE  Sposato 2019  Higher blood eosinophil levels after omalizumab treatment associated with poorer asthma outcomes.  Caminati 2016 RWE from NEO-NET: 32% drop-out rate due to patient decision or lack of efficacy | Lombardi 2019  4.2 % discontinuation rate in RWE, only 1 case for AE  Cormier 2019; 2 case reports of loss of efficacy after several months or years of effective treatment. Loss of response is associated with recurrence of airway eosinophilia. | ACQ and FEV1 |
|  | Benralizumab | Dupilumab | Omalizumab | Mepolizumab | Reslizumab |
| Switching rules | Matsuno, Respir Med Case Rep. 2019 Jul 9;28:100899.  three case reports whose asthma symptoms were rapidly improved by benralizumab following favorable response to mepolizumab. Benralizumab-induced eosinophil depletion contributed to clinical improvement of severe asthma after mepolizumab-induced eosinophil reduction; thus, prior favorable responses to mepolizumab may predict benralizumab efficacy. |  |  | Chapman 2019: non-responders to oma- switched to mepo -: 62% reduction in exacerbation rate and improvement in ACQ and SGRQ  Bagnasco 2019, non-responders to oma switched to mepo: - 81% decrease in exac rate and improve in FEV1, ACT, decrease in OCS | Mukherjee, Am J Respir Crit Care Med. 2018;197(1):38-46  Weight-adjusted IV reslizumab was superior to fixed-dose SC mepo- in attenuating airway eosinophilia in prednisone-dependent patients with asthma, with associated improvement in asthma control.  Pérez de Llano 2019  weight-based intravenous reslizumab in patients who have previously failed therapy with omalizumab: improved ACT, decreased exacerbations and OCS |
|  | Benralizumab | Dupilumab | Omalizumab | Mepolizumab | Reslizumab |
| Defining efficacy |  |  | Bousquet 2014 GETE  Paganin 2017  FEV1, RV and RV/TLC improved at 6 months in responders patients and then remained stable for 2 years.  Singh, Ann Allergy Asthma Immunol. 2019;123(5):476-482  The Standardized Measure to Assess Response to Therapy (SMART) tool; assessed in the REALITY study; real-life setting, long term (2004-2011);  Response evaluated 1 year before to after treatment by 3 modules: (1) physician's subjective assessment of symptoms and control; (2) objective assessment of 6 parameters: improvement by 50% or more for asthma exacerbation, steroid bursts, emergency department visits, and hospitalizations; increase in FEV1 of 200 mL or greater; and improved Asthma Control Test score of 3 or higher; -and (3) true responders (patient meeting both module 1 and 2 criteria). | Gunsoy 2029  Predefined reduction in:  long-term (previous year) exacerbation frequency  OCS and ICS dose.  ACQ  ?blood eos  Predefined improvement in:  FEV1 versus baseline  QoL  Drick 2018: FEV1 improvement, patient subjective evaluation, decrease in eos  Farah 2019; early improvement in small airway function (Sacin) was associated with asthma control and may be a significant contributor to the therapeutic response.  Antonicelli, Allergy 2019  Forced oscillation technique changes showed to correlate with both eosinophil counts and asthma control scores. | Bateman 2016 ACQ and FEV1 |
|  | Benralizumab | Dupilumab | Omalizumab | Mepolizumab | Reslizumab |
| Time to achieve efficacy | Pelaia 2019 RWE  Within 4 weeks improvement in LF and ACT, OCS stopped | Corren, J Allergy Clin Immunol Pract. 2019  Improvements evident by the first evaluation at week 2 | Sorkness JACI Pract 2013. In urban minority children, the time of onset of omalizumab effect was <30 days. | Ortega 2018  Posthoc analysis of MUSCA and MENSA: > 150 fast effect (1st week) on morning PEF  Pertzov 2019 within 6 months (composite end-point)  Pelaia 2018  Within 4 weeks for LF, Eos, ACT and 24 weeks for exacerbations and OCS reduction  Caminati 2019, RWE from RINOVA  The greatest clinical change (ACT and FEV1) was observed within the first month. | No data |
| Treatment duration | No data | No data | Molimard 2014  A treatment of longer than 3.5 years was associated with no loss of control during the following 6 months.  Pace 2011  marked improvement in clinical parameters and lung function in seven severe asthmatic patients after a 7-year course of omalizumab  Ledford 2017, X‐PORT: discontinuation after a 5‐year course of oma- in adults.  A higher blood eosinophil count at baseline and a significant increase in FeNO from baseline to week 12 after discontinuation were associated with clinical deterioration  Deschildre 2019 RWE for discontinuation of omalizumab in children  allergic multimorbidity and decreased lung function argue for treatment continuation.  Discontinuation could be safely proposed after long‐term use (>2 years) in children with nonactive allergic disease, prolonged controlled asthma, and no severe exacerbations for at least one year.  Deschildre 2015  After 2 years, pediatric population  persistent positive effect on the severe exacerbation rate, and a modest effect on asthma control in the children who continued omalizumab but lack of further lung function improvement  20.7% cessation during the second year due to treatment failure, patients' own decisions and loss to follow-up  Colombo 2019  AQLQ showed a clear increase over time, following 9 years of observation  Singh, Ann Allergy Asthma Immunol. 2019;123(5):476-482  RWE for long-term efficacy from the REALITY study (2004-2011); 198 patients  OMADORE STUDY  (A step-down protocol for omalizumab  treatment in oral corticosteroid-dependent  allergic asthma patients  Domingo et al.  Br J Clin Pharmacol 2917).  The OMADORE study found that in more than 50% of Severe Allergic Asthma patients on Oral Corticosteroids, OMALIZUMAB dose can be safely reduced or withdrawn based  on a progressive dose reduction protocol.  Exacerbations did not occur during the 18-30 month follow-up after drug withdrawn. | Ortega; Allergy Asthma Clin Immunol. 2019 ;15:37.  Follow up of COSMOS; Cessation of mepolizumab was associated with a rise in the blood eosinophil count and loss of asthma control 12 weeks after stopping therapy.  4.5 years  extension of DREAM shows  NO evidence that any continuation  rule adds value to established initiation criteria for mepolizumab | No data |
|  | Benralizumab | Dupilumab | Omalizumab | Mepolizumab | Reslizumab |
| Combinations between biologicals |  |  |  | Altman MC, JACI -P 2017:  mepolizumab as an additional and effective treatment option for severe ABPA resistant to corticosteroids, antifungal therapy, and omalizumab. The case-report demonstrates a potentially synergistic effect of using mepolizumab with omalizumab |  |
|  | Benralizumab | Dupilumab | Omalizumab | Mepolizumab | Reslizumab |
| Other potential indications | Nowak 2015  1 dose of benralizumab reduced the rate and severity of exacerbations experienced over 12 weeks by subjects who presented to the ED with acute asthma  Ferguson 2017 BISE trial in mild to moderate asthma  Some effect on lung function although did not reach the MID |  |  |  |  |
| effects after administration in ED | Nowak RM, et al.  Am J Emerg Med. 2015;33(1):14-20.  Randomized, double-blind, placebo-controlled study; subjects presented to the ED with an asthma exacerbation, had partial response to treatment, and greater than or equal to 1 additional exacerbation within the previous year. 1 iv infusion of benralizumab added to outpatient management reduced the rate and severity of exacerbations over the next 12 weeks |  |  |  |  |
| RWE |  |  | Brusselle 2009, PERSIST study: greater efficacy compared to RCTs  Pelaia 2019:  5 years reduce exac, eos and OCS, improves ACT and LF  Bhutani 2017 ASTERIX study: reduce exac and OCS, improves control and QoL  Adachi 2018 post-marketing surveillance for oma 52 weeks, safety and efficacy proved, including elderly population  Brodlie 2012 OCS-sparing effect equal in children <12 and >12  Rottem 2012 RWE for reducing OCS | Caminati 2019, RINOVA data, significant improvement in exacerbation rate and decrease in OCS + safety + ACT, FeNO, LF  Bagnasco; Pulm Pharmacol Ther. 2019 ;58:101836. retrospective analysis was performed on 138 patients, treated with mepolizumab for at least 12 months, and referred to eleven severe asthma clinics in Italy.  exacerbation rate, systemic steroids intake and safety similar to clinical trials  Pertzov, J Asthma. 2019 Sep 3:1-6  Prospective observational trial in 61 patients >18 years treated with mepolizumab between March 2016 to March 2019; well tolerated and significantly lowered the exacerbation rate and OCS  Harvey ES, et al. [published online ahead of print, 2020 Mar 5]. Eur Respir J. 2020;1902420. doi:10.1183/13993003.02420-2019  Format:  Data from the Australian Mepolizumab Registry show that mepolizumab therapy effectively reduces the significant and long-standing disease burden faced by patients with severe eosinophilic asthma in a real-world setting |  |
|  | Benralizumab | Dupilumab | Omalizumab | Mepolizumab | Reslizumab |
| Health economics |  |  | Shaker, J Allergy Clin Immunol Pract. 2019, at-home administration of omalizumab may be a cost-effective strategy.  Sullivan, Curr Med Res Opin. 2019  Based on RW outcomes omalizumab may be cost-effective for uncontrolled asthma from the US payer perspective.  Entrenas, Pharmacoecon Open. 2019 ; 3(3):333-342  RWE, 220 patients  Omalizumab effective add-on therapy for patients with persistent severe asthma allowing reducing key drivers of asthma-related costs. | García-Mochón, Farm Hosp. 2019;43(6):187-193.  Prioritizing mepo use for non Ig E-mediated severe refractory eosinophilic asthma with ≥ 500 eosinophils/μL improve its efficiency as well as reduces its budgetary impact.  Shaker, J Allergy Clin Immunol Pract. 2019, at-home administration of mepolizumab may be a cost-effective strategy. |  |

| **Table S3: Summary of findings for benralizumab compared to standard of care for eosinophilic asthma** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcomes** | **№ of participants (studies) Follow-up (range)** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects** | | |
| **Risk with standard of care** | | **Risk difference with benralizumab** |
| **Exacerbations**  Assessed with annualised asthma exacerbation rate | 1373 (3 RCTs) 39,40,,41  28 to 56 weeks | ⨁⨁⨁⨁ HIGH 3,a,b | Incidence r**ate ratio 0.53** (0.39 to 0.72) c,d | 1500 exacerbations per 1000 patients per year | **705 fewer exacerbations per 1.000 patients per year** (915 fewer to 420 fewer) | |
| **Asthma Control**  Assessed with ACQ-6 score between-group-difference at the end of the study | 1373 (3 RCTs) 39,40,,41  28 to 56 weeks | ⨁⨁⨁⨁ HIGH 3,4,b,e,f | - |  | | mean difference - **0.26**  (- 0.46 to - 0.07) c,g |
| **Quality of life** Assessed with Asthma Quality of Life Questionnaire for 12 years and older | 1333 (3 RCTs) 39,40,,41  28 to 52 weeks | ⨁⨁⨁⨁ HIGH 3,6,b,j,k | - |  | | mean difference+ **0.23**  (+0.11 to +0.36) c |
| **Any drug related adverse event (AE)**  Assessed with number of events | 478 (1 RCT) 40  56 weeks | ⨁⨁⨁◯ MODERATE 3,b,l | **Risk ratio 1.41** (0.87 to 2.27) | 105 per 1.000 | | **43 more per 1.000** (14 fewer to 133 more) |
| **Any serious adverse event (SAE) unrelated to asthma exacerbation**  Assessed with number of events | 148 (1 RCT) 41  28 weeks | ⨁⨁◯◯ LOW 3,b,l | **Risk ratio 0.56** (0.22 to 1.44) | 147 per 1.000 | | **65 fewer per 1.000** (114 fewer to 65 more) |
| **Decrease in OCS use**  Assessed with reduction in daily OCS dose of ≥50% | 148 (1 RCT) 41  28 weeks | ⨁⨁⨁⨁ HIGH 3,b | **Risk ratio 1.76** (1.26 to 2.47) | 373 per 1.000 | | **284 more per 1.000** (97 more to 549 more) |
| **Lung function**  Assessed with pre-bronchodilator FEV1 (mL) between-group-difference at the end of the study | 1370 (3 RCTs) 39,40,,41  28 to 56 weeks | ⨁⨁⨁◯ MODERATE 3,4,5,b,h,i | - |  | | mean difference +**140 mL**  (+90 to +190) c |
| **Rescue medication use**  Assessed with puffs/day | 0 studies | - | not estimable |  | |  |
| \***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). | | | | | | |
| **GRADE Working Group grades of evidence** **High certainty:** High confidence that the true effect lies close to that of the estimate of the effect **Moderate certainty:** Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect **Very low certainty:** Little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect | | | | | | |

#### Explanations

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

b. All included studies were funded by industry, and all showed positive results. No industry-independent observational or randomized studies were identified to contrast results. Therefore, the quality of the evidence was downgraded for potential publication bias

c. The pooled data were assessed at 28 weeks (41) and at 48-52 weeks (71). Goldman 2017 included patients aged 12-17 years old.

d. In the current systematic review 2 studies reporting the effect on exacerbation leading to emergency room visits or hospitalizations were also included. The pooled risk ratio was 0.24 (95% CI 0.03-1.72)

e. Statistically significant (I2=61%) but probably unimportant heterogeneity.

f. The minimal important difference (MID) for ACQ-6 is 0.5 points

g. In the current systematic review 3 studies reporting the effect on total asthma control score change were also included. The pooled mean difference was -0.19 (95CI% -0.31 to -0.08), see full text report.

h. Quality of the evidence was downgraded because FEV1 is considered a surrogate outcome for asthma control, with a variable correlation with asthma symptoms.

i. The GDG agreed that minimal important difference for FEV1 is 0.20 L.

j. Statistically significant (I2=55%) but probably unimportant heterogeneity.

k. For AQLQ(S)+12 the MID is 0.5

l. The effect may both be harmful or beneficial. Small sample size and number of events.

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

| **Quality assessment** | | | | | | | **Summary of resources and costs** | | | **Quality** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Nº. of studies** | **Study design** | **Limitations** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Incremental cost per patient\*** | **Incremental effect per patient\*** | **ICER** |
| ICER per QALY (high quality study - not funded by Industry) | | | | | | | | | | |
| 1a | Cost-utility,  Markov model | Not serious1 | Not serious | Serious2 | Serious3 | Not serious | 581,000 $  (lifetime horizon) | 1.41 QALYs  (lifetime horizon) | 412,000 $ / QALY4 | ⨁⨁⨁◯  MODERATE |
| ICER per QALY (high quality study - funded by Industry) | | | | | | | | | | |
| 1b | Cost-utility,  Markov model | Not serious5 | Not serious | Serious6 | Serious7 | Not serious | NR £  (lifetime horizon) | NR QALYs  (lifetime horizon) | 39,135 £ / QALY4 | ⨁⨁◯◯  LOW |

\*Incremental cost and effect due to the addition of benralizumab.

ICER: Incremental cost-effectiveness ratio. QALY: Quality adjusted life years. $: US Dollar. £: British pounds. NR: Not reported.

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

**References**

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

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

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

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

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

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

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

**Table S8 – benralizumab efficacy stratified according to blood eosinophils**

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

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

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

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

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

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

| **Outcomes** | **№ of participants (studies) Follow-up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
| --- | --- | --- | --- | --- | --- |
| **Risk with standard of care** | **Risk difference with Benralizumab** |
| Exacerbations assessed with annual asthma exacerbation rate | 297 (2 RCTs) 34  48 weeks to 56 weeks | ⨁⨁⨁⨁ HIGH 2,a | **Incidence rate ratio**  **0.63** (0.50 to 0.81) | 13 per 1.000 | **5 fewer per 1.000** (6 fewer to 2 fewer) |
| Asthma Control  assessed with: ACQ-6 score between-group-difference at the end of treatment | 414 (2 RCTs) 34  48 weeks to 56 weeks | ⨁⨁⨁⨁ HIGH 2,3,a,b | - | The mean asthma Control was **0** | MD - **0.17**  (-0.34 to 0 ) |
| Quality of Life assessed with: Quality of Life Questionnaire for 12 years and older [AQLQ(S)+12], between-group-difference at the end of treatment | 404 (2 RCTs) 34  48 weeks to 56 weeks | ⨁⨁⨁⨁ HIGH 2,5,a,e | - | The mean quality of Life was **0** | MD +**0.1**  (-0.08 to +0.28) |
| Any drug related adverse event  assessed with: Number of events- Urgent care visit, or admission to hospital | 478 (1 RCT) 35  56 weeks | ⨁⨁◯◯ LOW 2,a,f,g | **Risk ratio 1.41** (0.87 to 2.27) | 105 per 1.000 | **43 more per 1.000** (14 fewer to 133 more) |
| Any drug related serious adverse event  assessed with: Number of SAE unrelated to asthma exacerbation | 148 (1 RCT) 36  28 weeks | ⨁⨁◯◯ LOW 2,a,f,g | **Risk ratio 0.56** (0.22 to 1.44) | 147 per 1.000 | **65 fewer per 1.000** (114 fewer to 65 more) |
| Lung function  assessed with: Pre-bronchodilator FEV1 (mL) between-group-difference at the end of treatment) | 490 (2 RCTs) 34  48 weeks to 56 weeks | ⨁⨁⨁◯ MODERATE 2,3,4,a,c,d | - | The mean lung function was **0** L | MD + **0.055 L**  (-0.025 to + 0.136) |
| \***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).   **CI:** Confidence interval; **MD:** Mean difference; **RR:** Risk ratio | | | | | |
| **GRADE Working Group grades of evidence** **High certainty:** High confidence that the true effect lies close to that of the estimate of the effect **Moderate certainty:** Moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect **Very low certainty:** Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect | | | | | |

#### Explanations

1. Included studies were all funded by industry, and all showed positive results. No industry-independent observational or randomized studies were identified to contrast the results. Therefore, evidence was downgraded for potential publication bias (102).
2. For ACQ-6 the minimal important difference is 0.5 points (30)
3. Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a variable correlation with asthma symptoms (103).
4. The effect may both be harmful or beneficial. The minimal important difference (MID) for FEV1 is 0.20 L (Guidelines development group consensus).
5. For AQLQ(S) + 12 the minimal important difference is 0.5 (32)
6. Downgraded one level due to indirectness (data from severe asthma patients that may have or may have not allergic asthma)
7. The effect may both be harmful or beneficial. Estimations are based on less than 300 events, thus there is probably important imprecision.

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

| **Quality assessment** | | | | | | | **Summary of resources and costs** | | | **Quality** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Nº. of studies** | **Study design** | **Limitations** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Incremental cost per patient\*** | **Incremental effect per patient\*** | **ICER** |
| ICER per QALY (high quality study - not funded by Industry) | | | | | | | | | | |
| 1a | Cost-utility,  Markov model | Not serious1 | Not serious | Serious2 | Serious3 | Not serious | 581,000 $  (lifetime horizon) | 1.41 QALYs  (lifetime horizon) | 412,000 $ / QALY4 | ⨁⨁⨁◯  MODERATE |
| ICER per QALY (high quality study - funded by Industry) | | | | | | | | | | |
| 1b | Cost-utility,  Markov model | Not serious5 | Not serious | Serious6 | Serious6 | Not serious | NR £  (lifetime horizon) | NR QALYs  (lifetime horizon) | 39,135 £ / QALY4 | ⨁⨁◯◯  LOW |

\*Incremental cost and effect due to the addition of Benralizumab.

ICER: Incremental cost-effectiveness ratio. QALY: Quality adjusted life years. $: US Dollar. £: British pounds. NR: Not reported.

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

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

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

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

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

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

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

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

| **Table S16: Summary of findings of Dupilumab compared to standard of care for eosinophilic asthma** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Outcomes** | **№ of participants (studies) Follow-up (range)** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
| **Risk with standard of care** | **Risk difference with dupilumab** |
| **Exacerbations**  Assessed with annualised asthma exacerbation rate | 1712  (3 RCTs) 42,43,44  24 to 52 weeks | ⨁⨁⨁⨁ HIGH4,a,b | **Incidence rate ratio 0.44**(0.32 to 0.59) | 1570 exacerbations per 1000 patients per year | **894 fewer exacerbations per 1000 patients per year** (1086 fewer to 655 fewer)c |
| **Asthma control**  assessed with: Asthma Control Questionnaire -5 Scale from: 1 to 5 | 507 (1 RCT) 42  24 weeks | ⨁⨁⨁◯ MODERATE 4,8,a,b,g | - |  | mean difference - **0.48**  (-0.88 to - 0.09) |
| **Quality of life** Assessed with asthma Quality of Life Questionnaire  Scale from: 1 to 7 | 958 (2 RCTs) 43,44  24 to 52 weeks | ⨁⨁⨁◯ MODERATE 4,9,a,b,h | - |  | mean difference + **0.42**  (+0.25 to +0.59) |
| **Treatment-related adverse events (AE)** Assessed with number of events | 264 (1 RCT) 42  24 weeks | ⨁⨁⨁◯ MODERATE 4,a,b,m | **Risk ratio 1.00** (0.88 to 1.13) | 794 per 1.000 | **0 fewer per 1.000** (95 fewer to 103 more) |
| **Treatment-related serious adverse events (SAE)** Assessed with number of events | 264 (1 RCT) 42  24 weeks | ⨁⨁◯◯ LOW 4,a,b,m | **Risk ratio 1.46** (0.60 to 3.54) | 59 per 1.000 | **27 more per 1.000** (24 fewer to 149 more) |
| **Decrease in OCS dose**  Assessed with percentage of reduction compared to baseline | 150 (1 RCT) 42  24 weeks | ⨁⨁⨁⨁ HIGH 4,a,b | - |  | mean difference - **29.4 %**  (-43.23 to -15.57 ) |
| **Lung function**  Assessed with FEV1 in mL | 1030 (3 RCTs) 42,43,44  24 to 52 weeks | ⨁⨁◯◯ LOW 4,5,6,7,a,b,d,e,f | - |  | mean difference + **180 mL**  (+110 to +250) |
| **Fraction of exhaled nitric oxide**  Assessed with mean % change (ppb) from baseline | 150 (1 RCT) 42  24 weeks | ⨁⨁◯◯ LOW 4,10,11,12,a,b,i,j | - |  | mean difference - **40.11 %**  (-78.68 to -1.55) |
| **Rescue medication use**  Assessed with puffs/day | 143 (1 RCT) 42  24 to 52 weeks | ⨁⨁⨁◯ MODERATE 4,7,a,b,k,l | - |  | mean difference - **0.56 puff/day**  (-2.28 to +1.16) |
| \***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). | | | | | |
| **GRADE Working Group grades of evidence** **High certainty:** High confidence that the true effect lies close to that of the estimate of the effect **Moderate certainty:** Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect **Very low certainty:** Little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect | | | | | |

#### Explanations

a. All included studies had a high risk of selective reporting bias (42,43,44). However, the evidence quality was not downgraded because most of the outcomes of interest for our analysis were reported.

b. All included studies were founded by industry and the same company (Sanofi and Regeneron Pharmaceuticals), and all showed positive results. No industry-independent observational or randomized trials were identified to contrast the results. Therefore, the quality of the evidence was downgraded for potential publication bias (70)

c. Two studies (Rabe 2018, Wenzel 2016) assessed exacerbations at 24 weeks, and Castro2018 at 52 weeks.

d. The quality of the evidence was downgraded because FEV1 is considered a surrogate outcome of asthma control, with a variable correlation with asthma symptoms (72).

e. The panel agreed that minimal important difference (MID) for FEV1 is 0.20 L and considered the effect as imprecise.

f. The panel agreed that minimal important difference (MID) for FEV1 is 0.20 L and thus the effect was considered as imprecise.

g. Downgraded because the effect of dupilumab is beneficial but the lower side of the CI is less than the MID( 0.5 points). (37)

h. Downgraded because the effect of dupilumab is beneficial but the lower side of the CI is less than the MID( 0.5 points). (37)

i. Downgraded because FeNO is not consistently considered a good surrogate of eosinophilic inflammation (73,74)

j. From one visit to the next a change greater than 20% for basal values over 50 ppb or more than 10 ppb for basal values lower than 50 ppb may indicate significant response (38).

k. Downgraded because the effect may both be beneficial and harmful.

l. The MID for rescue medication use is a reduction by 0.81 puffs/day (35).

m. The effect may both be harmful or beneficial. Small number of events.

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

| **Quality assessment** | | | | | | | **Summary of resources and costs** | | | **Quality** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Nº. of studies** | **Study design** | **Limitations** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Incremental cost per patient\*** | **Incremental effect per patient\*** | **ICER** |
| ICER per QALY (high quality study - not funded by Industry) | | | | | | | | | | |
| 1a | Cost-utility,  Markov model | Not serious1 | Not serious | Serious2 | Serious3 | Not serious | 704,000 $  (lifetime horizon) | 1.51 QALYs  (lifetime horizon) | 464,000 $ / QALY4 | ⨁⨁⨁◯  MODERATE |

\*Incremental cost and effect due to the addition of Dupilumab.

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

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

**References**

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

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

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

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

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

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

|  |  |  |
| --- | --- | --- |
| **Blood eos** | **Exacerbations – incidence rate ratio (95% CI)** | **FEV1 increase (95% CI)** |
| >300 | 0.35 (0.28-0.44) | + 0.23 (+0.18 to +0.29) |
| <300 | 0.63 (0.48 -0.83) | +0.08 (+0.04 to +0.13) |

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

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

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

| **Outcomes** | **№ of participants (studies) Follow-up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
| --- | --- | --- | --- | --- | --- |
| **Risk with standard of care** | **Risk difference with Dupilumab** |
| Clinically significant exacerbations rate ratio  assessed with: annual asthma exacerbations | 1083 (1 RCT) 38  52 weeks | ⨁⨁⨁⨁ HIGH 2,a | **Rate ratio 0.58** (0.47 to 0.73) | **Moderate** | |
| 10 per 1.000 | **4 fewer per 1.000** (5 fewer to 3 fewer) |
| Asthma control  assessed with: Asthma Control Questionnaire (ACQ-5) Scale from: 1 to 5 | 1013 (1 RCT) 38  24 weeks | ⨁⨁⨁⨁ HIGH 2,7,a,d | - | The mean asthma control was **0** | MD - **0.27**  (-0.4 to - 0.14) |
| Lung function  assessed with: Forced expiratory volume in one second (FEV1 in L) change from baseline | 1055 (1 RCT) 38  12 weeks | ⨁⨁◯◯ LOW 2,3,4,5,a,b,c | - | The mean lung function change from baseline was **0** L | MD + **0.15 L**  (+0.09 to + 0.2) |
| \***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).   **CI:** Confidence interval; **MD:** Mean difference | | | | | |
| **GRADE Working Group grades of evidence** **High certainty:** High confidence that the true effect lies close to that of the estimate of the effect **Moderate certainty:** Moderately confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect **Very low certainty:** Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect | | | | | |

#### Explanations

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

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

| **Quality assessment** | | | | | | | **Summary of resources and costs** | | | **Quality** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Nº. of studies** | **Study design** | **Limitations** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Incremental cost per patient\*** | **Incremental effect per patient\*** | **ICER** |
| ICER per QALY (high quality study - not funded by Industry) | | | | | | | | | | |
| 1a | Cost-utility,  Markov model | Not serious1 | Not serious | Serious2 | Serious3 | Not serious | 704,000 $  (lifetime horizon) | 1.51 QALYs  (lifetime horizon) | 464,000 $ / QALY4 | ⨁⨁⨁◯  MODERATE |

\*Incremental cost and effect due to the addition of Dupilumab.

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

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

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

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

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

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

## **Table S26 Summary of finding for dupilumab in severe T2 asthma**

| **Dupilumab compared to standard of care for asthma** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Population:** patients with severeasthma uncontrolled under ICS/OSC and 1-2 additional controllers  **Intervention:** dupilumab  **Comparison:** standard of care | | | | | |
| **Outcomes** | **№ of participants evaluated for a particular outcome (no of studies pooled for the SR) Follow-up range** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
| **Risk with placebo** | **Risk difference with dupilumab** |
| EXACERBATION RATE RATIO  assessed with annualised asthma exacerbations rate | 2735 (3 RCTs)  26, 27,28  24 to 52 weeks | ⨁⨁⨁⨁ HIGH 4,a | **Incidence risk ratio 0.51**  (0.45 to 0.59)b | **Moderate** | |
| 90 per 1,000 | **757 fewer** per 1,000  (from 836 fewer to 655 fewer) |
| LUNG FUNCTION  assessed with FEV1 in L | 2577 (3 RCTs) 26,27,28  24 to 52 weeks | ⨁⨁⨁◯ MODERATE 4,a,c,d | - | - | MD +**0.15** (+0.11 to +0.18)b |
| ASTHMA CONTROL  assessed with Asthma Control Questionnaire-5  (ACQ-5)  Scale from: 1 to 5 | 2516 (3 RCTs) 26,27,28  24 to 52 weeks | ⨁⨁⨁⨁ HIGH 4,a, e | - | - | MD -**0.28** (-0.39 to -0.17) b |
| QUALITY OF LIFE  assessed with Asthma Quality of Life  Questionnaire (AQLQ)  Scale from: 1 to 7 | 2046  (2 RCTs) 26,27  24 to 52 weeks | ⨁⨁⨁⨁ HIGH 4,a, f | - | - | MD +**0.28** (+0.2 to +0.37) b |
| SAFETY  Treatment-related adverse events (AE) | 356 (1 RCT) 26  mean 24 weeks | ⨁⨁⨁◯ MODERATE 4,a,j | **Risk ratio 1.12** (0.98 to 1.28) k | 711 per 1.000 | **85 more per 1.000** (14 fewer to 199 more) |
| SAFETY  Treatment-related serious adverse events (SAE) | 356 (1 RCT) 26  mean 24 weeks | ⨁⨁◯◯ LOW 4,a,k | **Risk ratio 1.23** (0.54 to 2.77) | 56 per 1,000 | **13 more per 1.000** (26 fewer to 98 more) |
| REDUCTION IN RESCUE MEDICATION USE  assessed with: puffs/day | 568  (1 RCT) 26  24 to 52 weeks | ⨁⨁⨁⨁ HIGH 4,a | **-** | - | MD -**0.35 lower** (-0.73 to -0.02) |
| REDUCTION OF ORAL CORTICOSTEROID USE assessed with mg/day decrease | 210  (1 RCT) 28  mean 24 weeks | ⨁⨁⨁⨁ HIGH 4,a | - | - | MD - **28.2**  (-40.7 to -15.7) |
| Fraction of exhaled nitric oxide (FeNO)  assessed with mean % change (ppb) | 2375  (2 RCTs)26,27  mean 24 weeks | ⨁⨁⨁◯ MODERATE 4,5,6,a,h | - | - | MD - **38.57** (-48.83 to -28.31)g |
| \***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).  **CI:** Confidence interval; **MD:** Mean difference; **RR:** Risk ratio | | | | | |
| **GRADE Working Group grades of evidence** **High certainty:** High confidence that the true effect lies close to that of the estimate of the effect **Moderate certainty:** Moderately confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Limited confidence in the effect estimate : the true effect may be substantially different from the estimate of the effect **Very low certainty:** Very limited confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect | | | | | |

**Explanations**

a. All three trials in our meta-analysis were industry-funded, all by the same company (Sanofi-Regeneron Pharmaceuticals), and all showed positive results. No observational or industry-independent randomized trials were identified to compare with the results derived from the included RCTs.

b. Testing for subgroup differences indicated that there was not relevant subgroup effect by dupilumab dose

c. Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a variable correlation with asthma symptoms (35).

d. Minimal important difference (MID) of 0.23 L (22).

e. The MID of ACQ-5 is 0.5 points (24)

f. The MID of AQLQ is 0.5 points (24)

g. The MID decrease of the FENO value is defined as a difference larger than 20% for values over 50ppb or more than 10ppb for values lower than 50ppb from one visit to the next (25).

h. Downgraded because FeNO is not consistently considered a good surrogate of inflammation (36,37)

i. For rescue medication use, the MID is a reduction by 0.81 puffs/day (22).

j. The effect may both be harmful or beneficial.

k. Few events reported in both intervention and control arm, and the effect may be both harmful and beneficial

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

| **Quality assessment** | | | | | | | **Summary of resources and costs** | | | **Quality** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Nº. of studies** | **Study design** | **Limitations** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Incremental cost per patient\*** | **Incremental effect per patient\*** | **ICER** |
| ICER per QALY (high quality study - not funded by Industry) | | | | | | | | | | |
| 1 | Cost-utility,  Markov model | Not serious1 | Not serious | Serious2 | Serious3 | Not serious | 704,000 $  (lifetime horizon) | 1.51 QALYs  (lifetime horizon) | 464,000 $ / QALY4 | ⨁⨁⨁◯  MODERATE |

\*Incremental cost and effect due to the addition of Dupilumab.

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

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

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

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

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

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

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

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

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

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

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

| **Table S32: Summary of findings of mepolizumab compared to standard of care for eosinophilic asthma** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Outcomes** | **№ of participants (studies) Follow-up (range)** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
| **Risk with standard of care** | **Risk difference with mepolizumab** |
| **Exacerbations**  Exacerbation rate ratio  Assessed witt the annualized rates of asthma exacerbations | 1071 (3 RCTs) 45,46,47  24 to 32 weeks | ⨁⨁⨁⨁ HIGH 4,5,a,b,c | **Incidence rate ratio 0.49** (0.38 to 0.66) | 1700 exacerbations per 1000 patients per year | **870 fewer exacerbations per 1000 patients per year** (592 fewer to 1079 fewer) |
| **Exacerbations leading to hospitalisation** Assessed with the annualized rate of asthma exacerbations leading to hospitalisation | (2 RCTs) 45,47  24 to 32 weeks | ⨁⨁⨁⨁ HIGH 4,5,a,c,d | **Incidence rate ratio 0.30** (0.13 to 0.71) | 100 exacerbations per 1000 patients per year | **70 fewer exacerbations per 1000 patients per year** (29 fewer to 87 fewer) |
| **Asthma control** Assessed with: ACQ-5 score between-group-difference at the end of the study Scale from: 0 to 6 9,j | 912 (3 RCTs) 45,47 | ⨁⨁⨁◯ MODERATE 4,5,a,c,i | - |  | mean difference - **0.43**  (- 0.56 to - 0.31) |
| **Quality of life** Assessed with St. George's Respiratory Questionnaire between-group-difference at the end of the study | 1045 (3 RCTs) 45,46,47  24 to 32 weeks 10,k | ⨁⨁⨁◯ MODERATE 4,5,a,c,l | - |  | mean difference - **7.14**  (- 9.07 to - 5.21) |
| **Treatment-related adverse events (AE)** Assessed with number of events | 1071 (3 RCTs) 45,46,47 | ⨁⨁⨁⨁ HIGH 4,5,c | **Risk ratio 1.35** (1.01 to 1.80) | 796 per 1.000 | **279 more per 1.000** (8 more to 637 more) |
| **Treatment-related serious adverse events (SAE)** Assessed with number of events | 385 (1 RCT) 47 | ⨁◯◯◯ VERY LOW 4,5,c,m,n | **Risk ratio 0.98** (0.06 to 15.63) | 5 per 1.000 | **0 fewer per 1.000** (-5 fewer to 77 more) |
| **Lung function** assessed with pre-bronchodilator FEV1 (mL) between-group-difference at the end of the study | 1043 (3 RCTs) 45,46,47  24 to 32 weeks 6,e | ⨁⨁⨁◯ MODERATE 4,5,7,a,c,f | - |  | mean difference +**110.9 mL**  (+58.91 to +162.89) |
| **Lung function** assessed with AM peak expiratory flow (PEF) | 936 (2 RCTs) 77  24 weeks 6,g | ⨁⨁◯◯ LOW 4,5,c,h,i | - |  | mean difference +**22.46**  (+13.98 to +30.94) |
| **Rescue medication use** assessed with puffs/day | (1 RCT) 45  21 to 24 weeks o | ⨁⨁⨁⨁ HIGH 4,5,c | - |  | mean difference -**0.1**  (-0.35 to +0.15) |
| \***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). | | | | | |
| **GRADE Working Group grades of evidence** **High certainty:** High confidence that the true effect lies close to that of the estimate of the effect **Moderate certainty:** Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect **Very low certainty:** Little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect | | | | | |

#### Explanations

a. Two of three studies had a high risk of attrition bias (45,47). Modified intention-to-treat analysis was conducted (i.e. patients were analysed as treated, not as randomized).

b. Probable unimportant heterogeneity

c. Included studies were all funded by industry, and all showed positive results. We identified two industry-independent observational trials that showed similar effects with our meta-analysis (76,77).

d. Mean rates of exacerbation requiring hospitalization across studies were very low (i.e. from 0.02 to 0.10 exacerbations requiring hospitalization per person-year), both in the placebo and intervention arms

e. The panel agreed that minimal important difference (MID) for FEV1 is 0.20 L

f. Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a variable correlation with asthma symptoms (72).

g. The MID of PEF is 18.8 L/min (35)

h. Potential attrition bias because PEF baseline values reported in the primary publication (47) differed from values reported in post-hoc analysis publication (77)

i. Downgraded because the lower CI boundary crosses the MID threshold

j. 0.5 points is the minimal important difference for the Asthma Control Questionnaire (ACQ-5 score) (37)

k. >-4.0 was considered the threshold for the MID for quality of life measured with the St.George's Respiratory Questionnaire (36)

l. The St.George's Respiratory Questionnaire SGRQ is not a disease-specific questionnaire for asthma

m. Findings from only 1 RCT available. Downgraded due to publication bias

n. Very few numbers of events per arm

o. The minimal important difference for rescue medication use is -0.81 puffs/day (35)

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

| **Quality assessment** | | | | | | | **Summary of resources and costs** | | | **Quality** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Nº. of studies** | **Study design** | **Limitations** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Incremental cost per patient\*** | **Incremental effect per patient\*** | **ICER** |
| ICER per QALY (high quality study - not funded by Industry) | | | | | | | | | | |
| 1a | Cost-utility,  Markov model | Not serious1 | Not serious | Serious2 | Serious3 | Not serious | 589,941 $  (Lifetime horizon) | 1.53 QALY  (Lifetime horizon) | 385,546 $ / QALY4 | ⨁⨁◯◯  LOW |

\*Incremental cost and effect due to the addition of Mepolizumab.

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

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

**References**

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

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

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

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

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

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

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

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

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

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

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

| **Table S39: Summary of findings of Omalizumab compared to standard of care for eosinophilic asthma** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Outcomes** | **№ of participants (studies) Follow-up (range)** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
| **Risk with standard of care** | **Risk difference with omalizumab** |
| **Exacerbations** Assessed with annual asthma exacerbations rate | 779 (3 RCTs) 48,50,51  16 to 48 weeks | ⨁⨁⨁⨁ HIGH 4,a,b | **Incidence rate ratio 0.56** (0.40 to 0.77) | 660 exacerbations per 1000 patients per year | **290 fewer exacerbations per 1.000 patients per year** (396 fewer to 152 fewer) |
| **Asthma Control** Assessed with Total Asthma Symptoms Score | 414 (1 RCT) 48  48 weeks | ⨁⨁◯◯ LOW 4,a,b,c,d | - |  | mean difference - **0.16**  (- 0.51 to +0.19) e,f |
| **Quality of Life**  Assessed with Asthma Quality of Life Questionnaire | 414 (1 RCT) 48  48 weeks | ⨁⨁⨁◯ MODERATE 4,a,b,d | - |  | mean difference + 0.13 (-0.11 to + 0.37) l |
| **Any adverse event**  Assessed with number of events | 414 (1 RCT) 48  48 weeks | ⨁⨁⨁◯  MODERATE 4,a,b,d | **R**isk **ratio 1.01**  (0.91 to 1.11) | 794 per 1.000 | **8 more per 1.000** (71 fewer to 87 more) |
| **Lung Function**  Assessed with % pre-bronchodilator FEV1 between-group-difference at the end of the study | (2 RCTs) 48,50  24 weeks to 48 weeks | ⨁⨁⨁◯ MODERATE 4,5,a,b,g,h,i | - |  | mean difference + **3.7 %**  (-2.1 to + 9.5) j,k |
| **Rescue medication use**  Assessed with puffs/day change from baseline | 414 (1 RCT) 48  48 weeks | ⨁⨁⨁◯ MODERATE 4,a,b,d | - |  | mean difference - **0.34**  (-0.83 to +0.15) 6,m,n |
| **GRADE Working Group grades of evidence** **High certainty:** High confidence that the true effect lies close to that of the estimate of the effect **Moderate certainty:** Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect **Very low certainty:** Little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect | | | | | |

#### Explanations

a. Information of included studies from non-predefined subgroup analysis.

b. Included studies were all funded by industry, and all showed positive results. We identified one industry-independent observational trial that showed similar effects with our meta-analysis (78).

c. The total asthma symptoms score is an unvalidated scale.

d. The effect may both be harmful or beneficial.

e. Data from subgroup of patients with blood eosinophil count ≥ 260/ul. This study also reported total asthma symptoms score for the subgroup of FeNO ≥ 24ppb, the mean difference is -0.25 (CI 95% -0.77 to 0.27).

f. In the current systematic review we also included one study (49) reporting the effect on the symptom days over the previous 2 weeks at 48 weeks follow up, the mean difference is -0.45 (p=0.05) (see full text report).

g. Statistically significant (I2=70%), but probably unimportant heterogeneity.

h. Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a variable correlation with asthma symptoms (72)

i. The panel agreed that minimal important difference (MID) for FEV1 is 0.20 L j. Population with different threshold of eosinophil counts across the studies: ≥ 200 cells/µl (51), ≥ 300 cells/µl (50) and ≥ 260 cells/µl (48).

k. One of the included studies (48) also reported the effect on FEV1 % change for a population with FeNO ≥ 24 ppb, the LS mean difference is 3.20 (CI 95% -0.74 to 0.27). The pooled effect evaluated at 48 weeks (48) and 24 weeks (50).

l. Data from subgroup of patients with blood eosinophil count ≥ 260/ul. This study also reported AQLQ for the subgroup of FeNO ≥ 24ppb , the mean difference is 0.37 (CI 95% 0.01 to 0.73).

m. This study also reported the effect on rescue medication use for the subgroup of FeNO ≥ 24 ppb, the mean difference is -0.49 (CI 95% -0.88 to -0.11).

n. The MID for rescue medication use is 0.81 puffs/day (35).

#### References

1. Busse W, Spector S,Rosén K,Wang Y,Alpan O. High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects. J Allergy Clin Immunol 2013

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

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

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

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

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

|  | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Outcomes** | **№ of participants (studies) Follow-up range** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
| **Risk with standard of care** | **Risk difference with Omalizumab** |
| Annual rate of clinically significant asthma exacerbations  assessed with annualised rate | 2772  (6 RCTs) 42,44,51,54,55,68  24 weeks to 52 weeks a | ⨁⨁⨁⨁ HIGH b,c,d | **Rate ratio 0.56** (0.45 to 0.69) e,f | **Low** | |
| 14 per 1.000 | **616 fewer per 1.000** (770 fewer to 378 fewer) |
| Asthma control  assessed with ACQ-6 score; | 939 (3 RCTs) 44,56,59  26 weeks to 52 weeks | ⨁⨁⨁◯ MODERATE 9,b,d,g | - | The mean asthma Control was **0** point | MD -**0.38**  (-0.68 to -0.09) h,i |
| Global evaluation of treatment effectiveness assessed with: physicians/investigators' assessment | 3783 (10 RCTs) 68, 54,59,62,66,40,48,47,43,63  16 weeks to 52 weeks | ⨁⨁⨁⨁ HIGH b,d,j | **Rate ratio 1.50** (1.32 to 1.70) k | 418 per 1.000 | **209 more per 1.000** (134 more to 292 more) k |
| Clinically significant improvement of Asthma Quality of Life (≥0.5 from baseline)  assessed with: AQLQ Questionnaire (S) | 3540 (9 RCTs) 40,47,51,52,54,55,62,63,67  12 weeks to 52 weeks | ⨁⨁⨁⨁ HIGH b,d,l | **Rate ratio 1.32** (1.16 to 1.51) m | 563 per 1.000 | **180 more per 1.000** (90 more to 287 more) m |
| Any drug-related AE | 2341 (7 RCTs) 68,54,66, 43, 63, 67, 50  16 weeks to 52 weeks | ⨁⨁⨁◯ MODERATE ab,b,d | **Rate ratio 1.27** (0.93 to 1.74) | 127 per 1.000 | **34 more per 1.000** (9 fewer to 94 more) |
| Any drug-related SAE) | 1163 (2 RCTs) 51, 60  16 weeks to 48 weeks | ⨁⨁⨁◯ MODERATE ab,b,d | **Rate ratio 1.62** (0.76 to 3.45) | 18 per 1.000 | **11 more per 1.000** (4 fewer to 43 more) |
| Lung function (FEV1) assessed with absolute FEV1 (L) change versus baseline | 1209 (6 RCTs) 55, 42,62, 43, 60, 61  range 12 weeks to 52 weeks n,o | ⨁⨁◯◯ LOW 21,22,23,b,p,q,r | - | The mean lung function was **0** L | MD +**0.17 L**  (+0.02 to + 0.32) s |
| Lung function (PEF) assessed with morning PEF rate change (L/m) versus baseline | 1735 (7 RCTs) 59, 48, 52,60, 41,58,49  12 weeks to 36 weeks t | ⨁⨁⨁◯ MODERATE 21,22,23,b,p,r,u | - | The mean lung function was **0** | MD +**10.04 higher** (+7.49 to +12.6) |
| Decrease in inhaled corticosteroid  assessed as µg/day variation versus baseline | 1861 (5 RCTs) 41, 42, 46, 52, 65  24 weeks to 52 weeks | ⨁⨁⨁⨁ HIGH 23,b,r,v | - | - | SMD -**0.38 SD**  (-0.48 to - 0.29) |
| Rescue medication use (puffs/day) assessed with change from baseline | 3367 (7 RCTs) 68, 54, 42, 59, 66, 52, 41  16 weeks to 52 weeks 22,w | ⨁⨁⨁⨁ HIGH b,d,x | - | The mean the change from baseline of Rescue medication use (puffs/day) was **0** puff/day | MD -**0.47 puff/day**  (-0.68 to -0.27) |
| FeNO level change from baseline 29,y | 495 (3 RCTs) 51, 65,41 | ⨁⨁⨁◯ MODERATE 32,33,b,d,z | - | The mean feNO leval change from baseline was **0** ppb | MD **4.65 ppb lower** (-7.39 to -1.92) aa |
| \***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).   **CI:** Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **SMD:** Standardised mean difference | | | | | |
| **GRADE Working Group grades of evidence** **High certainty:** High confidence that the true effect lies close to that of the estimate of the effect **Moderate certainty:** Moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect **Very low certainty:** Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect | | | | | |

#### Explanations

1. Clinical significant asthma exacerbation: episodes of asthma worsening requiring treatment with systemic corticosteroids.
2. Despite some studies being at high risk of bias for some of the domains, the effect observed in all of them is similar.
3. Lanier included patients aged 6-12 years old, all had allergic asthma (68).
4. Included studies were all funded by industry, and all showed positive results. No industry-independent observational or randomized studies were identified to compare the results. Therefore, evidence was downgraded for potential publication bias (102).
5. 9 studies included reported exacerbations as "patients who had ≥1 exacerbation", the pooled risk ratio was 0.59(95% CI 0.52-0.67). 3 studies included reported clinically significant severe asthma exacerbation, the pooled rate ration was 0.51 (95% CI 0.39-0.67)
6. The pooled effect of risk ratio evaluated at 24-28 weeks (44, 54, 68, 63) and at 48-52 weeks (42, 51, 68, 55). Lanier 2009 included patients aged 6-12 years old.
7. Downgraded because the effect of omalizumab is beneficial but the upper side of the CI is less than the minimal important difference (MID=0.5) (32).
8. Asthma control using asthma control test (ACT) was assessed by three studies (65, 43, 56), the pooled mean different was 0.57(95% CI 0.17-0.97). We also included the ACQ scores assessed by 5 studies (68, 51, 52, 59, 46), the pooled standard mean difference was -0.20 (95% CI -0.26 - -0.14)
9. The pooled effect of ACQ-6 evaluated at 16 weeks (44), 24-32 weeks (44, 59), and at 52 weeks (56).
10. Although there were a high I2 (67%.), this was influenced by only one study with low number of events.
11. The pooled data were assessed at 16 and 20 weeks (48, 62), and 52 weeks (68); Other studies evaluated at 24-28 weeks. GETE evaluated by patients show that omalizumab is more effective than placebo, the risk ratio was 1.49 (1.26-1.77), see full text report.
12. Statistically significant (I2=83%), but probably unimportant heterogeneity.
13. The mean change of AQLQ scores was assessed by 7 studies, the pooled standard mean difference was 0,34 (95% IC 0.18-0.49)
14. Milgrom reported FEV1 in children (6-12 years old) for 28 weeks follow up (64). The Mean change from baseline was 93.9 mL in the omalizumab group and 28.3 mL in the placebo group. Lanier reported between group differences in FEV1 at week 48 and 52 in 40 ml (p=0.28) and 52 ml (p=0.16) (41).
15. Lung function was also reported as ratio FEV1/FVCx100. Busse reported the ratio in 77.5±0.38 in the intervention group and 77.3±0.36 in the placebo group (63). Milgrom also reported mean FVC in children (6-12 years old) for 28 weeks follow up. Mean FVC change from baseline was 132.7 in the omalizumab group and 132.7 mL in the placebo group at week 28 (64). See full text report.
16. Downgraded because FEV1 and PEF are considered surrogate outcomes for asthma control, with an inconsistent correlation with asthma symptoms (101).
17. The minimal important difference (MID) for FEV1 is 0.20 L (Guidelines Development Group consensus).
18. Included studies were all funded by industry, and all showed positive results. One observational study showed similar results (102), therefore, we did not downgrade for potential publication bias.
19. The predicted value for pre-bronchodilator FEV1 was assessed by 6 studies, the pooled standard mean difference was 1.05 (95% CI 0.35-1.75), see full text report.
20. Milgrom 2001 reported PEFR in children (6-12 years old) with 28 weeks of follow up. Mean morning PEFR change from baseline was 8.5 L/min in the omalizumab group, and 1 L/min in the placebo group at week 28)
21. Average MID is 18.8L/min (30)
22. High heterogeneity (91%); Not downgraded as all effects favour intervention.
23. For rescue medication use MID is the reduction by 0.81 puffs/day (30)
24. Statistically significant (68% (p=0.004)) but probably unimportant heterogeneity.
25. The MID of FeNO change from baseline is more than 10ppb (33).
26. Downgraded because FeNO is not consistently considered a good surrogate of asthmatic inflammation (105, 106)
27. FeNO change was reported according to IgE level by one study (64). The median percentage change was -7.2 (for IgE 30-300 IU/ml) and -16 (for IgE 700–2,000 IU/ml) in the Omalizumab group and 64 in the placebo group.
28. The effect may both be harmful or beneficial

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

| **Quality assessment** | | | | | | | **Summary of resources and costs** | | | **Quality** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Nº. of studies** | **Study design** | **Limitations** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Incremental cost per patient (range)\*** | **Incremental effect per patient (range)\*** | **ICER**  **(range)** |
| ICER per QALY (high quality studies - not funded by Industry) | | | | | | | | | | |
| 7a-g | Cost-utility,  Markov model | Not serious1 | Not serious2 | Not serious3 | Serious4 | Not serious | 39,720 £ to 179,415 $  (5year to lifetime horizon) | 0.18 to 0.67 QALYs  (5year to lifetime horizon) | 53,348 £ to 821,000 $ / QALY5 | ⨁⨁⨁◯  MODERATE |
| ICER per QALY (high quality studies - funded by Industry) | | | | | | | | | | |
| 5h-l | Cost-utility,  Markov model | Not serious1 | Not serious2 | Not serious6 | Serious7 | Serious8 | 33,854 € to 91,100 $ (5year to lifetime horizon) | 0.32 to 1.46 QALYs  (5year to lifetime horizon) | 31,209 € to 287,200 $ / QALY5 | ⨁⨁◯◯  LOW |
| ICER per QALY (low quality studies) | | | | | | | | | | |
| 3m-o | Cost-utility, pre-post study | Very serious9 | Not serious10 | Not serious11 | Not serious12 | Serious13 | 3,581 € to 5,169 €  (10 months to 1 year horizon) | 0.13 to 0.22 QALYs  (10 months to 1 year horizon) | 23,880 € to 26,865 € / QALY | ⨁◯◯◯  VERY LOW |
| ICER per avoid exacerbation (low quality studies) | | | | | | | | | | |
| 4p-s | Cost-effectiveness, pre-post study | Very serious9 | Not serious10 | Not serious14 | Not serious12 | Serious15 | 8,731 € to NR  (1 year horizon) | NR to 7.72 avoided exacerbations  (1 year horizon) | 1,131 € to 17,721 € / avoided exacerbation | ⨁◯◯◯  VERY LOW |
| ICER per increase in ACT (Asthma Control Test) score | | | | | | | | | | |
| 2p,s | Cost-effectiveness, pre-post study | Very serious9 | Not serious10 | Not serious14 | Not serious12 | Serious16 | 8,731 € to 9,979 €  (1 year horizon) | 6.35 to 8.4 mean increase in ACT score  (1 year horizon) | 3,555 € to 4,124 € / 3 points increase in ACT score | ⨁◯◯◯  VERY LOW |
| ICER per increase in AQLQ (Juniper Asthma-Related Quality of Life Questionnaire) score | | | | | | | | | | |
| 1t | Cost-effectiveness, trial based study | Very serious9 | Not serious | Not serious | Not serious | Serious17 | NR | NR | 378 $ / 0.5-point increase in AQLQ score | ⨁◯◯◯  VERY LOW |
| ICER per controlled day | | | | | | | | | | |
| 1t | Cost-effectiveness, trial based study | Very serious9 | Not serious | Not serious | Not serious | Serious17 | NR | NR | 523 $ / day | ⨁◯◯◯  VERY LOW |

\*Incremental cost and effect due to the addition of omalizumab. Range (minor and maximum value) as reported by the studies.

ICER: Incremental cost-effectiveness ratio. QALY: Quality adjusted life years. ACT: Asthma Control Test. €: Euro. $: US Dollar. NR: Not clearly reported in the study. AQLQ: Juniper Asthma-Related Quality of Life Questionnaire.

1. Markov model studies with low risk of bias (CHEC score 13 or higher).
2. All studies reported an ICER higher than 30,000 €, which is the willingness to pay threshold in most European countries.
3. Six studies were performed in high-income countries (two in the UKa,c, three in the USAd,e,f, one in Japanb), and one in Chinag. Three studiesa,c,g included children, whereas the rest only adults.
4. Reported ICERs varied from 53,348 £ to 821,000 $ per QALY.
5. The incremental cost-effectiveness ratio drops substantially from ~400k/ QALY to ~200k/QALY when the responder definition is factored into the cost-effectiveness model.
6. Four studies were performed in high-income countries (two in Europeh,i, two in North Americaj,l), one in Brazil. All included adults.
7. Reported ICERs varied from 31,209 € to 287,200 $ per QALY.
8. All studies financed by Novartis (manufacturer of omalizumab) reported lower ICERs compared to those not financed by Industry.
9. CHEC score lower than 13 (see limitations and transferability assessment section). Cost-utility analysis based on a pre-post study has several limitations. The most important is the bias of not including all clinical health states and the potential exclusion of severe patients. Mortality was impossible to be measured (all included patients were alive). Utilities in post-omalizumab are conditioned by pre-omalizumab results.
10. All studies reported an ICER lower than 30,000 €, which is the willingness to pay threshold in most European countries.
11. All studies conducted in European countries (2 in Italy, 1 in Spain).
12. Reported ICERs showed scarce variation.
13. Two studies financed by Novartis, one by a research centre.
14. All studies conducted in European countries.
15. Three studies with ICER lower or equal than 2,273 € / avoided exacerbation were financed by Novartis. The higher ICER (17,721 €) was reported by a study non-Industry funded.
16. Novartis financed the studies.
17. Source of funding not reported.

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

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

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

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

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

|  |  |
| --- | --- |
| **Blood eos** | **Exacerbations – incidence rate ratio (95% CI)** |
| >200 | 0.59 (0.40-0.86) |
| >300 | 0.37 (0.22 – 0.61) |
| >400 | 0.26 (0.12 – 0.56) |

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

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

| **Table S48: Summary of findings of Reslizumab compared to standard of care for eosinophilic asthma** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Outcomes** | **№ of participants (studies) Follow-up (mean or range)** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
| **Risk with standard of care** | **Risk difference with reslizumab** |
| **Exacerbations**  Assessed with annualised rate of asthma exacerbationsa | 1059 (3 RCTs) 1,2  52 weeks | ⨁⨁⨁⨁ HIGH 3,b | **Incidence rate ratio 0.46** (0.37 to 0.58) c | 1800 exacerbations per 1000 patients per year | **972 fewer exacerbations per 1000 patients per year** (1134 fewer to 756 fewer) |
| **Exacerbations leading to ER visit or hospitalisation** Assessed with annualised rate of asthma exacerbations | 953 (2 RCTs) 1  52 weeks | ⨁⨁⨁◯ MODERATE 3,b,d | **Incidence rate ratio 0.67** (0.39 to 1.17) | 120 exacerbations per 1000 patients per year | **40 fewer exacerbations per 1000 patients per year**  (73 fewer to 20 more) |
| **Asthma control** Assessed with Asthma Control Questionnaire-7 Scale from: 0 to 6 | 1359 (5 RCTs) 1,2,4,5  15 weeks to 16 weeks | ⨁⨁⨁⨁ HIGH 3,8,b,h | - |  | mean difference - **0.25**  (- 0.34 to - 0.16) |
| **Quality of life** assessed with Asthma Quality of Life Questionnaire Scale from: 1 to 7 | 1153 (3 RCTs) 1,4  15 to 16 weeks | ⨁⨁⨁⨁ HIGH 3,10,b,k | - |  | mean difference + **0.17**  (+0.08 to + 0.25) l |
| **Treatment-related adverse events**  Assessed with number of events | 1269 (4 RCTs) 1,2,4  15 to 52 weeks | ⨁⨁⨁◯ MODERATE 3,b,o | **Risk ratio 1.18** (0.89 to 1.56) p | 125 per 1.000 | **22 more per 1.000** (14 fewer to 70 more) p |
| **Treatment-related serious adverse events**  Assessed with number of events | 1269 (4 RCTs) 1,2,4  15 to 52 weeks p | ⨁⨁◯◯ LOW 3,b,q | **Risk ratio 4.71** (0.54 to 41.31) | 0 per 1.000 | **0 fewer per 1.000** (0 fewer to 0 fewer) |
| **Decrease in inhaled corticosteroid (ICS) and oral corticosteroid (OCS) dose** | 0 studies | **-** | - | - | - |
| **Lung function**  Assessed with: FEV1 in mL | 1360 (5 RCTs) 1,2,4,5  15 to 16 weeks | ⨁⨁⨁◯ MODERATE 3,6,7,b,e,f | - |  | mean difference +**141.82 mL**  (+89.23 to 194.41) g+ |
| **Rescue medication use** Assessed with puffs/day | 1251 (4 RCTs) 1,4,5  16 weeks | ⨁⨁⨁⨁ HIGH 3,7,b,n | - |  | mean difference - **0.24**  (-0.46 to - 0.02) |
| **Asthma symptoms** Assessed with: Asthma Symptom Utility Index  Scale from: 0 to 1 | 1157 (3 RCTs) 1,4  16 weeks to 16 weeks | ⨁⨁⨁⨁ HIGH 3,9,b,j | - |  | mean difference +**0.05**  (+0.03 to +0.07 higher) |
| **Changes in blood eosinophil counts** Assessed with: cells/µL | 1264 (4 RCTs) 1,2,4  15 weeks to 16 weeks | ⨁⨁⨁◯ MODERATE 3,11,b,m | - |  | mean difference - **468.58**  (-494.92 to - 442.24) |
| \***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). | | | | | |
| **GRADE Working Group grades of evidence** **High certainty:** High confidence that the true effect lies close to that of the estimate of the effect **Moderate certainty:** Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect **Very low certainty:** Little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect | | | | | |

#### Explanations

a. Clinically significant asthma exacerbations: episodes of asthma worsening with systemic corticosteroids for 3 or more days, a two-times increase in the dose of either inhaled corticosteroids or the need for asthma-related emergency treatment.

b. All included studies were funded by industry, and all showed positive results. No industry-independent observational or randomized studies were identified to contrast the results. Therefore, the quality of the evidence was downgraded for potential publication bias (70).

c. The pooled effect of risk ratio was assessed at 15 weeks (52) and the rate ratio was evaluated at 52 weeks (53)

d. Downgraded because the absolute effect includes both potential clinically meaningful benefits and harms.

e. Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a variable correlation with asthma symptoms (72).

f. The panel agreed that minimal important difference (MID) for FEV1 is 0.20 L g. Castro 2015 also assessed FEV1 at 52 weeks, the mean difference from baseline was 122.28 mL(45.54, 199.02). We also included 3 studies (52,54, 55) reporting FVC (mL), the pooled mean difference was 205.94 (88.69, 323.19); see full text report.

h. MID for ACQ-7 is 0.5 points (Juniper 2005).

i. Castro 2015 also assessed ACQ-7 at 52 weeks, the mean difference from baseline of ACQ-7 was -0.25 (-0.34, -0.16), see full text report.

j. MID for the Asthma symptoms utility index is an increase of 0.09 points (79).

k. MID of AQLQ is 0.5 points (37).

l. Castro 2015 also assessed AQLQ at 52 weeks, the mean difference from baseline was 0.29 (0.18, 0.41), see full text report.

m. Reduction of blood eosinophil counts is a surrogate endpoint and not validated as a valuable outcome for monitoring asthma therapy (80).

n. MID for rescue medication use is a reduction by 0.81 puffs/day (35).

o. The effect may both be harmful or beneficial.

p. Data regarding this outcome was extracted from www.clinicaltrials.gov for ref.52 and ref.53

q. Very few events in both arms, thus it is not possible to estimate precisely the effect size between arms

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

| **Quality assessment** | | | | | | | **Summary of resources and costs** | | | **Quality** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Nº. of studies** | **Study design** | **Limitations** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Incremental cost per patient\*** | **Incremental effect per patient\*** | **ICER** |
| ICER per QALY (high quality study - not funded by Industry) | | | | | | | | | | |
| 1a | Cost-utility,  Markov model | Not serious1 | Not serious | Serious2 | Serious3 | Not serious | 24,404 $  (5-year horizon) | 0.035 QALYs  (5-year horizon) | 697,403 $ / QALY4 | ⨁⨁⨁◯  MODERATE |
| ICER per QALY (high quality study - funded by Industry) | | | | | | | | | | |
| 1b | Cost-utility,  Markov model | Not serious1 | Not serious | Serious5 | Not serious6 | Serious7 | 119,394 $  (lifetime horizon) | 5.17 QALYs  (lifetime horizon) | 23,081 $ / QALY | ⨁⨁◯◯  LOW |

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

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

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

**References**

1. Lam, J. et al. A cost-effectiveness analysis of reslizumab in the treatment of poorly controlled eosinophilic asthma. J Asthma. 2019; 56 (8): 872-881.
2. Han, S. et al. Cost–utility analysis of reslizumab for patients with severe eosinophilic asthma inadequately controlled with high-dose inhaled corticosteroids and long-acting β2-agonists in South Korea. Current medical research and opinion. 2019; 10.1080/03007995.2019.1605159.

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

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

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

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

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

\*IRR : incidence rate ratio

\*\*MD: mean difference

\*\*\*RR: risk ratio

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

**Table S53: Efficacy of reslizumab stratified by blood eosinophils**

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

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

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

| **Table S55: Evidence profile for tezepelumab as add-on treatment in asthma** | | | | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **tezepelumab** | **standard of care** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Annual exacerbation rates (follow up: mean 52 weeks; assessed with: annual asthma exacerbations)1a** | | | | | | | | | | | | |
| 1 2 | randomised trial | not serious | not serious | not serious | not serious | publication bias strongly suspected 3,b | 0/412 | 0.7% | **I**RR **0.33** (0.21 to 0.51) | **757 fewer per 1000 patient(s) per years**  (from 836 fewer to 655 fewer) | ⨁⨁⨁◯ MODERATE | Critical |
| **Lung function (follow up: mean 52 weeks; assessed with: Pre-bronchodilator Forced Expiratory Volume in One Second (FEV1 in L))1a** | | | | | | | | | | | | |
| 1 2 | randomised trial | not serious | not serious | serious 4,c | serious 5,d | publication bias strongly suspected 3,b | 0 | 0 | - | MD +**0.15 SD**  (-0.01 to + 0.3) | ⨁◯◯◯ VERY LOW | Important |
| **Asthma control (follow up: mean 52 weeks; assessed with: Asthma Control Questionnaire (ACQ-6); Scale from: 1 to 6)1a** | | | | | | | | | | | | |
| 1 2 | randomised trials | not serious | not serious | not serious | serious 6,e | publication bias strongly suspected 3,b | 0 | 0 | - | MD -**0.31**  (-0.44 to -0.18) | ⨁⨁◯◯ LOW | Critical |
| **Quality of life (follow up: mean 52 weeks; assessed with: Asthma Quality of Life Questionnaire (AQLQ); Scale from: 1 to 7)1a** | | | | | | | | | | | | |
| 1 2 | randomised trials | not serious | not serious | not serious | serious 7,f | publication bias strongly suspected 3,b | 0 | 0 | - | MD +**0.04**  (-0.4 to +0.48) | ⨁⨁◯◯ LOW | Critical |
| **Fraction of exhaled nitric oxide (FeNO) (follow up: mean 52 weeks; assessed with: mean change (ppb))1a** | | | | | | | | | | | | |
| 1 2 | randomised trials | not serious | not serious | serious g | serious 8,h | publication bias strongly suspected 3,b | 0 | 0 | - | MD -**7.74**  (-21.79 to +7.2) | ⨁◯◯◯ VERY LOW | Low |
| **Treatment-related adverse events (AE) (follow up: mean 52 weeks)1a** | | | | | | | | | | | | |
| 1 2 | randomised trials | not serious | not serious | not serious | serious i | publication bias strongly suspected 3,b | 272/412 (66.0%) | 91/138 (65.9%) | **Risk ratio 1.00** (0.87 to 1.15) | **0 fewer per 1.000** (from 86 fewer to 99 more) | ⨁⨁◯◯ LOW | Critical |
| **Treatment-related serious adverse events (SAE) (follow up: mean 52 weeks)1a** | | | | | | | | | | | | |
| 1 2 | randomised trials | not serious | not serious | not serious | serious i | publication bias strongly suspected 3,b | 48/412 (11.7%) | 18/138 (13.0%) | **Risk ratio**  **0.90** (0.53 to 1.50) | **13 fewer per 1.000** (from 61 fewer to 65 more) | ⨁⨁◯◯ LOW | Critical |
| **Rescue medication use - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - |  |
| **Reduction in corticosteroid use - not reported** | | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - |  |

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

**Explanations**

1. As there were three intervention arms and one placebo arm, an adjusted standard error (SE) analysis was used for the calculation of the confidence interval (CI) for the overall effect (1).
2. The only study was funded by industry, and showed positive results. No industry-independent observational or randomized studies were identified to contrast the results. Therefore, evidence was downgraded for potential publication bias (3).
3. Evidence was downgraded because FEV1 is considered a surrogate outcome for asthma control, with a variable correlation with asthma symptoms (4).
4. The effect may both be harmful or beneficial. The Minimal Important Difference (MID) is 0.23 L (5).
5. The MID is 0.5 points (6).
6. The effect may both be harmful or beneficial. The MID is 0.5 points (6).
7. Evidence was downgraded because FeNO is considered a surrogate outcome of T2 inflammation, with a variable correlation with asthma symptoms.
8. The effect may both be harmful or beneficial. The MID of FeNO change from baseline is more than 10ppb (8).
9. The effect may both be harmful or beneficial.

#### References

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|  |  |  |  |
| --- | --- | --- | --- |
| Table S56: Previous targeted interventions in asthma, currently discontinued | | | |
| Biological/small molecule | Target/mechanism of action/characteristics | Outcomes | References |
| Pascolizumab | Humanised Mab selective blocking the interaction of IL-4 with its receptor | Preclinical efficacy; clinical development programmed discontinued to lack of efficacy | Hart TK et al. Clin. Exp. Immunol. 2003; 130, 93–100. |
| Pitrakinra | IL-4 variant inhibiting the binding of interleukin 4 and interleukin 13 to IL-4R alpha receptor complexes | Modest efficacy in phase IIa trial | Wenzel S et al. Lancet. 2007; 370(9596):1422-31. |
| AMG317 | Fully human Mab to IL-4Ralpha that blocks both IL-4 and IL-13 pathways | No clinical efficacy | Corren J et al. Am J Respir Crit Care Med. 2010;181(8):788–796 |
| Lebrikizumab | Anti-IL-13 humanised Mab; binds to and blocks the activity of IL-13 | In phase II trials reduced exacerbation rate in periostin-high patients  Failed to reduce exacerbations in phase III trials | Corren J et al. N Engl J Med. 2011; 365(12):1088-98  Hanania N et al. Thorax. 2015; 70(8):748-56  Hanania N et al. Lancet Respir Med. 2016; 4(10):781-796 |
| Tralokinumab | Human IL-13-neutralising immunoglobulin G4 Mab | Failed in both in phase II and phase III trials (asthma control, exacerbation rate, OCS sparing effect) | Piper E et al. Respir. J. 2013; 41, 330–338  Brightling C et al. Lancet Respir. Med. 2015; 3, 692–701  Panettieri R et al. Lancet Respir. Med. 2018; 6, 511–525.  Russel J et al. Lancet Respir. Med. 2018; 6, 499–510  Busse WW et al. Eur Respir J. 2019; 53(2) |
| Quilizumab | Humanised IgG1 Mab targeting the M1-prime segment of membrane-expressed IgE, leading to depletion of IgE-switched and memory B cells | No impact on asthma exacerbations, lung function, or patient-reported symptom measures in phase II trial; biomarker subgroups (periostin, blood eosinophils, serum IgE, and exhaled nitric oxide) without meaningful efficacy benefits | Harris JM et al. Respir Res. 2016;17:29. |
| Ligelizumab | Mab with greater affinity for IgE than omalizumab | Failed to demonstrate superiority over placebo or omalizumab in treating asthma patients not adequately controlled with high-dose inhaled corticosteroids (ICS) plus long-acting beta2-agonists (LABA) after 16 weeks of treatment | <https://www.novctrd.com/CtrdWeb/>  displaypdf.nov?trialresultid=15687 |
| Brodalumab | Human Mab anti-IL-17 receptor alpha | No treatment effect | Busse WW et al. Am J Respir Crit Care Med. 2013; 188(11):1294–1302 |
| Golimumab | Human Mab against TNF-alpha | Unfavourable risk-benefit profile led to early discontinuation of the study | Wenzel SE, et al. Am J Respir Crit Care Med. 2009; 179(7):549–558 |
| Etanercept | Fully soluble, human dimeric fusion protein, functions as a TNF inhibitor by competitively binding to TNF and preventing its activation of the inflammatory cascade | No clinical efficacy | Holgate ST et al. Eur Respir J. 2011;37(6):1352–1359 |
| Etokimab (ANB020) | Mab inhibiting the activity of IL-33 | Positive results in phase IIa study (25 severe adult eosinophilic asthma patients)  Phase 2b trial in eosinophilic asthma, a multi-dose, randomized, double-blinded, placebo-controlled trial in 300-400 patients was postponed until results from the ECLIPSE trial (CRSwNP) are analysed | Londei et al., 2019 June. Presented at the 2019 European Academy of Allergy and Clinical Immunology (EAACI) Congress |