

Supplemental materials

Table S1 PubMed and Ovid (Embase and MEDLINE) search strategy

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(((asthma[Title/Abstract] OR asthmatic[Title/Abstract]) AND crossover[Title/Abstract]) OR  
((asthma[Title/Abstract] OR asthmatic[Title/Abstract]) AND (randomized [Title/Abstract] OR  
randomised OR clinical trial[Title/Abstract]) AND placebo[Title/Abstract])) AND  
((tezepelumab[Title/Abstract] OR dupilumab[Title/Abstract] OR benralizumab[Title/Abstract] OR  
mepolizumab[Title/Abstract] OR reslizumab[Title/Abstract] OR omalizumab[Title/Abstract] OR  
tralokinumab[Title/Abstract] OR pitrakinra[Title/Abstract] OR lebrikizumab[Title/Abstract] OR  
lirentelimab[Title/Abstract] OR AK002[Title/Abstract] OR anti-[Title/Abstract] OR  
biologic[Title/Abstract] OR monoclonal[Title/Abstract] OR anti-TNF*[Title/Abstract] OR (TNF-  
alpha[Title/Abstract] AND antagonists[Title/Abstract]))) AND ((airway[Title/Abstract] OR  
hyperresponsiveness[Title/Abstract] OR hyper responsiveness[Title/Abstract] OR hyper-  
responsiveness[Title/Abstract] OR hyperreactivity[Title/Abstract] OR hyper  
reactivity[Title/Abstract] OR hyper-reactivity[Title/Abstract] OR  
bronchoprovocation[Title/Abstract] OR eucapnic voluntary hyperpnea[Title/Abstract] OR  
EVH[Title/Abstract] OR acetylcholine[Title/Abstract] OR adenosine  
monophosphate[Title/Abstract] OR methacholine[Title/Abstract] OR mannitol[Title/Abstract] OR  
histamine[Title/Abstract] OR cyclic AMP[Title/Abstract] OR cAMP[Title/Abstract] OR  
exercise[Title/Abstract] OR allergen challenge[Title/Abstract] OR early phase  
response*[Title/Abstract] OR early-phase response*[Title/Abstract] OR early phase allergic  
response*[Title/Abstract] OR early-phase allergic response*[Title/Abstract] OR late phase  
response*[Title/Abstract] OR late-phase response*[Title/Abstract] OR late phase allergic  
response*[Title/Abstract] OR late-phase allergic response*[Title/Abstract]))
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|--|---|---|--|---------|----------------------------------|
| The effect of IVX-0142, a heparin-derived hypersulfated disaccharide, on the allergic airway responses in asthma | Duong M, Cockcroft D, Boulet LP, Ahmed T, Iverson H, Atkinson DC, Stahl EG, Watson R, Davis B, Milot J, Gauvreau GM, O'Byrne PM. | Allergy. 2008 Sep;63(9):1195-201. doi: 10.1111/j.1398-9995.2008.01707.x. | 10.1111/j.1398-9995.2008.01707.x | Exclude | Not biologic |
| The effect of marimastat, a metalloprotease inhibitor, on allergen-induced asthmatic hyper-reactivity | Bruce C, Thomas PS. | Toxicol Appl Pharmacol. 2005 Jun 1;205(2):126-32. doi: 10.1016/j.taap.2004.10.005. | 10.1016/j.taap.2004.10.005 | Exclude | Not biologic |
| The effect of montelukast (MK-0476), a cysteinyl leukotriene receptor antagonist, on allergen-induced airway responses and sputum cell counts in asthma | Diamant Z, Grootendorst DC, Veselico-Charvat M, Timmers MC, De Smet M, Leff JA, Seidenberg BC, Zwinderman AH, Peszek I, Sterk PJ. | Clin Exp Allergy. 1999 Jan;29(1):42-51. doi: 10.1046/j.1365-2222.1999.00447.x. | 10.1046/j.1365-2222.1999.00447.x | Exclude | Not biologic |
| The effect of montelukast on lung function and exhaled nitric oxide in infants with early childhood asthma | Straub DA, Moeller A, Minocchieri S, Hamacher J, Sennhauser FH, Hall GL, Wildhaber JH. | Eur Respir J. 2005 Feb;25(2):289-94. doi: 10.1183/09031936.05.00031904. | 10.1183/09031936.05.00031904 | Exclude | Not biologic |
| The effect of omalizumab on basophil and mast cell responses using an intranasal cat allergen challenge. | Eckman J.A. Sterba P.M. Kelly D. Alexander V. Bochner B.S. MacGlashan D.W. Saini S.S. | Journal of Allergy and Clinical Immunology. Conference: 2009 American Academy of Allergy, Asthma and Immunology (AAAAI) Annual Meeting, Washington, DC United States. Conference Publication: (var.pagings). 123(2 SUPPL. 1) (pp S196), 2009. Date of Publication: February 2009. | 10.1016/j.jaci.2009.09.012 | Exclude | EAR, LAR or AHR not measured |
| The effect of omalizumab on small airway inflammation as measured by exhaled nitric oxide in moderate-to-severe asthmatic patients. | Pasha MA, Jourdh'euil D, Jourdh'euil F, Mahon L, Romero F, Feustel PJ, Evans M, Smith T, Mitchell J, Gendapodi P, Demeveve-Coursey KC, Townley RG. | Allergy Asthma Proc. 2014 May-Jun;35(3):241-9. doi: 10.2500/aap.2014.35.3741. | 10.2500/aap.2014.35.3741 | Exclude | No relevant data |
| The effect of prasugrel on bronchial hyperreactivity in patients with chronic asthma: A pilot, proof-of-concept randomized controlled trial (prina study). | Lussana F, Di Marco F, Terraneo S, Razzari C, Centanni S, Cattaneo M. | Blood Transfusion. Conference: 22nd National Congress of the Italian Society for Thrombosis and Hemostasis - SISET. Vicenza Italy. Conference Publication: (var.pagings). 10(SUPPL. 4) (pp s102), 2012. Date of Publication: September 2012. | | Exclude | Not biologic |
| The effect of salmeterol on markers of airway inflammation following segmental allergen challenge | Calhoun WJ, Hinton KL, Kratzberg JJ. | Am J Respir Crit Care Med. 2001 Mar;163(4):881-6. doi: 10.1164/ajrccm.163.4.2001060. | 10.1164/ajrccm.163.4.2001060 | Exclude | Not biologic |
| The effect of seratodast on eosinophil cationic protein and symptoms in asthmatics | Fukuoka T, Miyake S, Umino T, Inase N, Tojo N, Yoshizawa Y. | J Asthma. 2003 May;40(3):257-64. doi: 10.1081/jas-120018322. | 10.1081/jas-120018322 | Exclude | Not biologic |
| The effect of the ET-1 receptor antagonist, bosentan, on patients with poorly controlled asthma: A 17 week, double-blind, placebo-controlled crossover pilot study. | Metersky M, Coyle T. | Chest. Conference: CHEST 2011, Honolulu, HI United States. Conference Publication: (var.pagings). 140(4 MEETING ABSTRACT) (no pagination), 2011. Date of Publication: October 2011. | | Exclude | Not biologic |
| The effect of the inhaled PDE4 inhibitor CHF6001 on allergen-induced inflammation in asthmatic subjects. | Singh D, Leaker B.R. Boyce M. Nandeuil M.A. Collarini S. Mariotti F. Santoro D. Barnes P.J. | American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS 2014, San Diego, CA United States. Conference Publication: (var.pagings). 189(MeetingAbstracts) (no pagination), 2014. Date of Publication: 2014. | | Exclude | Not biologic |
| The effect of the inhaled PDE4 inhibitor CHF6001 on allergen-induced inflammation in asthmatics. | Singh D, Leaker B, Boyce M, Nandeuil M-A, Collarini S, Mariotti F, Santoro D, Barnes P.J. | European Respiratory Journal. Conference: European Respiratory Society Annual Congress 2014, Munich Germany. Conference Publication: (var.paainas). 44(SUPPL. 58) (no pagination), 2014. Date of Publication: 01 Sep 2014. | | Exclude | Not biologic |
| The effect of the novel phosphodiesterase-4 inhibitor MEM 1414 on the allergen induced responses in mild asthma | Leaker BR, Singh D, Ali FY, Barnes PJ, O'Connor B. | BMC Pulm Med. 2014 Oct 28;14:166. doi: 10.1186/1471-2466-14-166. | 10.1186/1471-2466-14-166 | Exclude | Not biologic |
| The effect of the novel phosphodiesterase-4 inhibitor mem 1414 on the allergen-induced responses in mild asthma. | Leaker B.R. Singh D. Barnes P.J. Irmie M. Hughes R. O'Connor B. | American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS 2010, New Orleans, LA United States. Conference Publication: (var.pagings). 181(1 MeetingAbstracts) (no pagination), 2010. Date of Publication: 01 May 2010. | | Exclude | Not biologic |
| The effect of the novel SHIP1 activator AQX-1125 on allergen-induced responses in mild to moderate asthma. | Leaker B, O'Connor B, Barnes P, Mckenzie L, Chernoff D, Neville J, Tam P, Stenton G, Harwig C, MacRury T. | European Respiratory Journal. Conference: European Respiratory Society Annual Congress 2013, Barcelona Spain. Conference Publication: (var.pagings). 42(SUPPL. 57) (no pagination), 2013. Date of Publication: 01 Sep 2013. | | Exclude | Not biologic |
| The effect of Theophylline in patients with allergic rhinitis: A double-blind, randomised, crossover study. | Sankaran P, Brockwell C, Wilson A. | European Respiratory Journal. Conference: European Respiratory Society Annual Congress 2014, Munich Germany. Conference Publication: (var.paainas). 44(SUPPL. 58) (no pagination), 2014. Date of Publication: 01 Sep 2014. | | Exclude | Not asthma |
| The effect of vitamin D on airway reactivity and inflammation in asthmatic children: A double-blind placebo-controlled trial | Bar Yoseph R, Livnat G, Schnapp Z, Hakim F, Dabbah H, Goldbart A, Bentur L. | Pediatr Pulmonol. 2015 Aug;50(8):747-53. doi: 10.1002/ppul.23076. Epub 2014 Jul 2. | 10.1002/ppul.23076 | Exclude | Not biologic |
| The effect of vitamin D therapy on airway reactivity and airway inflammation in asthmatic children. | Bar-Yoseph R, Livnat G, Schnapp Z, Dabbah H, Goldbart A, Bentur L. | European Respiratory Journal. Conference: European Respiratory Society Annual Congress 2013, Barcelona Spain. Conference Publication: (var.paainas). 42(SUPPL. 57) (no pagination), 2013. Date of Publication: 01 Sep 2013. | | Exclude | Not biologic |
| The effects of spirulina (Arthrospira platensis) dietary supplement as an adjunct therapy for children aged 7 to 14 years old with asthma: A randomized - double blind placebo controlled clinical trial. | Ver Leigh Ariaga Manzon L, Agnes Gonzalez Andaya P. | World Allergy Organization Journal. Conference: XXIV World Allergy Congress 2015, Seoul South Korea. 9(SUPPL.1) (pp 7), 2016. Date of Publication: 14 Apr 2016. | | Exclude | Not biologic |
| The effects of statin therapy on inflammatory markers in patients with copd: A double blind randomised controlled trial. | John M, Knox A.J, McKeever T.M, Meakin G, Bailey H, Cockcroft J.R, Shale D.J, Harrison T.W, Bolton C.E. | Thorax. Conference: British Thoracic Society Winter Meeting 2013, Westminster United Kingdom. Conference Publication: (var.paainas). 68(SUPPL. 3) (pp A16-A17), 2013. Date of Publication: December 2013. | | Exclude | Not biologic |
| The effects of the novel SHIP1 activator AQX-1125 on allergen-induced responses in mild to moderate asthma. | Leaker B.R, O'Connor B.J, Barnes P.J, Chernoff D, Tam P, Neville J, Toews J, Stenton G.R, Harwig C, MacRury T, Mackenzie L. | American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS 2013, Philadelphia, PA United States. Conference Publication: (var.pagings). 187(MeetingAbstracts) (no pagination), 2013. Date of Publication: 2013. | | Exclude | Not biologic |
| The effects of the novel SHIP1 activator AQX-1125 on allergen-induced responses in mild-to-moderate asthma | Leaker BR, Barnes PJ, O'Connor BJ, Ali FY, Tam P, Neville J, Mackenzie LF, MacRury T. | Clin Exp Allergy. 2014 Sep;44(9):1146-53. doi: 10.1111/cea.12370. | 10.1111/cea.12370 | Exclude | Not biologic |
| The ELSA trial: single versus combinatory effects of non-prohibited beta-2 agonists on skeletal muscle metabolism, cardio-pulmonary function and endurance performance-study protocol for a randomized 4-way balanced cross-over trial | Zigel M, Bizjak DA, Nussbaumer D, Winkert K, Takabayashi K, Kirsten J, Washington M, Treff G, Dreyhaupt J, Steeb L, Diel P, Parr MK, Steinacker JM, Persch H. | Trials. 2021 Dec 11;22(1):903. doi: 10.1186/s13063-021-05862-w. | 10.1186/s13063-021-05862-w | Exclude | Not biologic |
| The extent of serum periostin reduction in asthma patients treated with lebrikizumab is related to baseline periostin levels: A pooled analysis of phase II studies. | Choy D.F, Holweg C.T.J, Cai F, Arron J.R, Matthews J.G, Scheerens H. | Journal of Allergy and Clinical Immunology. Conference: 2016 Annual Meeting of the American Academy of Allergy, Asthma and Immunology, AAAAI 2016, Los Angeles, CA United States. Conference Publication: (var.pagings). 137(2 SUPPL. 1) (pp AB15), 2016. Date of Publication: February 2016. | | Exclude | AHR not measured |
| The Impact of Food Histamine Intake on Asthma Activity: A Pilot Study | Vassilopoulos E, Konstantinou GN, Dimitriou A, Manios Y, Koumbi L, Papadopoulos NG. | Nutrients. 2020 Nov 5;12(11):3402. doi: 10.3390/nu12113402. | 10.3390/nu12113402 | Exclude | Not biologic |
| The influence of intravenous hydrocortisone on cytokine levels in children with asthma | Landstra AM, Kauffman HF, Mariké Boezen H, van Aalderen WM, Zonderland J, Postma DS. | Pediatr Allergy Immunol. 2005 Jun;16(4):299-305. doi: 10.1111/j.1399-3038.2005.00282.x. | 10.1111/j.1399-3038.2005.00282.x | Exclude | Not biologic |
| The Intriguing Role of Interleukin 13 in the Pathophysiology of Asthma | Marone G, Granata F, Pucino V, Pecoraro A, Heffler E, Loffredo S, Scadding GW, Varricchi G. | Front Pharmacol. 2019 Dec 6;10:1387. doi: 10.3389/fphar.2019.01387. eCollection 2019. | 10.3389/fphar.2019.01387 | Exclude | Review |
| The inverse agonist propranolol confers no corticosteroid-sparing activity in mild-to-moderate persistent asthma | Anderson WJ, Short PM, Williamson PA, Manoharan A, Lipworth BJ. | Clin Sci (Lond). 2014 Dec;127(11):635-43. doi: 10.1042/CS20140249. | 10.1042/CS20140249 | Exclude | Not biologic |
| The inverse agonist propranolol does not confer steroid-sparing activity in persistent asthma. | Anderson W, Short P, Williamson P, Manoharan A, Lipworth B. | European Respiratory Journal. Conference: European Respiratory Society Annual Congress 2014, Munich Germany. Conference Publication: (var.paainas). 44(SUPPL. 58) (no pagination), 2014. Date of Publication: 01 Sep 2014. | | Exclude | Not biologic |
| The long-acting beta2-agonist salmeterol xinafoate: effects on airway inflammation in asthma | Roberts JA, Bradding P, Britten KM, Walls AF, Wilson S, Gratzou C, Holgate ST, Howarth PH. | Eur Respir J. 1999 Aug;14(2):275-82. doi: 10.1034/j.1399-3003.1999.14b07.x. | 10.1034/j.1399-3003.1999.14b07.x | Exclude | Not biologic |
| The Predicting Response to Inhaled Corticosteroid Efficacy (PRICE) trial | Martin RJ, Szefer SJ, King TS, Kraft M, Boushey HA, Chinchilli VM, Craig TJ, Dimango EA, Deykin A, Fahy JV, Israel E, Lazarus SC, Lemanske RF Jr, Leone FT, Pesola GR, Peters SP, Sorkness CA, Swzejbka LA, Wechsler ME, National Heart, Lung, and Blood Institute's Asthma Clinical Research Center. | J Allergy Clin Immunol. 2007 Jan;119(1):73-80. doi: 10.1016/j.jaci.2006.10.035. | 10.1016/j.jaci.2006.10.035 | Exclude | Not biologic |
| The role of leukotriene receptor antagonists in the treatment of chronic asthma in childhood | Warner JO. | Allergy. 2001;56 Suppl 66:22-9. doi: 10.1034/j.1398-9995.2001.00005.x. | 10.1034/j.1398-9995.2001.00005.x | Exclude | Review |
| The role of oral magnesium supplements for the management of stable bronchial asthma: a systematic review and meta-analysis | Abuabat F, AlAlwan A, Masuadi E, Murad MH, Jaddali HA, Ferwana MS. | NPJ Prim Care Respir Med. 2019 Feb 18;29(1):4. doi: 10.1038/s41533-019-0116-z. | 10.1038/s41533-019-0116-z | Exclude | Not biologic |
| The Sputum Transcriptome of Mild Atopic Asthma Following Bronchoprovocation and Inhaled Anti-TSLP Antibody Fragment Treatment. | Cabanski M, Xu H, Zhao X, Fernandez A, Khokhlovich E, Rowlands M, Schuhmann I, Grant S.S, Pertel P. | American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS 2021, Virtual. 203(9) (no pagination), 2021. Date of Publication: May 2021. | 10.1164/ajrccm-conference.2021.TP112 | Exclude | No relevant data |
| Tralokinumab for the treatment of severe, uncontrolled asthma: the ATMOSPHERE clinical development program | Gauvreau G.M, O'Byrne P., Hohlfeld J.M, Vitaliti A, Obeidat M. | Immunotherapy. 2018 Mar 1;10(6):473-490. doi: 10.2217/imt-2017-0191. Epub 2018 Mar 14. | 10.2217/imt-2017-0191 | Exclude | Not RCT |
| Treatment of allergic rhinitis with theophylline : A double-blind, randomised, crossover study. | Panettieri RA Jr, Wang M, Braddock M, Bowen K, Colice G. | Thorax. Conference: British Thoracic Society Winter Meeting 2014, London United Kingdom. Conference Publication: (var.pagings). 69(SUPPL. 2) (pp A179), 2014. Date of Publication: December 2014. | | Exclude | Not biologic |
| Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab) | Sankaran P, Brockwell C, Clark A, Wilson A.M. | Respir Med. 2010 May;104(5):668-74. doi: 10.1016/j.rmed.2009.11.006. Epub 2009 Nov 26. | 10.1542/peds.108.2.e36 10.1016/j.rmed.2009.11.006 | Exclude | AHR not measured Not biologic |
| Treatment with a peroxisomal proliferator activated receptor gamma agonist has a modest effect in the allergen challenge model in asthma: a randomised controlled trial | Milaram H, Berser W, Nayak A, Gupta N, Pollard S, McAlary M, Taylor AF, Rohane P. | Pediatric Pulmonology. Conference: 13th International Congress on Pediatric Pulmonology, Bruges Belgium. Conference Publication: (var.paainas). 49(SUPPL. 37) (pp S12-S13), 2014. Date of Publication: September 2014. | | Exclude | Review |
| Understanding distinct RSV related wheezing phenotypes. | Richardson DB, Barelle P, Lindo EL, Quinn D, Farrow SN. | Drug Saf. 2013 Nov;36(11):1097-104. doi: 10.1007/s40264-013-0093-z. | 10.1007/s40264-013-0093-z | Exclude | Not biologic |
| Use of acid-suppressive drugs in pregnancy and the risk of childhood asthma: bidirectional crossover study using the general practice research database | Mazur N, Bont L. | American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS 2017, Washington, DC United States. 195 (no pagination), 2017. Date of Publication: 2017. | | Exclude | Not biologic |
| Vitamin e (gamma tocopherol) reduces acute airway neutrophilia in mild asthmatics. | Hak E, Mulder B, Schuiling-Veninga CC, de Vries TW, Jick SS. | Journal of Allergy and Clinical Immunology. Conference: 2012 Annual Meeting of the American Academy of Allergy, Asthma and Immunology, AAAAI 2012, Orlando, FL United States. Conference Publication: (var.pagings). 129(2 SUPPL. 1) (pp AB130), 2012. Date of Publication: February 2012. | | Exclude | Not biologic |
| Vitamin E reduces airway granulocyte recruitment after inhaled endotoxin challenge in normal volunteers. | Hernandez M.L. Alexis N.E. Lay J.C. Zhou H. JIANG Q. Peden D.B. | Free Radic Biol Med. 2013 Jul;60:56-62. doi: 10.1016/j.freeradbiomed.2013.02.001. Epub 2013 Feb 9. | 10.1016/j.freeradbiomed.2013.02.001 | Exclude | Not biologic |
| Vitamin E, γ-tocopherol, reduces airway neutrophil recruitment after inhaled endotoxin challenge in rats and in healthy volunteers | Hernandez ML, Wagner JG, Kala A, Mills K, Wells HB, Alexis NE, Lay JC, Jiang Q, Zhang H, Zhou H, Peden DB. | Am J Respir Crit Care Med. 2018 Jan 1;197(1):38-46. doi: 10.1164/rccm.201707-1323OC. | 10.1164/rccm.201707-1323OC | Exclude | AHR not measured |
| Weight-adjusted Intravenous Reslizumab in Severe Asthma with Inadequate Response to Fixed-Dose Subcutaneous Mepolizumab | Mukherjee M, Aleman Paramo F, Kjarsgaard M, Salter B, Nair G, LaVigne N, Radford K, Sehmi R, Nair P. | | | | |

Table S3 Study design, inclusion and exclusion criteria of included trials

| Study identifiers | | | | Population and treatment | | Study design | Key inclusion criteria | Key exclusion criteria | |
|-------------------|------------------------------------|---|---|---|--|---|--|--|---|
| Biologic | Reference | Article title | Article / Published link | Population | Study duration (number of patients) | | | | Treatment arm |
| Omaliuzumab | Boulet et al 1997 ⁷⁴ | Inhibitory Effects of an Anti-IgE Antibody E25 on Allergen-Induced Early Asthmatic Response | https://pubmed.ncbi.nlm.nih.gov/9196927/ | Stable mild allergic asthma | 10 weeks (n = 20) | Placebo rhMAb-E25 (initial active drug at a dose of 2.0 mg/kg or placebo was administered in subsequent doses of rhMAb-E25 at 1.0 mg/kg or placebo) | Multicenter, randomized, double-blind, parallel-group, placebo-controlled trial consisting of 10 wk of study drug administration and 1 wk of follow-up. | All patients had a highly positive allergy skin prick test to at least one common aeroallergen, an early asthmatic response ($\geq 15\%$ decrease in FEV1 on allergen inhalation in the laboratory, a forced expiratory volume in one second (FEV1) $\geq 70\%$ predicted, and a methacholine provocative concentration causing a 20% fall in FEV1 (PC20) ≤ 0.4 mg/ml). Allergens types: Birch, Horse, Weed, Grass, Ragweed, Cat, Mite | Exclusion criteria included history of anaphylaxis or significant medical illness other than mild allergic asthma, evidence of recently unstable asthma (emergency room visit in the previous 6 wk, intubation and mechanical ventilation for asthma in the past 12 mo), respiratory infection or aeroallergen exposure (greater than household level) within the past 4 wk, smoking within the last 12 mo, a history of smoking ≥ 10 pack-years and for women of childbearing potential, a lack of effective contraception. Patients were studied outside of relevant allergen seasons when asthma symptoms were absent or very mild. |
| Omaliuzumab | Fahy et al 1997 ⁷⁵ | The Effect of an Anti-IgE Monoclonal Antibody on the Early- and Late-Phase Responses to Allergen Inhalation in Asthmatic Subjects | https://pubmed.ncbi.nlm.nih.gov/9196927/ | Mild asthma | 9 weeks (n = 18) | Placebo IV rhMAb-E25 IV (5 mg/ml) and placebo (rhMAb-E25 excipient [150 mM NaCl, 10 mM acetate, pH = 7.2] were delivered by 5-min intravenous infusion [0.1 mg/ml in a dose of 0.5 mg/kg for 9 visits. | Assessed the effects of 9 wk of treatment with rhMAb-E25 in a parallel group, randomized, double-blind, placebo-controlled study of 19 allergic asthmatic patients. | History of mild asthma requiring treatment only with inhaled beta2 agonists, FEV1 $\geq 70\%$ predicted, bronchial hyperreactivity to methacholine, positive skin prick tests to house dust mite, cat, pollen, or ryegrass, and serum IgE level ≤ 500 IU/ml. | Exclusion criteria were the use of corticosteroids or symptoms of an upper respiratory tract infection in the previous 6 wk, tobacco use, or a history of a significant medical illness other than asthma. |
| Omaliuzumab | Fahy et al 1997 ⁷⁶ | Effect of Aerosolized Anti-IgE (E25) on Airway Responses to Inhaled Allergen in Asthmatic Subjects | https://pubmed.ncbi.nlm.nih.gov/10471635/ | Allergic asthma | 8 weeks (n = 33) | Placebo E25 1mg E25 10mg | Randomized, placebo-controlled, parallel group clinical trial of the effects of 8 wk of once daily treatment with aerosolized E25 in two doses (1 mg and 10 mg) on the early and late phase responses to allergen challenge in allergic subjects with mild asthma | Asthma with FEV1 $\geq 70\%$ predicted, bronchial hyperreactivity to methacholine, serum IgE ≤ 500 IU/L, a positive skin prick test to aeroallergens (house dust mite, perennial grasses, birch, cat, pollen, or horse hair) were studied. | Exclusion criteria were the use of any corticosteroids or symptoms of an upper or lower respiratory tract infection in the previous 6 wk, and history of tobacco use (any in the past 12 mo and total use ≥ 10 pack-years). |
| Omaliuzumab | Naga et al 2003 ⁷⁸ | Immunological and Clinical Changes in Allergic Asthmatics Following Treatment with Omaliuzumab | https://pubmed.ncbi.nlm.nih.gov/12737489/ | Moderate to severe allergic asthma | 12 weeks (n = 35) | Placebo SC Omaliuzumab SC (administration of at least 0.016 mg/kg IgE (IU/ml) every 4 weeks) | Sub-study of a large multicentre randomised, double-blind, placebo-controlled, parallel-group trial | All patients had at least a 1-year history of allergic asthma, a positive skin prick test (SPT) to at least one of the tested allergens (Dermatophagoides farinae, Dermatophagoides pteronyssinus (house dust mite) (cat or dog dander), specific IgE (CAP Pharmacia, Uppsala, Sweden), inhaled corticosteroids at doses equivalent to budesonide/dipropionate requirement for treatment with 500–1,000 µg/day for at least 2 months and demonstrated a reversibility of 12% in FEV1 over the baseline value within 30 min after taking 200 µg of salbutamol. | NR |
| Omaliuzumab | Djukanovic et al 2004 ⁸ | Effects of Treatment with Anti-immunoglobulin E Antibody Omaliuzumab on Airway Inflammation in Allergic Asthma | https://pubmed.ncbi.nlm.nih.gov/15172896/ | Stable, mild to moderate asthma | 16 weeks (n = 45) | Placebo Omaliuzumab SC (administration of at least 0.016 mg/kg IgE (IU/ml) every 4 weeks) | 4-month, randomized, double-blind, placebo-controlled, parallel group study was conducted in five centers: University of California, San Francisco (San Francisco, CA); University of Southampton (Southampton, UK); National Jewish Medical and Research Center (Denver, CO); University of Wisconsin (Madison, WI); and Imperial College (London, UK). After a run-in period of 3 weeks, during which asthma activity and airway responsiveness were assessed to determine inclusion eligibility, patients were randomized to 16 weeks of treatment with either omaliuzumab or placebo. Patients were treated subcutaneously with omaliuzumab (150–300 mg every 4 weeks or 225–375 mg every 2 weeks) on the basis of the concentration of serum total IgE and patient body weight at baseline | Stable, mild to moderate asthma (defined by the criteria of the National Heart, Lung, and Blood Institute Expert Panel Report [23]) for at least 1 year; treatment with inhaled β_2 -agonists only; no acute exacerbations requiring rescue corticosteroid medication for at least 6 weeks before screening for the study; age 18 to 50 years; total serum IgE ≥ 30 IU/L or no more than 700 IU/L; positive skin prick test for at least one common allergen (house dust mite, cockroach, dog, or cat); airway hyperresponsiveness as defined by a methacholine PC20 value (provocative concentration inducing a 20% drop in FEV1) of less than 8 mg/ml; and sputum eosinophils of 2% or more of total nonsquamous cells. | NR - See some inclusion |
| Omaliuzumab | Prisco et al 2006 ⁷⁷ | Effect of Omaliuzumab on Adenosine 5'-Monophosphate Responsiveness in Subjects with Allergic Asthma | https://pubmed.ncbi.nlm.nih.gov/16374623/ | Mild to moderate persistent allergic asthma | 12 weeks (n = 34) | Placebo SC Omaliuzumab SC (administration of at least 0.016 mg/kg IgE (IU/ml) every 4 weeks) | Randomized, double-blind, placebo-controlled, parallel-group trial conducted in four centers in Spain. After a 5- to 10-day baseline period, patients were randomized to receive either omaliuzumab or placebo administered subcutaneously every 2 or 4 weeks over a 12-week period. The dose and dosing intervals were based on the subject's body weight and baseline serum IgE. This ensured for each patient a dose of at least 0.016 mg/kg per intravenous unit per milliliter of IgE every 4 weeks; patients thus received 150–300 mg every 4 weeks or 225–300 mg every 2 weeks. Trial personnel administered medication in a blinded fashion, which was maintained at each center by using a central randomization procedure to prepare the medication or placebo injections before administration. | Mild to moderate persistent allergic asthma, positive immediate responses (wheal diameter ≥ 3 mm) on skin prick testing to house dust mite allergens (Dermatophagoides pteronyssinus and Dermatophagoides farinae), dog, or cat; baseline FEV1 $\geq 80\%$ of the predicted value and FEV1/FVC $\geq 70\%$; total serum IgE ≥ 30 IU/L or ≥ 700 IU/L; and body weight ≥ 150 kg to allow optimal dosing of omaliuzumab; treatment with inhaled short-acting β_2 -agonists alone or with inhaled corticosteroids (ICS) in doses equivalent to 200–1,000 µg of budesonide/dipropionate per day for ≥ 6 months prior to randomization; no specific immunotherapy within the past 3 months; and bronchoconstriction in response to both AMP and methacholine at screening. All patients were to be exposed to at least one of the perennial allergens to which they had a positive skin prick test result for the duration of the study. Asthma had to be stable, with no significant change in regular medication for ≥ 3 months prior to the screening visit. Females of childbearing potential to use reliable contraceptives. None had chronic bronchitis, emphysema, allergic bronchopulmonary aspergillosis or respiratory tract infections during the 4 weeks before the study. No relevant concomitant diseases were present. | Pregnant or lactating women were excluded from participation. Unstable asthma |
| Omaliuzumab | Patel et al 2009 ⁸ | Effects of Omaliuzumab (Xolair) on Airway Hyperresponsiveness | https://www.jcoonline.asia/article/0094-9296/09/27/3610/3614-8/ | Mild allergic asthma | 12 weeks (n = 18) | Placebo Omaliuzumab | Patients (FEV1 $> 70\%$) were randomized to receive either omaliuzumab or placebo in a 2:1 fashion. | Not available (abstract) | Not available (abstract) |
| Omaliuzumab | van Rensen et al 2009 ⁸ | Eosinophils in bronchial mucosa of asthmatics after allergen challenge: effect of anti-IgE treatment | https://pubmed.ncbi.nlm.nih.gov/19072931/ | Asthma - type and severity not specified | 12 weeks (n = 25) | Placebo SC Omaliuzumab SC (administration of at least 0.016 mg/kg IgE (IU/ml) every 4 weeks) | This study had a randomized, placebo-controlled, parallel, double-blind design. Anti-IgE or placebo was administered for 12 weeks every 2 or 4 weeks. At baseline, after 8 and 12 weeks of treatment, PC20 methacholine was determined and sputum induced. Allergen challenge followed by a bronchoscopy at 24 h was performed at baseline and at 12 weeks. | All patients had a history of episodic chest tightness and wheezing and were only using short-acting β_2 -agonists on demand. All were atopic to house dust mite (HDM) and were having a total serum IgE level between 30 and 700 IU/L. The baseline forced expiratory volume in 1 s (FEV1) was $\geq 70\%$ predicted (17) and all patients were hyper-responsive to inhaled methacholine (provocative concentration causing a 20% fall in FEV1 (PC20) ≤ 4 mg/ml) (18). The fall in FEV1 during the LAR following inhaled allergen was at least 15%. All patients were clinically stable and had no respiratory chest infection 5 weeks prior to the study. | NR - See some inclusion |
| Omaliuzumab | Zelen et al 2013 ⁸ | Omaliuzumab Protects against Allergen-Induced Bronchoconstriction in Allergic (Immunoglobulin E-Mediated) Asthma | https://pubmed.ncbi.nlm.nih.gov/23194547/ | Allergic asthma | 12-14 weeks (n = 50) | Placebo Omaliuzumab low IgE (30-300 IU/ml) Omaliuzumab high IgE (700-2000 IU/ml) | Multicenter, randomized, double-blind, parallel group, placebo-controlled study of omaliuzumab in two groups of patients with different pretreatment IgE concentrations | Patients aged 18-65 years with a body weight of 40-150 kg were eligible if they had asthma, prebronchodilator FEV1 $\geq 65\%$ predicted and had been asthma exacerbation-free for ≥ 4 weeks. Patients had to have had well-characterized skin reactivity to a specific allergen within 1 year before screening. At screening, patients had to demonstrate a 20% fall in FEV1 in response to methacholine at a provocative concentration ≤ 16 mg/ml and a 20% fall in FEV1 in response to an allergen at a cumulative PC20 in a bronchoprovocation test. | Exclusion criteria included history of an asthma attack requiring a visit to an emergency room in the 6 weeks before or during screening, history of an asthma attack requiring treatment with inhaled and mechanical ventilation in the 12 months before day 1 of the study, asthma exacerbation requiring treatment with oral or intravenous corticosteroids in the previous 3 months and history of intolerance to methacholine or AMP. Current active smokers with a smoking history of ≥ 5 pack-years or patients with elevated IgE due to suspected parasitosis were also excluded. |
| Omaliuzumab | Hendekx et al 2015 ¹⁷ | Omaliuzumab Therapy for Asthma Patients with Poor Adherence to Inhaled Corticosteroids | https://pubmed.ncbi.nlm.nih.gov/25127736/ | Persistent asthma | 16 weeks per treatment period (n = 17) (crossover study) | Placebo SC Omaliuzumab SC (mean [SD]: 118 [38] mg; range: 300-375 mg; administration every 2 or 4 weeks) | Randomized, double-blind, three-period, placebo-controlled, crossover study | Study included patients (ages 6-26 yr) with persistent asthma for whom ICS were prescribed for at least 3 months, either alone or in combination with a long-acting β_2 -agonist or leukotriene modifier. They had poor asthma control (defined by any of the following: FEV1 $\leq 80\%$ predicted, short-acting β_2 -agonist use ≥ 3 times/wk, nocturnal symptoms ≥ 2 times/wk, exercise-induced bronchospasm, activities of daily living, unscheduled physician visits or hospitalization for asthma, or ≥ 1 prednisone burst in previous 3 months). Other inclusion criteria were a pharmacy prescription with history of $\leq 50\%$ predicted dose of ICS for ≥ 3 months; sensitization to one or more indoor allergens or outdoor allergens, total IgE of 30 to 700 IU/ml for patients ≥ 12 years or up to 130 IU/ml for those 6 to 12 years; baseline FEV1 $\geq 60\%$ predicted; and a 20% decrease in FEV1 after inhaling ≤ 60 mg/ml of AMP (i.e., PC20 FEV1 ≤ 60 mg/ml). | NR - See some inclusion |
| Mapolizumab | Leskie et al 2009 ⁸ | Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response | https://pubmed.ncbi.nlm.nih.gov/19114524/ | Mild allergic asthma | 16 weeks (n = 24) | Placebo IV humanized IgG4 mAb to IL-5 - dose 2.5 mg/kg IV humanized IgG4 mAb to IL-5 - dose 10.0 mg/kg IV | This study was a double-blind, randomized, placebo-controlled, single dose, parallel group study of three centres. | Mild allergic asthma (as defined by the American Thoracic Society) and a history of episodic wheeze and shortness of breath. The patients were atopic, as defined by positive skin tests in response to common airborne allergens (Dermatophagoides pteronyssinus, mixed grass pollen, and cat hair) and were maintained on shortacting inhaled beta2-agonist treatment as required. Patients had neither worsening asthma nor a respiratory infection in the preceding 6 weeks. FEV1 at baseline was at least 70% of the predicted value and there was a documented airway hyperresponsiveness to histamine, with a provocative concentration causing a 20% reduction in FEV1 (PC20) ≤ 8 mg/ml. Patients had documented early and late asthmatic responses (defined as a $\geq 15\%$ reduction in FEV1 on at least three occasions between 4 and 10 h after allergen) to inhaled incremental allergen challenge between 3 and 6 weeks before the study treatment was given. | NR - See some inclusion |
| Mapolizumab | Flood-Page et al 2013 ⁸ | Eosinophils' Role Remains Uncertain as Anti-interleukin-5 only Paradoxically Depletes Numbers in Asthmatic Airway | https://pubmed.ncbi.nlm.nih.gov/21406833/ | Mild asthma | 20 weeks (n = 24) | Placebo IV Mapolizumab 750mg IV (three doses Q4W) | This was a two-center, double-blind, placebo-controlled, parallel-group study based at the Royal Brompton and London Chest hospitals. | Mild asthma with a FEV1 of 70% or more of predicted, all were atopic, as defined by a positive skin prick test to one or more aeroallergens. All were well-controlled with short-acting β_2 -agonists, with no use of corticosteroids or other antiasthmatic drugs in the preceding 8 weeks. All volunteers gave a clear history of asthma, demonstrated airway hyperresponsiveness with a PC20 to histamine of 4.0 mg/ml or less and were non-smokers | NR - See some inclusion |
| Mapolizumab | Haidar et al 2009 ⁸ | Mapolizumab and Exacerbations of Refractory Eosinophilic Asthma | https://pubmed.ncbi.nlm.nih.gov/19246686/ | Refractory eosinophilic asthma | 50 weeks (n = 61) | Placebo IV Mapolizumab 750mg IV Q4W | The study was a single-center, randomized, double-blind, placebo-controlled, parallel-group clinical trial | Clinical diagnosis of asthma that was supported by one or more of the following criteria: variability in the maximum diurnal peak expiratory flow of more than 20% over the course of a 14-day, an increase in FEV1 of more than 15% after inhalation of 200 µg of albuterol, and a 20% reduction in FEV1 in response to a provocative concentration of inhaled methacholine (PC20) of less than 8 mg per milliliter. Inclusion criteria were a diagnosis of asthma according to American Thoracic Society criteria, 15 \pm 5 sputum eosinophils/percentage of more than 3% on at least one occasion in the previous 2 years despite high-dose corticosteroid treatment, and at least two exacerbations requiring rescue prednisolone treatment in the previous 12 months. Additional criteria for inclusion were stable treatment requirements and an absence of exacerbations for more than 6 weeks before enrollment in the study. | Exclusion criteria were current smoking, serologic evidence of a parasitic infection, the possibility of conception, and poor adherence to treatment. |

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| Benzluzumab | Gauvreau et al 2021 ¹⁴ | The Effect of Benralizumab On Allergen-Induced Responses in Subjects With Mild Allergic Asthma | https://doi.org/10.1016/j.clin.2020.12.063 | Mild Allergic Asthma | 9 weeks (n = 48) | Placebo Benralizumab 30 mg SC QW | Patients were randomized to benralizumab or placebo | Not available (abstract) | Not available (abstract) |
| Tezepelumab | Gauvreau et al 2014 ¹⁵ | Effects of an Anti-TSLP Antibody on Allergen-Induced Asthmatic Responses | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4105649/ | Mild allergic asthma | 12 weeks (n = 31) | Placebo IV Tezepelumab (AMG 157) 700 mg IV (93 doses) | We conducted this proof-of-concept, randomized, double-blind, placebo-controlled study at five centers in Canada. Eligible patients were nonsmoking men and women, 18 to 60 years of age, with mild, stable atopic asthma, as confirmed by positive results on a spirometry test; a forced expiratory volume in 1 second (FEV1) of 70% or more of the predicted value; and airway hyperresponsiveness to allergens with seasonal variation. Patients were tested out of season for pollen affecting their asthma; all patients had no other lung disease. No asthma-controller treatments were allowed during the study, although the use of inhaled short-acting β2-agonists as rescue treatment administered fewer than 2 days per week was permitted. All other asthma medications were discontinued at least 4 weeks before enrollment. Patients were excluded from the study if they had worsening of asthma, respiratory-related visits to the emergency department within 6 weeks before study enrollment, previous use of AMG 157, or known sensitivity to any AMG 157 excipients. | Eligible patients were nonsmoking men and women, 18 to 60 years of age, with mild, stable atopic asthma, as confirmed by positive results on a spirometry test; a forced expiratory volume in 1 second (FEV1) of 70% or more of the predicted value; and airway hyperresponsiveness to allergens with seasonal variation. Patients were tested out of season for pollen affecting their asthma; all patients had no other lung disease. No asthma-controller treatments were allowed during the study, although the use of inhaled short-acting β2-agonists as rescue treatment administered fewer than 2 days per week was permitted. All other asthma medications were discontinued at least 4 weeks before enrollment. Patients were excluded from the study if they had worsening of asthma, respiratory-related visits to the emergency department within 6 weeks before study enrollment, previous use of AMG 157, or known sensitivity to any AMG 157 excipients. | Patients were excluded from the study if they had worsening of asthma, respiratory-related visits to the emergency department within 6 weeks before study enrollment, previous use of AMG 157, or known sensitivity to any AMG 157 excipients. |
| Tezepelumab | Diver et al 2021 ¹⁶ | Effect of tezepelumab on airway inflammatory cells, remodeling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomized, placebo-controlled, phase 2 trial | https://pubmed.ncbi.nlm.nih.gov/34259631/ | Uncontrolled, moderate to-severe asthma | 28 weeks (n = 99) | Placebo SC Tezepelumab 210mg SC QW | CASCADE was an exploratory, double-blind, randomized, placebo-controlled, parallel-group, phase 2 study. Potential participants were screened at 27 centres | <ul style="list-style-type: none"> Male or female, aged 18–75 years, weight 1–40 kg at visit 1 Documented physician-diagnosed asthma for 2 months before visit 1 Physician-prescribed asthma controller medication with medium- or high-dose ICS for at least 12 months before visit 1 (as per GINA 2019 guidelines) Documented use of at least one additional maintenance asthma controller medication (e.g. LABA, LTRA, theophylline or LAMA) for at least 3 months before visit 1 Predicted normal value for morning ambrochondilator FEV1 >50% and >1 L at visit 1 or visit 2 Documented historical FEV1 reversibility of ≥12% and ≥200 mL in the 12 months before visit 1 or at visit 2 ACQ-6 score ≤ 1.5 at visit 1 or visit 2 | <ul style="list-style-type: none"> Any clinically important pulmonary disease, other than asthma, associated with high peripheral eosinophil counts Any disorder that could, in the opinion of the investigator, affect the safety of the patient or influence the study findings Exacerbation resulting in hospitalization or requiring OCS within 6 weeks of enrollment; more than three asthma exacerbations requiring OCS or hospitalization in the 12 months before visit 1 or exacerbation requiring intubation or admission to the ICU in the year before enrollment Any clinically significant infection requiring antibiotic or antiviral treatment within 2 weeks of visit 1 or during the run-in period Use of intravitreal or intravitreal injections within 6 months of visit 1 that has not been treated with, or is unresponsive to, standard-of-care therapy History of cancer, HIV or hepatitis B or C Current smokers or patients with a smoking history of 10 pack-years Use of any medical or investigational biologic agent within 4 months or 5 half-lives of visit 1, or any investigational non-biologic agent within 30 days or 5 half-lives of visit 1 Use of any immunosuppressive medication within 12 weeks of randomization History of anaphylaxis after biologic therapy Pregnant, breastfeeding or lactating |
| Tezepelumab | Sverrild et al 2021 ¹⁴ | The effect of tezepelumab on airway hyperresponsiveness to mannitol in asthma (UPSTREAM) | https://pubmed.ncbi.nlm.nih.gov/34049431/ | Uncontrolled asthma | 12 weeks (n = 40) | Placebo IV Tezepelumab 700 mg IV QW | Double-blind, placebo-controlled randomized trial of adults with uncontrolled asthma. | Eligible participants were non-smoking adults between the ages of 18 and 75 years old with uncontrolled asthma (ACQ-6 score ≥1) and an FEV1-inhaled mannitol baseline (provisional dose of mannitol causing a 35% reduction in FEV1 (FEV1) 315) despite any stable dose of ICS. Second-line controller (leukotriene-modifiers, long-acting beta2-agonists, and long-acting muscarinic antagonists) were allowed, but treatment with oral corticosteroids (12 weeks prior to inclusion), immunosuppressive drugs, or biologics (4 months prior to inclusion) were not. Patients were included independent of their levels of blood eosinophils or atopic status, had to demonstrate acceptable spirometry and spirometry techniques as well as ≥70% compliance with their usual asthma controller during screening. | A full list of inclusion and exclusion criteria, and medications withheld before testing are available in the Supplementary Appendix. |
| Lefkizumab | Scheerens et al 2014 ¹⁷ | The effects of leflizumab in patients with mild asthma following whole lung allergen challenge | https://pubmed.ncbi.nlm.nih.gov/24131304/ | Mild allergic asthma | 13 week treatment period but allergen and MCh challenges done before and after study weeks (n = 29) | Placebo Lefkizumab 5 mg/kg QW | phase II, multi-centre, randomized, double-blind, parallel group, placebo-controlled trial was designed to evaluate safety and efficacy of leflizumab compared with placebo in reducing the airway reaction to an inhaled aeroallergen solution in adult patients with mild allergic asthma (EU study sites) | Allergic asthma diagnosed for ≥ 6 months, which was being treated with only intermittent short-acting inhaled β2-adrenergic agonists, and a stable dose of ICS for at least one of the following allergens: house dust mite, cat dander, ragweed, and had a FEV1 of 70% of predicted, showed both an early asthmatic response (EAR) of ≥20% reduction in FEV1 5–30 min following allergen challenge, and a late asthmatic response (LAR) of ≥15% reduction in FEV1 ≥ 8 h following allergen challenge, and had a PC20 ≤ 8 mg/mL, defined as the provocative methacholine concentration that caused a >20% fall in FEV1 from the saline alone value. | Subjects were excluded from participation if they required daily controller medication for asthma, had a history of hypersensitivity to study drug or to drug with similar chemical structure or ingredients, had a documented medical history of anaphylaxis, had lung disease other than mild allergic asthma, had significant concurrent medical illness other than asthma, had clinically significant laboratory or electrocardiogram abnormalities at screening, had smoked in the previous 6 months or had a history of smoking more than 10 pack-years, had a history of hepatitis infections, or had a history of drug or alcohol abuse. Use of the following medications was not allowed during the time period specified prior to screening or during screening or the first 16 weeks of the study: oral or inhaled corticosteroids (6 weeks prior to screening), inhaled corticosteroids or inhaled corticosteroids (6 weeks prior to screening), methylxanthines (2 days prior to screening), leukotriene receptor antagonists (6 weeks prior to screening), inhaled long-acting β2-adrenergic agonists (4 weeks prior to screening), or any other non-systemic steroid immunosuppressive medication. |
| Tralokinumab | Rusoff et al 2018 ¹⁸ | Effect of tralokinumab, an interleukin-13 neutralizing monoclonal antibody, on eosinophilic airway inflammation in uncontrolled moderate-to-severe asthma (MISTO): a multicentre, double-blind, randomized, placebo-controlled phase 2 trial | https://pubmed.ncbi.nlm.nih.gov/29793657/ | Inadequately controlled moderate to severe asthma | 12 weeks (n = 79) | Placebo SC Tralokinumab 300mg SC QW | multicentre, double-blind, randomized, placebo-controlled, 12-week phase 2 trial, we recruited participants from 15 centres in the UK, Denmark, and Canada | Documented history of physician-diagnosed asthma for 12 months or more, requiring treatment with inhaled corticosteroids (≥250 µg/day of fluticasone or equivalent at a stable dose with or without other asthma controller medications). All participants were required to be exacerbation free for 6 weeks or more before enrollment, and to have had no more than three asthma exacerbations requiring treatment with oral corticosteroids in the preceding 12 months. Furthermore, all participants had post-bronchodilator FEV1 reversibility of ≥15% or more and 200 mL or more, and evidence of uncontrolled asthma defined by an Asthma Control Questionnaire (ACQ-6) score ≤1.5) during the run-in period. | We excluded participants receiving regular systemic corticosteroids or biologics, current smokers and past smokers of more than 10 pack-years, and participants with clinically significant comorbidities. Criteria for withdrawal from the trial were defined a priori, and included withdrawal of consent, pregnancy, and the occurrence of an adverse event for which continued exposure to treatment could be detrimental to the participant. |
| Tocilizumab | Revez et al 2019 ¹⁹ | Effects of interleukin-6 receptor blockade on allergen induced airway responses in mild asthmatics | https://pubmed.ncbi.nlm.nih.gov/31724890/ | Mild, stable allergic asthma as well as rs2228145-AC or CC genotype | Completing the study could take 5-10 weeks (n = 11) | Placebo Tocilizumab 8 mg/kg IV (single dose) | Proof-of-concept, randomized, double-blind, parallel-group, placebo-controlled study. Patients completed the baseline phase of the trial and remained eligible to continue were the subset confirmed to have the rs2228145-AC or CC genotype, as well as mild, stable allergic asthma | Patients invited to participate in the trial were men or women who, in previous studies or in response to media approach, reported being 18–65 years of age, non-smokers, of general good health and with a history of asthma that did not require regular treatment with corticosteroids. | NR |
| Efalunumab | Gauvreau et al 2008 ²⁰ | The effects of an anti-CD11a mAb, efalunumab, on allergen-induced airway responses and airway inflammation in subjects with atopic asthma | http://pubmed.ncbi.nlm.nih.gov/1877739/ | Mild Allergic Asthma | 8 weeks (n = 35) | Placebo SC Efalunumab SC (0.7 mg/kg conditioning dose followed by 7 weekly doses of 2.0 mg/kg) | Multicenter, double-blind, placebo-controlled (D efalunumab), randomized, parallel group study was carried out | Inclusion criteria required patients to be nonsmokers with mild atopic asthma, free of other lung disease, and no history of recurrent bacterial, viral, or fungal infection. Although efalunumab was anticipated to have beneficial effects in severe asthma, patients with mild asthma were recruited for allergen challenge and subsequent evaluation of the allergen-induced airway inflammation. Patients were required to have stable asthma with FEV1 greater than 70% of predicted on at study date before allergen challenge, baseline methacholine PC20 of 16 mg/mL or less, to use no regular asthma medication during the study other than that more than twice weekly inhaled β2-agonists, which was withheld for 8 hours before each visit, to have no exposure to sensitizing allergens apart from house dust mite, to have no asthma exacerbations or respiratory tract infections for 4 weeks before entering the study, and to refrain from rigorous exercise, tea, or coffee in the morning before visits to the laboratory. | NR. See same in inclusion |
| Etanercept | Berry et al 2006 ²¹ | Evidence of a Role of Tumor Necrosis Factor in Refractory Asthma | https://pubmed.ncbi.nlm.nih.gov/14814813/ | Mild to Moderate asthma; refractory asthma | 10 weeks (n = 30) | Placebo SC twice weekly Mild-to-moderate: Etanercept 25mg SC twice weekly Refractory: Etanercept 25mg SC twice weekly | randomized, double-blind, crossover study comparing the effect of 10 weeks of treatment with etanercept at the dose used in a previously reported uncontrolled study and placebo | Patients with asthma had clinical features consistent with the presence of asthma and at least one of the following objective measures of airway hyperresponsiveness and variable airway obstruction: The concentration of methacholine required to provoke a 20 percent decrease (PC20) in the forced expiratory volume in one second (FEV1) was less than 8 mg per milliliter; the FEV1 increased by at least 15 percent after the inhalation of 200 mg of albuterol; or the variation in peak flow, expressed as a percentage of the mean, exceeded 20 percent over a period of 14 days. All patients classified as having mild-to-moderate asthma met the Global Initiative for Asthma criteria for intermittent or mild persistent asthma. All patients with refractory asthma met the Global Initiative for Asthma criteria for severe persistent asthma, and met at least one major and two minor criteria for refractory asthma and were considered to be compliant with treatment. | Excluded patients who were thought to be symptomatic because of uncontrolled coexisting conditions such as rhinitis and gastroesophageal reflux disease. Patients were also excluded if they had any of the following: recent contact with a patient with pulmonary tuberculosis, a personal history of tuberculosis, any radiologic features suggestive of current or previous tuberculosis, or a grade III or IV tuberculin (heaf) test. |
| Etanercept | Rahmani et al 2005 ²² | Effect of tumor necrosis factor antagonism on allergen-mediated asthmatic airway inflammation | https://pubmed.ncbi.nlm.nih.gov/1608220/ | Mild intermittent or mild/moderate persistent asthma (allergic) | 2 weeks (n = 21) | Placebo Etanercept | Randomized, double-blind, placebo-controlled study was performed. Participants were randomized to receive four doses of either TNF-α or placebo 25 mg subcutaneously, twice per week for 2 weeks | Allergy was defined by skin test reactivity to cat dander, Dermatophagoides farinae, short ragweed, or Timothy grass using a Multi-Test kit (Applied Allergy). Allergic asthma was established by reversible airway obstruction: FEV1 70% of predicted, medications limited to inhaled beta-agonists, and both early and late phase responses to inhalational allergen challenge. Patients had mild intermittent or mild/moderate persistent asthma. | NR |
| Piraraktin | Winnal et al 2007 ²³ | Effect of an interleukin-4 variant on late phase asthmatic response to allergen challenge in asthmatic patients: results of two phase 2a studies | https://pubmed.ncbi.nlm.nih.gov/17926821/ | Atopic asthma - study 1 Atopic asthma - study 2 | 4 weeks (n = 56) | Placebo SC Piraraktin SC Placebo nebulization (inhaled) Piraraktin nebulization (inhaled) | Two independent randomized, double-blind, placebo-controlled, parallel group phase 2a clinical trials | Patients with asthma were included if they had a baseline forced expiratory volume in 1 s (FEV1) of 70% or more of predicted, needed regular or as required use of β2-agonists, and showed a late phase response (≥15% drop in FEV1 between 4–24 h) to allergen challenge at screening. They must have been on a stable regimen of medications for asthma for 1 month or more, and could not have had systemic immunosuppressive therapy within 1 month of screening. Additionally, patients were screened for allergy reactivity. In study 1, patients were required to have a PC20 (provocative concentration that causes a 20% fall in FEV1 from the saline alone value) to methacholine of less than 8 mg/mL and in study 2, participants were required to have a PC20 to adenosine monophosphate of more than 3.125 mg/mL. | Individuals were excluded if they had any medical condition that would preclude allergen challenge, had a greater than 10 pack-year smoking history, or had smoked in the 3 months before screening. Patients were also excluded if they had received any corticosteroid medications (systemic or inhaled) in the 3 months before screening. Participants were to continue their non-steroidal concomitant treatments without change during the study. Participants used leukotriene receptor antagonists with our study. |
| IMA-638 | Gauvreau et al 2011 ²⁴ | Effects of Interleukin-13 Blockade on Allergen-Induced Airway Responses in Mild Asthma | https://pubmed.ncbi.nlm.nih.gov/21057005/ | Mild Atopic Stable Asthma | 5 weeks (n = 56 overall, n = 27 for IMA-638 study) | Placebo IMA-638 | Two clinical trials were conducted at four study centers. Each trial was designed as double-blind, randomized, placebo-controlled, arm with parallel groups, and each compared treatment with a humanized IL-13 antibody (either IMA-638 or IMA-206, 2 mg/kg) to treatment with placebo | Patients were nonsmoking, 18 to 60 years old, with body weight between 50 and 115 kg, FEV1 was at least 70% of predicted and the provocative concentration of methacholine causing a 20% fall in FEV1 (methacholine PC20) was not more than 16 mg/mL. Patients had no other lung disease, no self-reported lower respiratory tract infection or worsening of asthma for 4 weeks before screening, and applied exposure to sensitizing allergens apart from house dust mite. | Patients were not currently using inhaled corticosteroids and used no asthma medication with the exception of inhaled inhaled beta2-agonists, which was withheld for 8 hours before spirometry. Rigorous exercise and caffeinated beverages were avoided before laboratory visits. |
| ATI-M1 Prime | Gauvreau et al 2012 ²⁵ | Effect Of An Anti-M1 Prime Monoclonal Antibody, MEMP1972a In A Phase I Proof-Of-Activity Allergen Challenge Study In Patients With Mild Asthma | https://www.atsjournals.org/doi/pdf/10.1164/ajrccm.2012.185.1.MeetingAbstracts.A6793 | Mild asthma | 12 weeks (n = 28) | Placebo IV MEMP1972a IV 5mg/kg QW | Randomized, double-blind, placebo-controlled, multicenter study | Not available (abstract) | Not available (abstract) |

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|--------------------------|-----------------------------------|--|---|----------------------|------------------------------------|---|--|--|---|
| Anti-TSLP Fragment CS117 | Gauvreau et al 2020 ¹⁶ | Efficacy and Safety of an Inhaled Anti-TSLP Antibody Fragment in Adults with Mild Atopic Asthma | https://www.atsjournals.org/doi/abs/10.1164/ajrccm.2020.201.1.MeetingAbstracts.A8207 | Mild Atopic Asthma | 12 weeks (n = 28) | Placebo CS117 | Proof-of-concept, randomized, double-blind, placebo-controlled study of 28 mild, atopic asthma patients. | Not available (abstract) | Not available (abstract) |
| rh-PAF-AH | Huang et al 2006 ¹⁷ | Effect of Recombinant Human Platelet-Activating Factor Acetylcholinesterase on Allergen-Induced Asthmatic Responses | https://pubmed.ncbi.nlm.nih.gov/16934081/ | Mild Atopic Asthma | 5-7 week treatment period (n = 14) | Placebo IV rh-PAF-AH 1mg/kg IV | Randomized, double-blind, placebo-controlled, two-period crossover study | Patients had a history of wheezing or chest tightness, and asthma was previously diagnosed by a physician. Patients were clinically stable in the 2 mo prior to this study, had no other major medical conditions, controlled their symptoms with short-acting β_2 -agonists alone, and were atopic. Inhaled sympathomimetics and caffeinated beverages were withheld for at least 8 h prior to each study visit. | Females of childbearing age not using an acceptable form of contraception, tobacco smokers, and patients with abnormalities in baseline serum hematology or chemistry studies or electrocardiogram (ECG) were excluded. |
| Ro-24-7472 (1L-12) | Bryan et al 2006 ¹⁸ | Effects of recombinant human interleukin-12 on eosinophils, airway hyper-responsiveness, and the late asthmatic response | https://pubmed.ncbi.nlm.nih.gov/11193141/ | Mild allergic asthma | 4 weeks (n = 39) | Placebo SC Human rIL-17 SC (Ro-24-7472), weekly increasing dose of 0.1, 0.25, 0.5 μ g/kg | Double-blind, randomized, parallel group clinical study, in which patients with mild allergic asthma | We studied 39 adults with allergic asthma. The inclusion criteria were a history of mild asthma requiring inhaled beta-2 agonists only, forced expiratory volume in 1 s (FEV1) 70% or more of predicted normal, a positive allergen skin prick test, no use of corticosteroids for the previous month, no tobacco smoking within the past 5 years, provocative concentration of histamine 8 mg/mL, and early and late responses to inhaled allergen. | Exclusion criteria were symptoms of an upper respiratory tract infection in the previous 2 weeks, allergy to grass pollen during the pollen season, and a history of a medical illness other than asthma. |
| Anti-OM40 ligand (mAb) | Gauvreau et al 2014 ¹⁹ | OM40 blockade and allergen-induced airway responses in subjects with mild asthma | https://pubmed.ncbi.nlm.nih.gov/24212471/ | Mild Atopic Asthma | 12 weeks (n = 28) | Placebo IV Anti-OM40 ligand IV | This Phase II, double-blind, placebo-controlled, randomized, parallel group study, conducted in 5 sites in Canada. | A history of episodic wheezes and shortness of breath were recruited for a clinical trial. Patients were screened for the following inclusion and exclusion criteria: non-smoking, 18-45 years old, with body weight between 55 and 125 kg, forced expiratory volume in 1 s (FEV1) \geq 70% of predicted and the provocative concentration of methacholine causing a 20% fall in FEV1 (methacholine PC20) \leq 16 mg/mL. Feasibility was not tested, as lung function was nearly normal; patients had no other lung disease, no self-reported lower respiratory tract infection or worsening of asthma for 6 weeks before screening. Sensitizing allergens were avoided with the exception of house dust mite. Patients allergic to pollens were tested out of season. Patients were steroid naive and did not use any asthma medications with the exception of infrequently inhaled short-acting beta ₂ -agonists, which was withheld for at least 8 h before spirometry. Rigorous exercise and caffeinated beverages were avoided before laboratory visits. | NR - See some in inclusion |

Table S5 Summary of extracted outcomes data

Where + indicates the biologic reduced EAR, LAR or AHR; - indicates the biologic had no effect on EAR, LAR or AHR
 ND; not determined

| Notes | Study Identifiers | | | | | EAR | | LAR | | AHR | | |
|------------------------------------|--|-------------------------------------|--|--|---|----------|---|----------|---------------|----------|----------|---------------|
| | Biologic | Reference | Article title | Citation | Article / PubMed link | Response | p value | Response | p value | Stimuli | Response | p value |
| Allergen challenge | Omalizumab | Boulet et al 1997 ¹⁸ | Inhibitory Effects of an Anti-IgE Antibody E25 on Allergen-induced Early Asthmatic Response | Boulet LP et al. Am J Respir Crit Care Med 1997;155:1835-40. | https://pubmed.ncbi.nlm.nih.gov/9196083/ | + | ≤ 0.002 | ND | | MCh | + | < 0.05 |
| Allergen challenge | Omalizumab | Fahy et al 1997 ¹⁹ | The Effect of an Anti-IgE Monoclonal Antibody on the Early- and Late-Phase Responses to Allergen Inhalation in Asthmatic Subjects | Fahy JV et al. Am J Respir Crit Care Med 1997;155:1828-34. | https://pubmed.ncbi.nlm.nih.gov/9196082/ | + | < 0.02 | + | < 0.02 | MCh | - | ns (NR) |
| Aerosolized E25 allergen challenge | Omalizumab | Fahy et al 1999 ²⁰ | Effect of Aerosolized Anti-IgE (E25) on Airway Responses to Inhaled Allergen in Asthmatic Subjects | Fahy JV et al. Am J Respir Crit Care Med 1999;160:1023-1027. | https://pubmed.ncbi.nlm.nih.gov/10471635/ | - | ns (NR) | - | ns (NR) | MCh | - | ns (NR) |
| | Omalizumab | Noga et al 2003 ²¹ | Immunological and Clinical Changes in Allergic Asthmatics following Treatment with Omalizumab | Noga O et al. Int Arch Allergy Immunol 2003;131:46-52. | https://pubmed.ncbi.nlm.nih.gov/12759489/ | ND | | ND | | ACh | + | < 0.05 |
| | Omalizumab | Djukanovic et al 2004 ²² | Effects of Treatment with Anti-immunoglobulin E Antibody Omalizumab on Airway Inflammation in Allergic Asthma | Djukanovic R et al. Am J Respir Crit Care Med 2004;170:583-93. | https://pubmed.ncbi.nlm.nih.gov/15172898/ | ND | | ND | | MCh | - | 0.14 |
| | Omalizumab | Prieto et al 2006 ²³ | Effect of Omalizumab on Adenosine 5'-Monophosphate Responsiveness in Subjects with Allergic Asthma | Prieto L et al. Int Arch Allergy Immunol 2006;139:122-31. | https://pubmed.ncbi.nlm.nih.gov/16374021/ | ND | | ND | | AMP/MCh | - | 0.24/0.11 |
| | Omalizumab | Patel et al 2009 ²⁴ | Effects of Omalizumab (Xolair) on Airway Hyperresponsiveness | Patel BM et al. J Allergy Clin Immunol 2009;123:5263 (Abstract) | https://www.jacionline.org/article/S0091-6749(08)03442-8/fulltext | ND | | ND | | MCh | - | ns (NR) |
| Allergen challenge | Omalizumab | van Rensen et al 2009 ²⁵ | Eosinophils in bronchial mucosa of asthmatics after allergen challenge: effect of anti-IgE treatment | van Rensen EJ et al. Allergy 2009;64:72-80. | https://pubmed.ncbi.nlm.nih.gov/19076931/ | + | 0.002 | + | 0.000 | MCh | - | > 0.18 |
| | Omalizumab | Zielen et al 2013 ²⁶ | Omalizumab Protects against Allergen-induced Bronchoconstriction in Allergic (Immunoglobulin E-Mediated) Asthma | Zielen S et al. Int Arch Allergy Immunol 2013;160:102-10. | https://pubmed.ncbi.nlm.nih.gov/22948447/ | + | p = 0.087 and p < 0.001 for group 1 and 2, respectively | ND | | ND | ND | |
| | Omalizumab | Hendeles et al 2015 ²⁷ | Omalizumab Therapy for Asthma Patients with Poor Adherence to Inhaled Corticosteroids | Hendeles L et al. Ann Allergy Asthma Immunol 2015;114:58-62. | https://pubmed.ncbi.nlm.nih.gov/25528738/ | ND | | ND | | AMP | + | 0.022 |
| Allergen challenge | Mepolizumab | Leckie et al 2000 ²⁸ | Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response | Leckie MJ et al. Lancet 2000;356:2144-48. | https://pubmed.ncbi.nlm.nih.gov/11191252/ | - | 0.1610/0.2654 | - | 0.5050/1.0000 | His | - | 0.9248/1.0000 |
| | Mepolizumab | Flood-Page et al 2003 ²⁹ | Eosinophil's Role Remains Uncertain as Anti-Interleukin-5 only Partially Depletes Numbers in Asthmatic Airway | Flood-Page PT et al. Am J Respir Crit Care Med 2003;167:199-204. | https://pubmed.ncbi.nlm.nih.gov/12406833/ | ND | | ND | | His | - | 0.49 |
| | Mepolizumab | Haldar et al 2009 ³⁰ | Mepolizumab and Exacerbations of Refractory Eosinophilic Asthma | Haldar P et al. N Engl J Med 2009;360:973-84. | https://pubmed.ncbi.nlm.nih.gov/19264686/ | ND | | ND | | MCh | - | 0.70 |
| Abstract, allergen challenge | Benralizumab | Gauvreau et al 2021 ³¹ | The Effect of Benralizumab On Allergen-Induced Responses in Subjects With Mild Allergic Asthma | Gauvreau GM et al. J Allergy Clin Immunol Pract 2021;147:AB157. | https://doi.org/10.1016/j.jaci.2020.12.563 | ND | | - | NR | ND | ND | |
| Allergen challenge | Tezepelumab | Gauvreau et al 2014 ³² | Effects of an Anti-TSLP Antibody on Allergen-Induced Asthmatic Responses | Gauvreau GM et al. N Engl J Med 2014;370:2102-10. | https://www.nejm.org/doi/full/10.1056/nejmoa1402895 | + | < 0.05 | + | < 0.05 | MCh | + | 0.04 |
| | Tezepelumab | Diver et al 2021 ³³ | Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled, phase 2 trial | Diver S et al. Lancet Respir Med 2021;9:1299-1312. | https://pubmed.ncbi.nlm.nih.gov/34256031/ | ND | | ND | | Man | + | 0.030 |
| | Tezepelumab | Sverrild et al 2021 ³⁴ | The effect of tezepelumab on airway hyperresponsiveness to mannitol in asthma (UPSTREAM) | Sverrild A et al. Eur Respir J 2021;59:2101296 | https://pubmed.ncbi.nlm.nih.gov/34049943/ | ND | | ND | | Man | + | 0.04 |
| Allergen challenge | Lebrikizumab | Scheerens et al 2014 ³⁵ | The effects of lebrikizumab in patients with mild asthma following whole lung allergen challenge | Scheerens H et al. Clin Exp Allergy 2014;44:38-46. | https://pubmed.ncbi.nlm.nih.gov/24131304/ | - | ns (NR) | - | ns (NR) | MCh | - | ns (NR) |
| | Tralokinumab | Russell et al 2018 ³⁶ | Effect of tralokinumab, an interleukin-13 neutralising monoclonal antibody, on eosinophilic airway inflammation in uncontrolled moderate-to-severe asthma (MESOS): a multicentre, double-blind, randomised, placebo-controlled | Russell RJ et al. Lancet Respir Med 2018;6:499-510. | https://pubmed.ncbi.nlm.nih.gov/29793857/ | ND | | ND | | MCh | - | 0.74 |
| Allergen challenge | Tocilizumab | Revez et al 2019 ³⁷ | Effects of interleukin-6 receptor blockade on allergen induced airway responses in mild asthmatics | Revez JA et al. Clin Trans Immunol 2019;8:e1044. | https://pubmed.ncbi.nlm.nih.gov/31223480/ | - | 0.741 | - | 0.697 | MCh | - | 0.676 |
| | Efalizumab | Gauvreau et al 2003 ³⁸ | The effects of an anti-CD11a mAb, efalizumab, on allergen-induced airway responses and airway inflammation in subjects with atopic asthma | Gauvreau GM et al. J Allergy Clin Immunol 2003;112:331-8. | https://pubmed.ncbi.nlm.nih.gov/12897739/ | - | > 0.05 | - | 0.098 | MCh | - | > 0.05 |
| Allergen challenge | Etanercept (anti-TNF-α fusion protein) | Berry et al 2006 ³⁹ | Evidence of a Role of Tumor Necrosis Factor α in Refractory Asthma | Berry MA et al. N Engl J Med 2006;354:697-708. | https://pubmed.ncbi.nlm.nih.gov/16481637/ | ND | | ND | | MCh | + | 0.05 |
| | Etanercept (anti-TNF-α fusion protein) | Rouhani et al 2005 ⁴⁰ | Effect of tumor necrosis factor antagonism on allergen-mediated asthmatic airway inflammation | Rouhani FN et al. Respir Med 2005;99:1175-82 | https://pubmed.ncbi.nlm.nih.gov/16085220/ | ND | | ND | | MCh | - | 0.4 |
| Subcutaneous / inhaled | Pitrakinra (anti-IL-4RA: IL-4 variant) | Wenzel et al 2007 ⁴¹ | Effect of an interleukin-4 variant on late phase asthmatic response to allergen challenge in asthmatic patients: results of two phase 2a studies | Wenzel S et al. Lancet 2007;370:1422-31. | https://pubmed.ncbi.nlm.nih.gov/17950857/ | -/+ | 0.56/0.94 | -/+ | 0.068/0.0001 | MCh, AMP | -/+ | 0.234/0.128 |
| Allergen challenge | IMA-638 (anti-IL-13 mAb) | Gauvreau et al 2011 ⁴² | Effects of Interleukin-13 Blockade on Allergen-induced Airway Responses in Mild Atopic Asthma | Gauvreau GM et al. Am J Respir Crit Care Med 2011;183:1007-14. | https://pubmed.ncbi.nlm.nih.gov/21057005/ | - | 0.39 | - | 0.27 | MCh | - | ns (NR) |
| Abstract, allergen challenge | Anti-M1 Prime (MEMPI972a) Mab | Gauvreau et al 2012 ⁴³ | Effect Of An Anti-M1 Prime Monoclonal Antibody, MEMPI972A, In A Phase II Proof-Of-Activity Allergen Challenge Study In Patients With Mild Asthma | Gauvreau G et al. Am J Respir Crit Care Med 2012;185:A6793 | https://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2012.185.1.MeetingAbstracts.A6793 | + | 0.046 | - | 0.21 | MCh | - | ns (NR) |
| Abstract, allergen challenge | Anti-TSLP Fragment CS117 | Gauvreau et al 2020 ⁴⁴ | Efficacy and Safety of an Inhaled Anti-TSLP Antibody Fragment in Adults with Mild Atopic Asthma | Gauvreau G et al. Am J Respir Crit Care Med 2020;201:A4207 (Abstract). | https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2020.201.1.MeetingAbstracts.A4207 | - | 0.097 | + | 0.008 | ND | ND | |
| Allergen challenge | rh-PAF-AH | Henig et al 2000 ⁴⁵ | Effect of Recombinant Human Platelet-activating Factor-Acetylhydrolase on Allergen-induced Asthmatic Responses | Henig NR et al. Am J Respir Crit Care Med 2000;162:523-527. | https://pubmed.ncbi.nlm.nih.gov/10934081/ | - | ns (NR) | - | ns (NR) | ND | ND | |
| Allergen challenge | Ro-24-7472 (ril-12) | Bryan et al 2000 ⁴⁶ | Effects of recombinant human interleukin-12 on eosinophils, airway hyper-responsiveness, and the late asthmatic response | Bryan SA et al. Lancet 2000;356:2149-53. | https://pubmed.ncbi.nlm.nih.gov/11191543/ | ND | | - | 0.67 | His | - | 0.47 |
| Allergen challenge | Anti-OX40 ligand (mAb) | Gauvreau et al 2014 ⁴⁷ | OX40L blockade and allergen-induced airway responses in subjects with mild asthma | Gauvreau GM et al. Clin Exp Allergy 2014;44:29-37. | https://pubmed.ncbi.nlm.nih.gov/24224471/ | - | > 0.05 | - | > 0.05 | MCh | - | > 0.05 |

| Reference | Study | Biologic | Outcome | D1 | D2 | D3 | D4 | D5 | Overall | |
|-------------------------------------|----------|--------------|---------------|----|----|----|----|----|---------|---|
| Boulet et al 1997 ¹⁸ | NA | Omalizumab | EAR, LAR, AHR | + | + | + | + | ! | ! | + |
| Fahy et al 1997 ¹⁹ | NA | Omalizumab | EAR, LAR, AHR | + | + | + | + | ! | ! | ! |
| Fahy et al 1999 ²⁰ | NA | Omalizumab | EAR, LAR, AHR | + | + | + | + | ! | ! | - |
| Noga et al 2003 ²¹ | NA | Omalizumab | AHR | + | + | + | + | ! | ! | |
| Djukanovic et al 2004 ²² | NA | Omalizumab | AHR | + | + | + | + | ! | ! | D1 Randomization process |
| Prieto et al 2006 ²³ | NA | Omalizumab | AHR | + | + | + | + | ! | ! | D2 Deviations from the intended interventions |
| Patel et al 2009 ²⁴ | NA | Omalizumab | AHR | + | + | + | + | ! | ! | D3 Missing outcome data |
| van Rensen et al 2009 ²⁵ | NA | Omalizumab | EAR, LAR, AHR | + | + | + | + | ! | ! | D4 Measurement of the outcome |
| Zielen et al 2013 ²⁶ | NA | Omalizumab | EAR | + | + | + | + | ! | ! | D5 Selection of the reported result |
| Hendeles et al 2015 ²⁷ | NA | Omalizumab | AHR | + | + | + | + | ! | ! | |
| Leckie et al 2000 ²⁸ | NA | Mepolizumab | EAR, LAR, AHR | + | + | + | + | ! | ! | |
| Flood-Page et al 2003 ²⁹ | NA | Mepolizumab | AHR | + | + | + | + | ! | ! | |
| Haldar et al 2009 ³⁰ | NA | Mepolizumab | AHR | + | + | + | + | ! | ! | |
| Gauvreau et al 2021 ³¹ | NA | Benralizumab | LAR | + | + | + | + | ! | ! | |
| Gauvreau et al 2014 ³² | NA | Tezepelumab | EAR, LAR, AHR | + | + | + | + | + | + | |
| Diver et al 2021 ³³ | CASCADE | Tezepelumab | AHR | + | + | + | + | + | + | |
| Sverrild et al 2021 ³⁴ | UPSTREAM | Tezepelumab | AHR | + | + | + | + | + | + | |
| Scheerens et al 2014 ³⁵ | NA | Leprikizumab | EAR, LAR, AHR | + | + | + | + | + | + | |
| Russell et al 2018 ³⁶ | MESOS | Tralokinumab | AHR | + | + | + | + | + | + | |
| Revez et al 2019 ³⁷ | NA | Tocilizumab | EAR, LAR, AHR | + | + | + | + | + | + | |
| Gauvreau et al 2003 ³⁸ | NA | Efalizumab | EAR, LAR, AHR | + | + | + | + | ! | ! | |
| Berry et al 2006 ³⁹ | NA | Etanercept | AHR | + | + | + | + | + | + | |
| Rouhani et al 2005 ⁴⁰ | NA | Etanercept | AHR | + | + | + | + | ! | ! | |
| Wenzel et al 2007 ⁴¹ | NA | Pitakinra | EAR, LAR, AHR | + | + | + | + | + | + | |
| Gauvreau et al 2011 ⁴² | NA | IMA-638 | EAR, LAR, AHR | + | + | + | + | + | + | |
| Gauvreau et al 2012 ⁴³ | NA | MEMP1972a | EAR, LAR, AHR | + | + | + | + | + | + | |
| Gauvreau et al 2020 ⁴⁴ | NA | CSJ117 | EAR, LAR | + | + | + | + | ! | ! | |
| Henig et al 2000 ⁴⁵ | NA | rhPAF-AH | EAR, LAR | + | + | + | + | ! | ! | |
| Bryan et al 2000 ⁴⁶ | NA | Ro-24-7472 | LAR, AHR | + | + | + | + | ! | ! | |
| Gauvreau et al 2014 ⁴⁷ | NA | Anti-OX40 | EAR, LAR, AHR | + | + | + | + | + | + | |

Figure S1 Risk of bias. Risk of bias was assessed using the revised Cochrane risk-of-bias tool for randomized trials

Abbreviations: AHR, airway hyperresponsiveness; EAR, early allergic response; ID, identifier; LAR, late allergic response; NA, not applicable; rhPAF-AH, recombinant human platelet-activating factor acetylhydrolase.