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DERP VI Surveillance: Biologic Drugs to Treat Asthma and Chronic Spontaneous Urticaria

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Objectives

The purpose of this Drug Effectiveness Review Project (DERP) surveillance report is to preview the volume and nature of new research and relevant clinical information that has emerged since the last DERP systematic review on biologic drugs used to treat asthma and chronic spontaneous urticaria (CSU).[1] The literature search for this report focuses on new randomized controlled trials (RCTs) and actions the U.S. Food and Drug Administration (FDA) has taken since the last report (i.e., new drugs, formulations, indications, or identified serious harms). Comprehensive searches, quality assessment, and synthesis of evidence would follow only if DERP participants commission an update review or another research product type for this topic. Comprehensive searches might identify additional eligible studies.

Topic History and Context

This report is the first surveillance document produced on this topic since the completion of the systematic review in April 2018, which utilized a search strategy covering the period from database inception through October 2017.[1] A summary of the topic history is shown in Table 1.

Table 1. Topic History and Search Dates

Document Type	Date Presented	Search Dates
Systematic review	April 2018	Database inception through October 2017

Key Questions

1. Are there differences in effectiveness and adverse event outcomes of biologic medications compared with each other or placebo when added to other treatments for outpatients with asthma?
    a. Are there subgroups of patients (e.g., those with elevated baseline eosinophils) for which biologic medications used to treat asthma differ in efficacy, effectiveness, or frequency of adverse events?
2. Are there differences in effectiveness and adverse event outcomes of biologic medications compared with each other or placebo when added to other treatments for outpatients with CSU?
    a. Are there subgroups of patients for which biologic medications used to treat urticaria differ in efficacy, effectiveness, or frequency of adverse events?

Populations

- Adults or children with persistent or chronic asthma
- Adults with CSU

Interventions

Active interventions of interest are listed in Table 2.

Table 2. Included Interventions

Generic Name	Brand Name	Indication	Date of FDA Approval
Dupilumab	**Dupixent**	**Asthma**	**October 2018**
Benralizumab	Fasenra	Asthma	November 2017
Reslizumab	Cinqair	Asthma	March 2016
Mepolizumab	Nucala	Asthma	November 2015
Omalizumab	Xolair	Asthma CSU	June 2003

Abbreviations. CSU: chronic spontaneous urticaria. FDA: U.S. Food and Drug Administration. **Bold** indicates drugs newly approved since the last DERP report.

Comparators

- Placebo-controlled or usual care-controlled (including add-on studies)
- Anti-IL-4 or Anti-IL-5 antibodies versus each other

Outcomes

Asthma

- Severe exacerbations requiring emergency department or hospital admission, symptom control, oral steroid use, quality of life assessed using validated scales, all-cause emergency department or hospital admissions, decreasing mortality

CSU

- Response (e.g., Urticaria Activity Score [UAS7] ≤ 6 or complete response [UAS7 = 0]), symptoms (e.g., itching), quality of life assessed using validated scales, use of other anti-urticaria medications

Study Design

- RCTs

Methods

Using the PICOS outlined above, we searched for eligible RCTs in ClinicalTrials.gov, the ISRCTN Registry, and the FDA website. Using relevant clinical trial numbers and other identifiers, we then searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations for studies published from October 2017 through August 20, 2019. We used the Google search engine to identify studies published since the implementation of the search strategy described in the April 2018 systematic review. We limited our search to studies written in English and involving human participants. We also searched the FDA website to identify newly approved drugs, formulations, and indications, as well as newly identified serious harms (e.g., boxed warnings) or warnings for the included interventions. To identify new drugs, we used Google and searched CenterWatch, a privately-owned database of clinical trials information.

Findings

New Drugs or Formulations

We identified one new drug, dupilumab (Dupixent), for this report. Dupilumab was initially approved by the FDA in March 2017 for atopic dermatitis. In October 2018 it was approved for use in patients aged 12 years or older with moderate-to-severe asthma as an add-on maintenance treatment for those with an eosinophilic phenotype or with oral corticosteroid-dependent asthma.[2] It is not indicated for the relief of acute bronchospasm or status asthmaticus.[2]

We identified one new formulation for mepolizumab related to severe asthma. Mepolizumab is now available as a prefilled autoinjector and prefilled syringe.[3] Previously, it was only available as lyophyilized powder in a vial for reconstitution.

We identified one new formulation for omalizumab related to CSU. Omalizumab is now available as a prefilled syringe.[4]

New Indications

No new indications were identified since the searches in the last systematic review.

New Serious Harms or Warnings

No new serious harms or warnings were identified since the searches in the last systematic review.

Randomized Controlled Trials (RCTs)

We identified 10 RCTs, 1 open-label extension, and 2 patient-level meta-analyses from RCTs since the last DERP systematic review. Three RCTs compared dupilumab to placebo at different dosages and/or frequencies of administration;[5-7] 4 RCTs evaluated benralizumab at different dosages, frequencies, or against placebo;[8-12] 1 open-label extension of reslizumab included participants from 3 RCTs;[13] 2 RCTs evaluated mepolizumab against placebo at different dosages and durations;[14,15] 2 patient-level meta-analyses evaluated the effectiveness of mepolizumab in 2 subgroups of patients, those with severe eosinophilic asthma and a Japanese cohort;[16,17] and 1 RCT compared omalizumab against placebo at different frequencies of administration.[18] Intervention periods ranged from 12 to 108 weeks with follow-up periods ranging from 8 to 56 weeks. All studies included sites within the U.S. Five studies admitted participants aged 17 or 18 years and older and the remaining studies admitted participants aged 12 years and older. All studies were conducted in participants with a diagnosed asthmatic condition; no studies included participants with CSU. Brief details of these studies are presented in Table 3.

Table 3. Studies Published Since the Previous DERP Systematic Review

Author, Year NCT (Trial Name) Location	N Duration Population	Interventions	Outcomes
Dupilumab			
Castro et al., 2018[5] NCT02414854 (Liberty Asthma Quest) U.S. and international sites	N = 1,902 52 weeks intervention + 12 weeks follow-up • Aged ≥ 12 years old • Persistent asthma for ≥ 12 months • Worsening of asthma in previous 12 months that led to hospitalization, emergency medical care, or treatment with systemic corticosteroids for ≥ 3 days	Every 2 weeks: • Dupilumab 200 mg • Dupilumab 400 mg • Placebo	• Annual asthma exacerbation rate
Rabe et al., 2018[6] NCT02528214 (Liberty Asthma Venture) U.S. and international sites	N = 210 24 weeks • Aged ≥ 12 years old • Persistent asthma for ≥ 12 months • Receiving regular systemic glucocorticoids in previous 6 months	Every 2 weeks: • Dupilumab 300 mg • Placebo	• Change in glucocorticoid dose • Maintenance of asthma control
Weinstein et al., 2018[7] NCT01854047 U.S. and international sites	N = 776 24 weeks • Subgroup (n = 392) from a phase 2b trial who have comorbid perennial allergic rhinitis • Adults ≥ 18 years old • Persistent asthma for ≥ 12 months • Treated with a stable medium-to-high dose of ICS for ≥ 1 month prior to screening	• Dupilumab 200 mg every 2 weeks • Dupilumab 300 mg every 2 weeks • Dupilumab 200 mg every 4 weeks • Dupilumab 300 mg every 4 weeks • Placebo every 2 weeks	• Patient-reported outcomes related to rhinitis-associated nasal symptoms • Severe exacerbation events • Quality of life

Author, Year NCT (Trial Name) Location	N Duration Population	Interventions	Outcomes
Benralizumab			
Ferguson et al., 2017[9] NCT02322775 (BISE) U.S. and international sites	N = 251 12 weeks • Aged 18 to 75 years old • Weight ≥ 40 kg • Evidence of asthma on basis of FEV screening • Receiving low-to-medium dose ICS or low-dosage ICS with LABA	Every 4 weeks: • Benralizumab 30 mg • Placebo	• Total asthma symptom scores • Annual asthma exacerbation rate
Goldman et al., 2017[11] NCT01928771 (SIROCCO) NCT01914757 (CALIMA) U.S. and international sites	N = 5,369 48 weeks (SIROCCO) 56 weeks (CALIMA) • Subgroup of patients with screening blood eosinophil counts ≥ 150 cells/μL and < 150 cells/μL from 2 trials (n = 1,456) • Aged 12 to 75 years old • Persistent asthma for ≥ 12 months • Treated with ICS and LABA for at least 3 months prior to screening	Every 8 weeks: • Benralizumab 30 mg • Placebo	• Annual asthma exacerbation rate • Total asthma symptom scores
Nair et al., 2017[12] NCT02075255 (ZONDA) U.S. and international sites	N = 220 28 weeks intervention + 8 weeks follow-up • Adults • Persistent asthma for ≥ 12 months • Blood eosinophil count ≥ 150 cells/μL • Treated with glucocorticoids and LABA for ≥ 6 months before enrollment	• Benralizumab 30 mg every 4 weeks • Benralizumab 30 mg every 8 weeks and placebo during interim 4-week visit • Placebo every 8 weeks	• Oral glucocorticoid dose • Annual asthma exacerbation rate • Total asthma symptom scores

Author, Year NCT (Trial Name) Location	N Duration Population	Interventions	Outcomes
Busse et al., 2019[8] NCT02258542 (BORA) U.S. and international sites	N = 654 56 weeks intervention + 12 weeks follow-up for ages ≥ 18; 108 weeks + 56 weeks follow-up for ages 12 to 17 • Aged ≥ 12 years old • Had received placebo in previous trials (SIROCCO and CALIMA)	• Benralizumab 30 mg every 4 weeks • Benralizumab 30 mg every 8 weeks	• Adverse events • Annual asthma exacerbation rate • Quality of life • Total asthma symptom scores
Reslizumab			
Murphy et al., 2017[13] NCT01290887 (open-label extension of 3 trials) U.S. and international sites	N = 1,052 Up to 24 months + 90-day follow-up • Previously enrolled in NCT01270464, NCT01287039, NCT01285323 • Aged 12 to 77 • Uncontrolled asthma • Blood eosinophils ≥ 400 cells/μL • Receiving at least a medium dose of ICS	• Reslizumab 3.0 mg/kg every 4 weeks	• Adverse events • Quality of life • Total asthma symptom scores
Mepolizumab			
Chupp et al., 2017[14] NCT02281318 (MUSCA) U.S. and international sites	N = 556 24 weeks • Aged ≥ 12 years old • Severe eosinophilic asthma • ≥ 2 exacerbations requiring treatment with systemic corticosteroids in previous 12 months	Every 4 weeks: • Mepolizumab 100 mg, subcutaneous • Placebo	• Health-related quality of life • Total asthma symptom scores

Author, Year NCT (Trial Name) Location	N Duration Population	Interventions	Outcomes
Shimoda et al., 2017[17] NCT01691521 (MENSA) U.S. and international sites	N = 576 32 weeks • Subgroup of Japanese participants from MENSA trial (n = 50) • Aged ≥ 12 years old • Clinically diagnosed asthma • ≥ 2 exacerbations requiring treatment with oral corticosteroids in previous 12 months	Every 4 weeks: • Mepolizumab 75 mg, intravenous • Mepolizumab 100 mg, subcutaneous • Placebo	• Clinically significant exacerbations (e.g., requiring hospitalization) • Annual asthma exacerbation rate
Albers et al., 2019[16] NCT02281318 (MUSCA) NCT01691521 (MENSA) U.S. and international sites	N = 936 Up to 32 weeks • Aged ≥ 12 years old • Clinically diagnosed asthma • Blood eosinophils ≥ 300 cells/μL in previous year or ≥ 150 cells/μL at screening plus ≥ 2 exacerbations requiring treatment with oral corticosteroids in previous 12 months	Every 4 weeks: • Mepolizumab 100 mg, subcutaneous • Placebo	Patient-level meta-analysis stratified by weight and BMI • Clinically significant exacerbations (e.g., requiring hospitalization) • Annual asthma exacerbation rate • Total asthma symptom scores

Author, Year NCT (Trial Name) Location	N Duration Population	Interventions	Outcomes
Humbert et al., 2019[15] NCT02281318 (MUSCA) NCT01691521 (MENSA) U.S. and international sites	N = 1,136 Up to 32 weeks • Aged ≥ 12 years old • Clinically diagnosed asthma • Blood eosinophils ≥ 300 cells/μL in previous year or ≥ 150 cells/μL at screening plus ≥ 2 exacerbations requiring treatment with oral corticosteroids in previous 12 months	Every 4 weeks: • Mepolizumab 100 mg, subcutaneous • Placebo	Patient-level meta-analysis stratified by omalizumab eligibility, IgE quartile, and blood eosinophils < 300 cells/μL or ≥ 300 cells/μL • Clinically significant exacerbations (e.g., requiring hospitalization) • Annual asthma exacerbation rate
Omalizumab			
Ledford et al., 2017[18] NCT00314574 (XPORT/EXTRA) U.S.	N = 176 52 weeks • Aged 17 to 70 years old • Receiving Omalizumab per US prescribing guidelines and stable doses of other asthma therapy for ≥2 months before enrollment	• Omalizumab 0.008 mg/kg/IgE every 2 weeks • Omalizumab 0.016 mg/kg/IgE every 4 weeks • Placebo	• Severe asthma exacerbations

Abbreviations. BMI: body mass index. ICS: inhaled corticosteroids. IgE: Immunoglobulin E. LABA: long-acting β2 agonist.

Ongoing Studies

We identified 23 ongoing studies. Most of the studies focused on participants diagnosed with an asthmatic condition (n = 19) and the remaining studies focused on participants diagnosed with CSU (n = 4).

The number of ongoing studies identified for each drug were:

- Dupilumab: 8 studies for asthmatic conditions, 1 study for CSU
- Benralizumab: 4 studies for asthmatic conditions, 1 study for CSU

- Reslizumab: 1 study for asthmatic conditions
- Mepolizumab: 3 studies for asthmatic conditions
- Omalizumab: 2 studies for asthmatic conditions, 2 studies for CSU
- 1 head-to-head study with mepolizumab and omalizumab for asthmatic conditions

Two studies published preliminary results on ClinicalTrials.gov[19,20] and 4 studies are open-label extensions. Study sizes range from 12 to 2,206 participants. Only one head-to-head study was identified. Four studies focus on pediatric populations with ages ranging from 2 to 17 years. Completion dates range from October 2017, with no results currently published, through December 2026. Brief details of ongoing studies related to asthma and CSU are presented in Table 4 and Table 5, respectively.

Table 4. Ongoing Studies for Asthma

NCT Number	Age Range Treatment Groups	Eligible Outcomes	Estimated Enrollment	Estimated Completion Date
Head-to-Head				
NCT03476109	Aged 18 to 80 • Mepolizumab • Omalizumab	• Asthma control • Asthma exacerbations	100	December 2020
Dupilumab				
NCT02573233[a,19]	Aged 18 to 65 Every 2 weeks: • Dupilumab 300 mg, subcutaneous • Placebo	• Adverse events	42	January 2018
NCT02134028[b]	≥ 12 years old Every 2 weeks: • Dupilumab, subcutaneous	• Long-term safety (up to 108 weeks) • Adverse events • Quality of life	2,206	November 2019
NCT03884842	≥ 18 years old • Dupilumab 300 mg, subcutaneous • Placebo	• Total asthma symptom scores	32	June 2021

NCT Number	Age Range Treatment Groups	Eligible Outcomes	Estimated Enrollment	Estimated Completion Date
NCT03782532	≥ 18 years old Every 2 weeks: • Dupilumab • Placebo	• Annual asthma exacerbation rate • Annual rate of loss of asthma control • Daily use of rescue medication • Total asthma symptom scores • Quality of life	486	April 2021
NCT02948959	Aged 6 to 11 Every 2 weeks: • Dupilumab • Placebo	• Annual asthma exacerbation rate • Annual rate of loss of asthma control • Daily use of rescue medication • Total asthma symptom scores • Quality of life	471	July 2021
NCT03620747[b]	≥ 12 years old Every 2 weeks: • Dupilumab, subcutaneous	• Adverse events	750	September 2021
NCT03694158	Aged 12 to 65 Every 2 weeks: • Dupilumab 200 mg, subcutaneous • Dupilumab 300 mg, subcutaneous • Placebo	• Asthma exacerbations	126	October 2023
NCT03560466[b]	Aged 7 to 12 Every 2 weeks: • Dupilumab, subcutaneous	• Long-term safety (up to 108 weeks) • Adverse events	377	December 2026

NCT Number	Age Range Treatment Groups	Eligible Outcomes	Estimated Enrollment	Estimated Completion Date
Benralizumab				
NCT02869438	Aged 18 to 75 Every 4 weeks: • Benralizumab • Placebo	• Adverse events • Quality of life • Total asthma symptom scores	235	August 2018
NCT02808819[b]	≥ 18 years old • Benralizumab, every 4 weeks • Benralizumab, every 8 weeks	• Adverse events • Asthma exacerbations • Clinically significant exacerbations (e.g., requiring hospitalization)	447	June 2020
NCT03170271	Aged 18 to 75 Every 4 weeks: • Benralizumab • Placebo	• Asthma exacerbations • Clinically significant exacerbations (e.g., requiring hospitalization) • Quality of life	659	September 2020
NCT03186209	Aged 12 to 75 • Benralizumab • Placebo	• Annual asthma exacerbation rate • Clinically significant exacerbations (e.g., requiring hospitalization) • Change in use of rescue medication • Adverse events	666	February 2021
Reslizumab				
NCT02452190[a, 20]	≥ 12 years old Every 4 weeks: • Reslizumab, 110 mg • Placebo	• Asthma exacerbations • Clinically significant exacerbations (e.g., requiring hospitalization)	468	January 2018

NCT Number	Age Range Treatment Groups	Eligible Outcomes	Estimated Enrollment	Estimated Completion Date
		• Total asthma symptom scores • Quality of life		
Mepolizumab				
NCT02555371	≥ 12 years old Every 4 to 8 weeks: • Mepolizumab, 100 mg • Placebo	• Time to first clinically significant exacerbation • Asthma control	295	July 2019
NCT03292588	Aged 6 to 17 Every 4 weeks: • Mepolizumab, 40 mg or 100 mg (weight dependent) • Placebo	• Asthma exacerbations • Quality of life • Adverse events	320	September 2019
NCT03562195	≥ 12 years old • Mepolizumab, 100 mg • Placebo	• Clinically significant exacerbations (e.g., requiring hospitalization) • Adverse events	300	February 2021
Omalizumab				
NCT02966314	≥ 18 years old Every 4 weeks: • Omalizumab, 300 mg • Placebo	• Adverse events (angioedema episodes) • Quality of life	40	December 2019
NCT02570984	Aged 2 to 4 • Omalizumab • Placebo	• Asthma severity • Adverse events	250	November 2025

Notes. Where available, treatment dosage and frequency have been provided. [a]Preliminary results published on ClinicalTrials.gov. [b]Open-label extension.

Table 5: Ongoing Studies for Chronic Spontaneous Urticaria

NCT Number	Age Range Treatment Groups	Eligible Outcomes	Estimated Enrollment	Estimated Completion Date
Dupilumab				
NCT03749135	Aged 18 to 75 • Dupilumab • Placebo	• Urticaria activity score	72	May 2021
Benralizumab				
NCT03183024	Aged 19 to 70 Every 4 weeks: • Benralizumab • Placebo	• Urticaria activity score • Adverse events	12	November 2018
Omalizumab				
NCT03328897	Aged 18 to 75 Every 4 weeks: • Omalizumab, 150 mg • Omalizumab, 300 mg • Placebo	• Urticaria activity score • Adverse events	523	September 2019
NCT03580356[a] NCT03580369	≥ 12 years old Every 4 weeks: • Omalizumab, 300 mg • Ligelizumab[b] • Placebo	• Urticaria activity score • Adverse events • Quality of life	1,050	April 2021

Notes. Where available, treatment dosage and frequency have been provided. [a]Trial registered twice and given two identifiers. [b]Drug in development.

Summary

Since the completion of the April 2018 DERP systematic review, we identified:

- 1 new drug for treatment of asthma
    - Dupilumab for add-on treatment in moderate-to-severe asthma
- 2 new formulations
    - Mepolizumab is now available as a prefilled autoinjector and prefilled syringe
    - Omalizumab is now available as a prefilled syringe
- 13 RCTs
    - Zero head-to-head studies

    - 10 placebo-controlled trials
    - 1 open-label extension
    - 2 patient-level meta-analyses of large RCTs
- 23 ongoing studies
    - 1 head-to-head study
    - 18 placebo-controlled trials
    - 4 open-label extensions
- No new indications, serious harms, or warnings

Using the *Is There a There There Scale* (ITS) (Table 6), we rated this topic as *Yes* (see Appendix B for ratings and definitions).

Table 6. Summary and ITS Rating

Clinical Evidence	**Yes** **How many?**	**No**
New Comparative Trial		☒
New Placebo-Controlled Trial	☑ 10	
New Meaningful[a] Study	☑ 10	
Ongoing Study Likely to be Published in the Next Year	☑ 7	
FDA Actions	**Yes** **Description**	**No**
New Drug or Formulation	☑ New drug, dupilumab; New formulations for mepolizumab and omalizumab	
New Indication		☒
New Serious Harm or Warning		☒
ITS Rating: Yes		

Abbreviation. ITS: Is There a There There Scale. Note.[a] Large studies (> 600 participants), studies that have long-term follow-up (≥ 6 months), studies that compare one drug with another that is considered the standard of care or has not been reported and is clinically important, and studies that include an intervention or outcome that is not previously reported in the literature or is clinically important (e.g., mortality) and adds to the body of literature.

References

1. Mcdonagh M, Holmes R, Fulton M, Weeks C, Hsu F, Liebow S. *Biologic drugs to treat asthma and chronic spontaneous urticaria.* Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2018.

2. U.S. Food and Drug Administration. Dupixent drug label. 2019; https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761055s014lbl.pdf. Accessed August 19, 2019.

3. U.S. Food and Drug Administration. Mepolizumab drug label. 2019; https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761122s000lbl.pdf. Accessed August 19, 2019.

4. U.S. Food and Drug Administration. Xolair drug label. 2019; https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103976s5234lbl.pdf. Accessed August 19, 2019.

5. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med.* 2018;378(26):2486-2496. doi: 10.1056/NEJMoa1804092.

6. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med.* 2018;378(26):2475-2485. doi: 10.1056/NEJMoa1804093.

7. Weinstein SF, Katial R, Jayawardena S, et al. Efficacy and safety of dupilumab in perennial allergic rhinitis and comorbid asthma. *J Allergy Clin Immunol.* 2018;142(1):171-177 e171. doi: 10.1016/j.jaci.2017.11.051.

8. Busse WW, Bleecker ER, FitzGerald JM, et al. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. *Lancet Respir Med.* 2019;7(1):46-59. doi: 10.1016/S2213-2600(18)30406-5.

9. Ferguson GT, FitzGerald JM, Bleecker ER, et al. Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med.* 2017;5(7):568-576. doi: 10.1016/S2213-2600(17)30190-X.

10. Fitzgerald J, Bleecker E, Bourdin A, et al. Two-year integrated efficacy and safety analysis of benralizumab SIROCCO, CALIMA, ZONDA, and BORA trials in severe asthma. *Am J Respir Crit Care Med.* 2019;199:A2676-A2676.

11. Goldman M, Hirsch I, Zangrilli JG, Newbold P, Xu X. The association between blood eosinophil count and benralizumab efficacy for patients with severe, uncontrolled asthma: subanalyses of the phase III SIROCCO and CALIMA studies. *Curr Med Res Opin.* 2017;33(9):1605-1613. doi: 10.1080/03007995.2017.1347091.

12. Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med.* 2017;376(25):2448-2458. doi: 10.1056/NEJMoa1703501.

13. Murphy K, Jacobs J, Bjermer L, et al. Long-term safety and efficacy of reslizumab in patients with eosinophilic asthma. *J Allergy Clin Immunol Pract.* 2017;5(6):1572-1581 e1573. doi: 10.1016/j.jaip.2017.08.024.

14. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med.* 2017;5(5):390-400. doi: 10.1016/S2213-2600(17)30125-X.

15. Humbert M, Albers FC, Bratton DJ, et al. Effect of mepolizumab in severe eosinophilic asthma according to omalizumab eligibility. *Respir Med.* 2019;154:69-75. doi: 10.1016/j.rmed.2019.06.004.

16. Albers FC, Papi A, Taille C, et al. Mepolizumab reduces exacerbations in patients with severe eosinophilic asthma, irrespective of body weight/body mass index: meta-analysis of MENSA and MUSCA. *Respir Res.* 2019;20(1):169. doi: 10.1186/s12931-019-1134-7.

17. Shimoda T, Odajima H, Okamasa A, et al. Efficacy and safety of mepolizumab in Japanese patients with severe eosinophilic asthma. *Allergol Int.* 2017;66(3):445-451. doi: 10.1016/j.alit.2016.11.006.

18. Ledford D, Busse W, Trzaskoma B, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. *J Allergy Clin Immunol.* 2017;140(1):162-169 e162. doi: 10.1016/j.jaci.2016.08.054.

19. ClinicalTrials.gov. Evaluation of dupilumab's effects on airway inflammation in patients with asthma. 2015; https://clinicaltrials.gov/show/nct02573233. Accessed August 27, 2019.

20. ClinicalTrials.gov. Study of reslizumab in patients with uncontrolled asthma and elevated blood eosinophils. 2015; https://clinicaltrials.gov/show/nct02452190. Accessed August 27, 2019.

Appendix A. Abstracts of Eligible Studies

Albers FC, Papi A, Taille C, et al. Mepolizumab reduces exacerbations in patients with severe eosinophilic asthma, irrespective of body weight/body mass index: meta-analysis of MENSA and MUSCA. *Respir Res.* 2019;20(1):169. doi: 10.1186/s12931-019-1134-7.

BACKGROUND: We assessed the efficacy of the licensed mepolizumab dose (100 mg subcutaneously [SC]) in patients with severe eosinophilic asthma according to body weight/body mass index (BMI). METHODS: This was a post hoc individual patient-level meta-analysis of data from the Phase 3 studies MENSA (MEA115588/NCT01691521) and MUSCA (200862/NCT02281318). Patients aged >/=12 years with severe eosinophilic asthma and a history of exacerbations were randomised to 4-weekly placebo, mepolizumab 75 mg intravenously (IV) or 100 mg SC (MENSA) or placebo or mepolizumab 100 mg SC (MUSCA) for 32 (MENSA) or 24 (MUSCA) weeks. The primary endpoint was the annual rate of clinically significant exacerbations; other outcomes included the proportion of patients with no exacerbations, lung function, St George's Respiratory Questionnaire (SGRQ) and Asthma Control Questionnaire-5 (ACQ-5) scores and blood eosinophil counts. Analyses were performed by baseline body weight and BMI (</=60, > 60-75, > 75-90, > 90, < 100, >/=100 kg; </=25, > 25-30, > 30, < 36, >/=36 kg/m(2)). RESULTS: Overall, 936 patients received placebo or mepolizumab 100 mg SC. Across all body weight/BMI categories, mepolizumab reduced the rate of clinically significant exacerbations by 49-70% versus placebo. Improvements with mepolizumab versus placebo were also seen in lung function in all body weight/BMI categories except > 90 kg; improvements in SGRQ and ACQ-5 scores were seen across all categories. CONCLUSIONS: Mepolizumab 100 mg SC has consistent clinical benefits in patients with severe eosinophilic asthma across a range of body weights and BMIs. Data show that the fixed-dose regimen of mepolizumab is suitable, without the need for weight-based dosing. TRIAL REGISTRATION: This manuscript is a post hoc meta-analysis of data from the Phase 3 studies MENSA and MUSCA. ClinicalTrials.gov, NCT01691521 (MEA115588; MENSA). Registered September 24, 2012. ClinicalTrials.gov, NCT02281318 (200862; MUSCA). Registered November 3, 2014.

Busse WW, Bleecker ER, FitzGerald JM, et al. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. *Lancet Respir Med.* 2019;7(1):46-59. doi: 10.1016/S2213-2600(18)30406-5.

BACKGROUND: Benralizumab is an interleukin-5 receptor alpha-directed cytolytic monoclonal antibody that has been shown to safely reduce exacerbations and improve lung function for patients with asthma. We assessed the long-term safety and efficacy of benralizumab for patients with severe, uncontrolled eosinophilic asthma. METHODS: We conducted a randomised, double-blind, parallel-group, phase 3 extension study at 447 sites in 24 countries. Eligible patients had to have completed the SIROCCO or CALIMA trials and remained on subcutaneous benralizumab 30 mg every 4 weeks (Q4W) or every

8 weeks (Q8W). Patients who had received placebo in those trials were re-randomised in a 1:1 ratio, using an interactive web-based system, to benralizumab 30 mg either Q4W or Q8W (first three doses 4 weeks apart). Treatment lasted for 56 weeks for adult patients (age >/=18 years) and 108 weeks for adolescent patients (age 12-17 years). The primary endpoint was the safety and tolerability of the two dosing regimens of benralizumab up to 68 weeks for adult patients (including the follow-up visit post-treatment) and up to 56 weeks for adolescent patients. This endpoint was assessed in the full analysis set, which included all patients from the SIROCCO and CALIMA predecessor studies who received at least one dose of study treatment in BORA and did not continue into another trial. This study is registered with ClinicalTrials.gov (NCT02258542). FINDINGS: Between Nov 19, 2014, and July 6, 2016, we enrolled 1926 patients, of whom 633 had received benralizumab Q4W and 639 had received benralizumab Q8W in SIROCCO or CALIMA. The remaining 654 patients had received placebo in those trials and were randomly re-assigned in this trial to receive benralizumab Q4W (n=320) or Q8W (n=334). 1576 patients, including 783 who received benralizumab Q4W (265 newly assigned) and 793 who received benralizumab Q8W (281 newly assigned), were included in the full analysis set. The most common adverse events in all groups were viral upper respiratory tract infection (14-16%) and worsening asthma (7-10%). The most common serious adverse events were worsening asthma (3-4%), pneumonia (<1% to 1%), and pneumonia caused by bacterial infection (0-1%). The percentages of patients who had any on-treatment adverse event, any serious adverse event, or any adverse event leading to treatment discontinuation during BORA were similar between patients originally assigned benralizumab and those originally assigned placebo and between benralizumab treatment regimens. The percentage of patients who had any adverse event was similar between SIROCCO or CALIMA (71-75%; benralizumab group only) and BORA (65-71%), as was the percentage of patients who had an adverse event that led to treatment discontinuation (2% in SIROCCO and CALIMA vs 2-3% in BORA). INTERPRETATION: The 2 years of safety results validate that observations observed in the first year of benralizumab continued through a second year of treatment. No new consequences of long-term eosinophil depletion occurred, and the incidence of other adverse events, including opportunistic infections, were similar during the second year. FUNDING: AstraZeneca and Kyowa Hakko Kirin.

Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378(26):2486-2496. doi: 10.1056/NEJMoa1804092.

BACKGROUND: Dupilumab is a fully human anti-interleukin-4 receptor alpha monoclonal antibody that blocks both interleukin-4 and interleukin-13 signaling. We assessed its efficacy and safety in patients with uncontrolled asthma. METHODS: We randomly assigned 1902 patients 12 years of age or older with uncontrolled asthma in a 2:2:1:1 ratio to receive add-on subcutaneous dupilumab at a dose of 200 or 300 mg every 2 weeks or matched-volume placebos for 52 weeks. The primary end points were the annualized rate of severe asthma exacerbations and the absolute change from baseline to week 12 in the forced expiratory volume in 1 second (FEV1) before bronchodilator use

in the overall trial population. Secondary end points included the exacerbation rate and FEV1 in patients with a blood eosinophil count of 300 or more per cubic millimeter. Asthma control and dupilumab safety were also assessed. RESULTS: The annualized rate of severe asthma exacerbations was 0.46 (95% confidence interval [CI], 0.39 to 0.53) among patients assigned to 200 mg of dupilumab every 2 weeks and 0.87 (95% CI, 0.72 to 1.05) among those assigned to a matched placebo, for a 47.7% lower rate with dupilumab than with placebo (P<0.001); similar results were seen with the dupilumab dose of 300 mg every 2 weeks. At week 12, the FEV1 had increased by 0.32 liters in patients assigned to the lower dose of dupilumab (difference vs. matched placebo, 0.14 liters; P<0.001); similar results were seen with the higher dose. Among patients with a blood eosinophil count of 300 or more per cubic millimeter, the annualized rate of severe asthma exacerbations was 0.37 (95% CI, 0.29 to 0.48) among those receiving lower-dose dupilumab and 1.08 (95% CI, 0.85 to 1.38) among those receiving a matched placebo (65.8% lower rate with dupilumab than with placebo; 95% CI, 52.0 to 75.6); similar results were observed with the higher dose. Blood eosinophilia occurred after the start of the intervention in 52 patients (4.1%) who received dupilumab as compared with 4 patients (0.6%) who received placebo. CONCLUSIONS: In this trial, patients who received dupilumab had significantly lower rates of severe asthma exacerbation than those who received placebo, as well as better lung function and asthma control. Greater benefits were seen in patients with higher baseline levels of eosinophils. Hypereosinophilia was observed in some patients. (Funded by Sanofi and Regeneron Pharmaceuticals; LIBERTY ASTHMA QUEST ClinicalTrials.gov number, NCT02414854 .).

Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med*. 2017;5(5):390-400. doi: 10.1016/s2213-2600(17)30125-x.

BACKGROUND: Mepolizumab, an anti-interleukin-5 monoclonal antibody approved as add-on therapy to standard of care for patients with severe eosinophilic asthma, has been shown in previous studies to reduce exacerbations and dependency on oral corticosteroids compared with placebo. We aimed to further assess mepolizumab in patients with severe eosinophilic asthma by examining its effect on health-related quality of life (HRQOL). METHODS: We did a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial (MUSCA) in 146 hospitals or research centres in 19 countries worldwide. Eligible participants were patients aged 12 years or older with severe eosinophilic asthma and a history of at least two exacerbations requiring treatment in the previous 12 months before screening despite regular use of high-dose inhaled corticosteroids plus other controller medicines. Exclusion criteria included current smokers or former smokers with a history of at least ten pack-years. We randomly assigned participants (1:1) by country to receive a subcutaneous injection of either mepolizumab 100 mg or placebo, plus standard of care, every 4 weeks for 24 weeks (the final dose was given at week 20). We did the randomisation using an interactive voice response system and a centralised, computer-generated, permuted-block design of

block size six. The two treatments were identical in appearance and administered in a masked manner; patients, investigators, other site staff and the entire study team including those assessing outcomes data were also masked to group assignment. The primary endpoint was the mean change from baseline in the St George's Respiratory Questionnaire (SGRQ) total score at week 24 in the modified intention-to-treat (modified ITT) population (analysed according to their randomly assigned treatment). Safety was assessed in all patients who received at least one dose of trial medication (analysed according to the actual treatment received). This trial is registered with ClinicalTrials.gov, number NCT02281318. FINDINGS: We recruited patients between Dec 11, 2014, and Nov 20, 2015, and the study was undertaken between Dec 11, 2014, and June 10, 2016. The modified ITT population comprised 274 patients assigned to mepolizumab 100 mg and 277 assigned to placebo. Mepolizumab versus placebo showed significant improvements at week 24 from baseline in SGRQ total score (least squares mean [SE] change from baseline -15.6 (1.0) vs -7.9 (1.0), a treatment difference of -7.7 (95% CI -10.5 to -4.9; p<0.0001). No deaths occurred during the study. 192 (70%) of 273 patients who received mepolizumab and 207 (74%) of 278 who received placebo reported at least one on-treatment adverse event, the most common of which were headache (in 45 [16%] given mepolizumab vs 59 [21%] given placebo) and nasopharyngitis (in 31 [11%] given mepolizumab vs 46 [17%] given placebo). 15 (5%) and 22 (8%) patients had an on-treatment serious adverse event in the mepolizumab and placebo groups, respectively; the most common was asthma in both groups (in three [1%] given mepolizumab vs nine [3%] given placebo). INTERPRETATION: Mepolizumab was associated with significant improvements in HRQOL in patients with severe eosinophilic asthma, and had a safety profile similar to that of placebo. These results add to and support the use of mepolizumab as a favourable add-on treatment option to standard of care in patients with severe eosinophilic asthma. FUNDING: GlaxoSmithKline.

Ferguson GT, FitzGerald JM, Bleecker ER, et al. Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Respiratory Medicine*. 2017;5(7):568-576. doi: 10.1016/S2213-2600(17)30190-X.

Summary Background Benralizumab is a humanised, anti-interleukin 5 receptor α monoclonal antibody that directly and rapidly depletes eosinophils, reduces asthma exacerbations, and improves lung function for patients with severe eosinophilic asthma. The objective of this trial was to assess the safety and efficacy of benralizumab for patients with mild to moderate, persistent asthma. Methods In this randomised, double-blind, placebo-controlled, phase 3 trial, we recruited patients aged 18–75 years, weighing at least 40 kg, and with a postbronchodilator reversibility in forced expiratory volume in 1 s (FEV1) of at least 12% at screening, from 52 clinical research centres in six countries. Patients must have been receiving either low- to medium-dosage inhaled corticosteroids (ICS) or low-dosage ICS plus long-acting β2 agonist fixed-combination therapy at screening, had a morning prebronchodilator FEV1 of more than 50% to 90% predicted at screening, and had one or more of the following symptoms within the 7 days before randomisation: a daytime or night-time asthma symptom score of at least 1 for at least 2

days, rescue short-acting β2 agonist use for at least 2 days, or night-time awakenings due to asthma for at least one night. We converted patients' ICS treatments to 180 µg or 200 µg budesonide dry powder inhaler twice daily for the entire duration of the study using the approved dosages in the patients' respective countries and randomly allocated them (1:1; stratified by blood eosinophil count [<300 cells per µL vs ≥300 cells per µL] and region [USA vs the rest of the world]) with an interactive web-based voice response system to receive subcutaneous placebo or benralizumab 30 mg injections every 4 weeks for 12 weeks. All patients and investigators involved in patient treatment or clinical assessment and those assessing outcomes were masked to treatment allocation. The primary endpoint was change from baseline prebronchodilator FEV1 at week 12. Efficacy analyses used an intention to treat approach. This trial is registered with ClinicalTrials.gov, number NCT02322775. Findings Between Feb 2, 2015, and April 24, 2015, we enrolled 351 patients, with 211 (60%) randomly assigned (105 [50%] to placebo and 106 [50%] to benralizumab). Benralizumab resulted in an 80 mL (95% CI 0–150; p=0·04) greater improvement (least-squares mean difference) in prebronchodilator FEV1 after 12 weeks than did placebo (placebo group: 2246 mL [SD 768] at baseline vs 2261 mL [796] at week 12, change from baseline of 0 mL; benralizumab group: 2248 mL [606] vs 2310 mL [670], 70 mL). 44 (42%) patients in the benralizumab group had adverse events compared with 49 (47%) in the placebo group. The most common adverse events for both groups were nasopharyngitis (eight [8%] patients in each group) and upper respiratory tract infections (five [5%] patients in each group). Serious adverse events occurred in two (2%) patients each in the benralizumab (pancytopenia and a suicide attempt, both considered unrelated to treatment) and placebo (cervix carcinoma and colon adenoma) groups. Interpretation This study suggests that active and modifiable disease processes might be ongoing in patients with mild to moderate, persistent asthma receiving ICS. Although the lung function improvement observed does not warrant use of benralizumab in this population because it did not reach the minimum clinically important difference of 10%, further studies to assess this finding should be considered. Funding AstraZeneca.

Goldman M, Hirsch I, Zangrilli JG, Newbold P, Xu X. The association between blood eosinophil count and benralizumab efficacy for patients with severe, uncontrolled asthma: subanalyses of the phase III SIROCCO and CALIMA studies. *Curr Med Res Opin.* 2017;33(9):1605-1613. doi: 10.1080/03007995.2017.1347091.

OBJECTIVE: Benralizumab, an anti-eosinophilic monoclonal antibody, in combination with high-dosage inhaled corticosteroids and long-acting beta2-agonists (ICS/LABA), significantly reduced asthma exacerbations, improved lung function, and reduced symptoms for patients with severe, uncontrolled asthma with blood eosinophil counts >/=300 cells/muL in the Phase III SIROCCO and CALIMA studies. To understand the efficacy and safety of benralizumab for patients with eosinophil-driven disease with blood eosinophil counts lower than 300 cells/muL, we evaluated the effect of applying an eosinophil cutoff of >/=150 cells/muL. METHODS: Adult patients with uncontrolled asthma despite high-dosage ICS/LABA +/- additional asthma controller(s) received subcutaneous benralizumab 30 mg every 8 weeks (Q8W; first three doses every 4 weeks)

or placebo for 48 (SIROCCO) or 56 (CALIMA) weeks. Efficacy measures including annual exacerbation rate, prebronchodilator FEV1, and total asthma symptom score were analyzed by baseline blood eosinophil counts >/=150 vs. <150 cells/muL. RESULTS: Benralizumab reduced asthma exacerbation rates by 42% in SIROCCO (rate ratio = 0.58; 95% CI = 0.46-0.74; p < 0.001; n = 325) and 36% in CALIMA (rate ratio = 0.64; 95% CI = 0.50-0.81; p < 0.001; n = 300) vs. placebo (n = 306 for SIROCCO, n = 315 for CALIMA) for patients with blood eosinophil counts >/=150 cells/muL. Benralizumab increased prebronchodilator FEV1 (both studies, p </= 0.002) and improved total asthma symptom score in SIROCCO (p = 0.009) at end of treatment vs. placebo for patients with blood eosinophil counts >/=150 cells/muL. The overall adverse events frequency was similar between treatment groups and eosinophil count cohorts. CONCLUSION: These results support the efficacy and safety of benralizumab for patients with severe asthma and blood eosinophil counts >/=150 cells/muL.

Humbert M, Albers FC, Bratton DJ, et al. Effect of mepolizumab in severe eosinophilic asthma according to omalizumab eligibility. *Respir Med.* 2019;154:69-75. doi: 10.1016/j.rmed.2019.06.004.

BACKGROUND: Patients with severe asthma can present with overlapping eosinophilic and allergic phenotypes, which makes it challenging when deciding which biologic therapy is most appropriate to reduce exacerbations and help achieve asthma control. OBJECTIVE: This post hoc meta-analysis evaluated the efficacy of the licensed dose of mepolizumab (100mg administered subcutaneously [SC]) versus placebo in patients with severe eosinophilic asthma (SEA), according to omalizumab eligibility and associated allergic characteristics. METHODS: Data from two Phase 3 studies (MENSA [MEA115588/NCT01691521]; MUSCA [200862/NCT02281318]) were analyzed. Patients >/=12 years of age with SEA who experienced >/=2 exacerbations in the previous year received placebo, mepolizumab 100mg SC or 75mg intravenously, plus standard of care (high-dose inhaled corticosteroids and other controllers), every 4 weeks. Data from patients who received >/=1 dose placebo or mepolizumab 100mg SC were used for this analysis. The primary endpoint was the rate of clinically significant exacerbations; other outcomes included forced expiratory volume in 1s (FEV1), Asthma Control Questionnaire (ACQ-5) score and quality of life measured using St George's Respiratory Questionnaire (SGRQ). RESULTS: Rate reductions in clinically significant exacerbations with mepolizumab versus placebo were similar in omalizumab eligible and ineligible patients (57% vs 55%). FEV1, ACQ-5 and SGRQ scores improved with mepolizumab versus placebo regardless of omalizumab eligibility, Immunoglobulin E levels, or atopic status. CONCLUSION: This analysis indicated that mepolizumab 100mg SC has clinical benefit in patients with blood eosinophil counts >/=150cells/muL (or history of >/=300cells/muL), regardless of allergic characteristics or omalizumab eligibility.

Ledford D, Busse W, Trzaskoma B, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. *J Allergy Clin Immunol.* 2017;140(1):162-169.e162. doi: 10.1016/j.jaci.2016.08.054.

BACKGROUND: Few data are available to assist clinicians with decisions regarding long-term use of asthma therapies, including omalizumab. OBJECTIVE: We sought to evaluate the benefit and persistence of response in subjects continuing or withdrawing from long-term omalizumab treatment. METHODS: Evaluating the Xolair Persistency Of Response After Long-Term Therapy (XPORT) was a randomized, double-blind, placebo-controlled withdrawal study that included subjects with moderate-to-severe persistent asthma receiving long-term omalizumab. Subjects were randomized by using a hierarchical dynamic randomization scheme to continue their same dose of omalizumab or withdraw to placebo and were then followed every 4 weeks for 1 year. The primary outcome was any protocol-defined severe asthma exacerbation. The secondary outcome was time to first protocol-defined severe asthma exacerbation. Exploratory outcomes included changes in Asthma Control Questionnaire and Asthma Control Test scores. RESULTS: Significantly more subjects in the omalizumab group (67%) had no protocol-defined exacerbation than in the placebo group (47.7%); an absolute difference of 19.3% (95% CI, 5.0%, 33.6%) represents a 40.1% relative difference. Time to first protocol-defined exacerbation analysis revealed a significantly different between-group exacerbation pattern that was consistent with the primary analysis. Subjects continuing omalizumab had significantly better asthma control (mean [SD] change from baseline to week 52: Asthma Control Test score, -1.16 [4.14] vs placebo, -2.88 [5.38], P = .0188; Asthma Control Questionnaire score, 0.22 [0.66] vs placebo, 0.63 [1.13], P = .0039). Discontinuation of omalizumab was associated with an increase in free IgE levels and an increase in basophil expression of the high-affinity IgE receptor. No safety concerns were noted. CONCLUSION: Continuation of omalizumab after long-term treatment results in continued benefit, as evidenced by improved symptom control and reduced exacerbation risk.

Murphy K, Jacobs J, Bjermer L, et al. Long-term safety and efficacy of reslizumab in patients with eosinophilic asthma. *The Journal of Allergy and Clinical Immunology: In Practice.* 2017;5(6):1572-1581.e1573. doi: 10.1016/j.jaip.2017.08.024.

Background In placebo-controlled trials, reslizumab, an anti-IL-5 monoclonal antibody, significantly reduced asthma exacerbations and improved lung function and asthma control in patients with eosinophilic asthma. Objective This open-label extension study evaluated safety and efficacy of reslizumab for up to 24 months. Methods After participation in 1 of 3 placebo-controlled, phase III trials in moderate-to-severe eosinophilic asthma, patients received reslizumab 3.0 mg/kg intravenously every 4 weeks for up to 24 months. Adverse events (AEs), lung function, and patient-reported asthma control were evaluated. Results In the open-label extension, 1,051 patients received ≥1 reslizumab dose (480 reslizumab-naïve, 571 reslizumab-experienced); median (range) exposure was 319 (36-840) and 343 (36-863) days in reslizumab-naïve and reslizumab-experienced patients, respectively. Continuous exposure, including during the placebo-controlled studies, was ≥12 months for 740 patients and ≥24 months for 249 patients. The most common AEs were worsening of asthma and nasopharyngitis. Serious AEs affected 78 of 1,051 (7%) patients; 18 of 1,051 (2%) discontinued treatment because of AEs; and there were 3 deaths (all non-treatment-related). Fifteen adult patients (15 of

1,023; 1%) had malignancies of diverse tissue types. Reslizumab-experienced patients maintained improved lung function and asthma control; reslizumab-naïve patients had improvements in these measures throughout open-label treatment. Blood eosinophil counts appeared to be returning to baseline after reslizumab discontinuation. Conclusions In patients with moderate-to-severe eosinophilic asthma, intravenous reslizumab 3.0 mg/kg displays favorable long-term safety and sustained long-term efficacy. Initial improvements in lung function and asthma control were maintained for up to 2 years. These findings substantially add to our understanding of the long-term safety and efficacy of anti-IL-5 strategies.

Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376(25):2448-2458. doi: 10.1056/NEJMoa1703501.

BACKGROUND: Many patients with severe asthma rely on oral glucocorticoids to manage their disease. We investigated whether benralizumab, a monoclonal antibody directed against the alpha subunit of the interleukin-5 receptor that significantly reduces the incidence of asthma exacerbations, was also effective as an oral glucocorticoid-sparing therapy in patients relying on oral glucocorticoids to manage severe asthma associated with eosinophilia. METHODS: In a 28-week randomized, controlled trial, we assessed the effects of benralizumab (at a dose of 30 mg administered subcutaneously either every 4 weeks or every 8 weeks [with the first three doses administered every 4 weeks]) versus placebo on the reduction in the oral glucocorticoid dose while asthma control was maintained in adult patients with severe asthma. The primary end point was the percentage change in the oral glucocorticoid dose from baseline to week 28. Annual asthma exacerbation rates, lung function, symptoms, and safety were assessed. RESULTS: Of 369 patients enrolled, 220 underwent randomization and started receiving benralizumab or placebo. The two benralizumab dosing regimens significantly reduced the median final oral glucocorticoid doses from baseline by 75%, as compared with a reduction of 25% in the oral glucocorticoid doses in the placebo group ($P<0.001$ for both comparisons). The odds of a reduction in the oral glucocorticoid dose were more than 4 times as high with benralizumab as with placebo. Among the secondary outcomes, benralizumab administered every 4 weeks resulted in an annual exacerbation rate that was 55% lower than the rate with placebo (marginal rate, 0.83 vs. 1.83, $P=0.003$), and benralizumab administered every 8 weeks resulted in an annual exacerbation rate that was 70% lower than the rate with placebo (marginal rate, 0.54 vs. 1.83, $P<0.001$). At 28 weeks, there was no significant effect of either benralizumab regimen on the forced expiratory volume in 1 second (FEV1), as compared with placebo. The effects on various measures of asthma symptoms were mixed, with some showing significant changes in favor of benralizumab and others not showing significant changes. Frequencies of adverse events were similar between each benralizumab group and the placebo group. CONCLUSIONS: Benralizumab showed significant, clinically relevant benefits, as compared with placebo, on oral glucocorticoid use and exacerbation rates. These effects occurred without a sustained effect on the FEV1. (Funded by AstraZeneca; ZONDA ClinicalTrials.gov number, NCT02075255 .).

Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med*. 2018;378(26):2475-2485. doi: 10.1056/NEJMoa1804093.

BACKGROUND: Dupilumab is a fully human anti-interleukin-4 receptor alpha monoclonal antibody that blocks both interleukin-4 and interleukin-13 signaling. Its effectiveness in reducing oral glucocorticoid use in patients with severe asthma while maintaining asthma control is unknown. METHODS: We randomly assigned 210 patients with oral glucocorticoid-treated asthma to receive add-on dupilumab (at a dose of 300 mg) or placebo every 2 weeks for 24 weeks. After a glucocorticoid dose-adjustment period before randomization, glucocorticoid doses were adjusted in a downward trend from week 4 to week 20 and then maintained at a stable dose for 4 weeks. The primary end point was the percentage reduction in the glucocorticoid dose at week 24. Key secondary end points were the proportion of patients at week 24 with a reduction of at least 50% in the glucocorticoid dose and the proportion of patients with a reduction to a glucocorticoid dose of less than 5 mg per day. Severe exacerbation rates and the forced expiratory volume in 1 second (FEV1) before bronchodilator use were also assessed. RESULTS: The percentage change in the glucocorticoid dose was -70.1% in the dupilumab group, as compared with -41.9% in the placebo group (P<0.001); 80% versus 50% of the patients had a dose reduction of at least 50%, 69% versus 33% had a dose reduction to less than 5 mg per day, and 48% versus 25% completely discontinued oral glucocorticoid use. Despite reductions in the glucocorticoid dose, in the overall population, dupilumab treatment resulted in a severe exacerbation rate that was 59% (95% confidence interval [CI], 37 to 74) lower than that in the placebo group and resulted in an FEV1 that was 0.22 liters (95% CI, 0.09 to 0.34) higher. Injection-site reactions were more common with dupilumab than with placebo (9% vs. 4%). Transient blood eosinophilia was observed in more patients in the dupilumab group than in the placebo group (14% vs. 1%). CONCLUSIONS: In patients with glucocorticoid-dependent severe asthma, dupilumab treatment reduced oral glucocorticoid use while decreasing the rate of severe exacerbations and increasing the FEV1. Transient eosinophilia was observed in approximately 1 in 7 dupilumab-treated patients. (Funded by Sanofi and Regeneron Pharmaceuticals; LIBERTY ASTHMA VENTURE ClinicalTrials.gov number, NCT02528214 .).

Shimoda T, Odajima H, Okamasa A, et al. Efficacy and safety of mepolizumab in Japanese patients with severe eosinophilic asthma. *Allergology International*. 2017;66(3):445-451. doi: 10.1016/j.alit.2016.11.006.

Background The MENSA trial assessed the efficacy and safety of mepolizumab in patients with severe eosinophilic asthma. This report describes the efficacy and safety of mepolizumab in Japanese patients from MENSA. Methods A post hoc analysis of the Japanese subgroup from the randomized, double-blind, placebo-controlled, double-dummy, Phase III MENSA trial (NCT01691521). Patients ≥12 years with severe eosinophilic asthma received mepolizumab 75 mg intravenously (IV), 100 mg subcutaneously (SC), or placebo, every 4 weeks for 32 weeks. The primary endpoint was the annualized rate of exacerbations. Secondary and other endpoints included

annualized rate of exacerbations requiring emergency department (ED) visit/hospitalization, morning peak expiratory flow (PEF), St George's Respiratory Questionnaire (SGRQ) score and eosinophil counts. Adverse events (AEs) were monitored. Results In the Japanese subgroup (N = 50), the rate of clinically significant exacerbations was reduced by 90% (rate ratio [RR]: 0.10; 95% confidence interval [CI]: 0.02–0.57; P = 0.010) with mepolizumab IV and 62% (RR: 0.38; 95% CI: 0.12–1.18; P = 0.094) with mepolizumab SC, versus placebo. No exacerbations requiring ED visit/hospitalization were reported with mepolizumab IV; exacerbations were reduced by 73% (RR: 0.27; 95% CI: 0.06–1.29; P = 0.102) with mepolizumab SC versus placebo. Compared with placebo, mepolizumab IV and SC numerically increased morning PEF from baseline by 40 L/min and 13 L/min, improved quality of life by greater than the minimal clinically important difference (SGRQ: 9.5 [P = 0.083] and 7.9 [P = 0.171] points) and reduced eosinophil counts. AE incidence was similar between treatments. Results were broadly consistent with the overall population. Conclusions Mepolizumab was efficacious and well tolerated in Japanese patients with severe eosinophilic asthma, producing similar responses to the overall MENSA population.

Weinstein SF, Katial R, Jayawardena S, et al. Efficacy and safety of dupilumab in perennial allergic rhinitis and comorbid asthma. *J Allergy Clin Immunol.* 2018;142(1):171-177.e171. doi: 10.1016/j.jaci.2017.11.051.

BACKGROUND: Dupilumab, an anti-IL-4 receptor alpha mAb, inhibits IL-4/IL-13 signaling, key drivers of type 2/TH2 immune diseases (eg, atopic/allergic disease). In a pivotal, phase 2b study (NCT01854047), dupilumab reduced severe exacerbations, improved lung function and quality of life, and was generally well tolerated in patients with uncontrolled persistent asthma despite using medium-to-high-dose inhaled corticosteroids plus long-acting beta2-agonists. OBJECTIVE: To examine dupilumab's effect on the 22-item Sino-Nasal Outcome Test (SNOT-22) total score and its allergic rhinitis (AR)-associated items in asthma patients with comorbid perennial allergic rhinitis (PAR). METHODS: A post hoc analysis reporting data from the phase 2b study for the 200 and 300 mg every 2 week (q2w) doses under investigation in phase 3 (NCT02414854) was carried out. PAR was defined at study entry as a specific response to typical perennial antigens (IgE >/=0.35 Ku/L). RESULTS: Overall, 241 (61%) patients had PAR. In asthma patients with PAR, dupilumab 300 mg q2w versus placebo significantly improved SNOT-22 total score (least squares mean difference, -5.98; 95% CI, -10.45 to -1.51; P = .009) and all 4 AR-associated symptoms evaluated (nasal blockage, -0.60; 95% CI, -0.96 to -0.25; runny nose, -0.67; 95% CI, -1.04 to -0.31; sneezing, -0.55; 95% CI, -0.89 to -0.21; postnasal discharge, -0.49; 95% CI, -0.83 to -0.16; all P < .01). Dupilumab 200 mg q2w demonstrated numerical, but not statistically significant, decreases in SNOT-22 total score (-1.82; 95% CI, -6.46 to 2.83; P = .443 vs placebo) and in each AR-associated symptom. In patients without PAR, no differences were observed for these measures versus placebo. CONCLUSIONS: Dupilumab 300 mg q2w significantly improved AR-associated nasal symptoms in patients with uncontrolled persistent asthma and comorbid PAR.

Appendix B. ITS Ratings and Definitions

The *Is There a There There Scale* (ITS) consists of 3 ratings: *no*, *maybe,* and *yes*. The definitions of these ratings and methods for selection are described below. Center for Evidence-based Policy (Center) researchers will use these definitions to rate each surveillance topic. The assigned rating is offered as guidance and does not require DERP participants to follow this recommendation. Each rating is strictly based on the identified new research and clinical information and is not comprehensive to all aspects of policy decision making, such as competing priorities, budget, contracting, or internal and external state agency needs.

No

- We did not find clinical evidence or information that would indicate a need to update the report or develop a derivative research product.
- A rating of *No* is typically given when there are few new studies and/or no new meaningful studies, and no new serious harms.

Maybe

- We found some clinical evidence or information that might suggest a need to update the report or develop a derivative research product.
- A rating of *Maybe* is typically given when there are multiple new comparative trials or at least 1 new meaningful study or serious harm.

Yes

- We found clinical evidence or information that suggests a need to update the report or develop a derivative research product.
- A rating of Yes is typically given when there are multiple new comparative trials and meaningful studies and/or new serious harms, drugs, formulations, or indications.