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Anti-interleukin-13 and anti-interleukin-4 agents versus placebo, anti-interleukin-5 or anti-immunoglobulin-E agents, for children and adults with asthma (Protocol)

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[Intervention Protocol]

Anti-interleukin-13 and anti-interleukin-4 agents versus placebo, anti-interleukin-5 or anti-immunoglobulin-E agents, for children and adults with asthma

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the efficacy and safety of anti-interleukin-13 or anti-interleukin-4 agents, compared with placebo, anti-Immunoglobulin E agents, or anti-interleukin-5 agents, for the treatment of children, adolescents, or adults with asthma.

BACKGROUND

Description of the condition

Asthma is a prevalent, non-communicable, heterogeneous disease, typically characterised by chronic airway inflammation (GINA 2017). Common symptoms include wheezing, chest tightness, a cough, and shortness of breath, and are frequently worse early in the morning or late at night (GINA 2017). Airflow limitation and symptoms vary over time and in intensity, and are known to be triggered by viral respiratory infections, changing weather, irritant and allergen exposure, and exercise (GINA 2017). Symptoms and airflow limitation can be absent for periods of weeks or months.

Asthma may affect up to 334 million individuals worldwide (Global Asthma Network 2014), and has been highlighted as one of the forum of international respiratory societies' 'Big 5' respiratory diseases (ERS 2017). It is noted as 'the most common chronic condition in children, and is more severe in children in non-affluent countries' (ERS 2017). Asthma is known to affect '1 to 18% of the population in different countries' (GINA 2017), and can carry a particularly serious burden in low- or middle-income countries, which find it more difficult to afford the associated costs (Global Asthma Network 2014).

The goal of asthma treatment is to maintain good activity levels and control symptoms (GINA 2017). In addition, the use of maintenance medication can reduce the future risk of exacerba-

tions (GINA 2017). Individuals should also be assessed for any relevant comorbidities (e.g. obstructive sleep apnoea, depression and anxiety, obesity, rhinosinusitis, rhinitis, and gastroesophageal reflux), which may contribute to asthma symptoms and poor control of asthma (GINA 2017).

It is increasingly accepted that asthma is a heterogeneous condition, with distinct clinical phenotypes. One of the better characterised phenotypes is that of eosinophilic asthma, where eosinophils infiltrate the bronchial mucosa and airways, and cause inflammation. Eosinophilic infiltration is a hallmark of both childhood-onset allergic asthma and late-onset non-allergic asthma. In both cases, the cytokines interleukin-4, -5, and -13 play a central role in the pathophysiology (de Groot 2015). Immunoglobulin E (IgE) also plays a role, and treatment with anti-IgE therapies can reduce airway and blood eosinophils, and associated inflammation. However, some patients with uncontrolled eosinophilic asthma do not respond to anti-IgE therapies, and continue to exhibit eosinophilic inflammation. Therefore, therapies targeting interleukin-4, -5, and -13, have been developed; the evidence around anti-interleukin-5 therapies has recently been synthesised elsewhere (de Groot 2015; Farne 2017).

Description of the intervention

The majority of anti-interleukin-13 and anti-interleukin-4 agents are humanised monoclonal antibodies (i.e. biological therapies) that bind to, and inhibit their respective inflammatory cytokines or their receptors (Bice 2014; Kau 2014). Antibodies targeting the interleukin-13 pathway alone include lebrikizumab, GSK67958, tralokinumab, anrukinzumab, and IMA-026. Antibodies inhibiting the interleukin-4 pathway alone include pascolizumab and altrakincept. Antibodies inhibiting both the interleukin-4 and -13 pathways include pitrakina, AMG-317, and dupilumab (Bice 2014; Kau 2014). All of the agents are administered by subcutaneous injection once every several weeks. However, pitrakina can also be administered by nebulised inhalation.

How the intervention might work

Interleukins are a broad group of proteins, which are important in cell signalling. Interleukin-13 is a pleiotropic cytokine produced by type 2 helper T cells (TH_2), and has been shown to drive airway eosinophilia and increase airway inflammation in asthma. Interleukin-13 contributes to goblet cell metaplasia, subepithelial cell fibrosis, smooth muscle hyperplasia, and stimulation of periostin secretion (Woodruff 2007); periostin is a matricellular protein, which has a role in fibroblast activation and increasing collagen gel elasticity (Sidhu 2010). These pathophysiological processes are hallmarks of asthma. In preclinical models, interleukin-13 has also been shown to increase airway hyper-responsiveness (Chiba 2009). Interleukin-4 is a closely related cytokine, which shares many of the biological and immunoregulatory functions of interleukin-13 (Chomorat 1998). In particular, interleukin-4 plays an important role in maintaining the TH_2 phenotype, leading to further secretion of interleukin-4 and -13 in a positive feedback effect (Bice 2014). Interleukin-4 also promotes B-cell isotype switching, affects the production of chemokines by the airway epithelium, and increases IgE production (Li-Weber 2003).

Anti-interleukin-13 and -4 agents target these pathways with the aim of reducing inflammation and airway remodelling, which are both features of asthma. Furthermore, these agents may be more effective in specific populations of people with asthma, such as those with eosinophilic asthma, where inhibition of these pathways may reduce infiltration of eosinophils into the airways. It is believed that blocking interleukin-13 may reduce very late antigen-4 expression, and thus, reduce the movement of eosinophils from circulation into airway tissue, and subsequently into the lumen (Pelaquini 2011). Glucorticosteroids have diverse effects on the airways, including inhibition of interleukin-13 production; however, some patients with poorly controlled asthma continue to have elevated levels of interleukin-13, despite the use of high dose inhaled or systemic glucocorticosteroids (Saha 2008). Therefore, direct inhibition of interleukin-13 is a potential therapeutic target in this group of patients, and agents, such as lebrikizumab, have been shown to be effective in reducing interleukin-13 levels following subcutaneous administration (Hanania 2016). Inhibition of the interleukin-4 pathway by dupilumab has also been shown to reduce levels of TH_2-associated inflammatory markers in patients with persistent, moderate to severe asthma, following the withdrawal of treatment with long-acting beta-adrenoceptor agonists (LABA) and glucocorticoid therapy (Wenzel 2013).

Why it is important to do this review

Whilst severe or difficult to treat asthma represents only 5% to 10% of the total asthma population, these patients carry a disproportionate burden of healthcare, socioeconomic, and personal costs (Sullivan 2007). Around 1200 people die of asthma each year in the UK, and approximately 40% of deaths occur in individuals with severe asthma (BLF 2012; RCoP 2014). Therefore, it is imperative to find therapies that will offer improvements in disease control for this group of patients.

It is important to synthesise the available evidence on the safety and efficacy of anti-interleukin-13 and anti-interleukin-4 agents, given that data from phase III clinical trials are becoming available (Hanania 2016). Whilst improvements in laboratory markers, such as forced expiratory volume in 1 second (FEV1; (Corren 2011)), and fraction of exhaled nitric oxide (FeNO; (Noonan 2013)) have been shown, a demonstration of consistent improvement in patient symptoms appear to be more elusive (Corren 2011; de Boever 2014). Furthermore, some markers, such as elevated periostin levels, may identify a subset of patients who are

more likely to have a favourable response. However, trial evidence is again mixed in this respect.

OBJECTIVES

To assess the efficacy and safety of anti-interleukin-13 or anti-interleukin-4 agents, compared with placebo, anti-Immunoglobulin E agents, or anti-interleukin-5 agents, for the treatment of children, adolescents, or adults with asthma.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs; parallel-group). Cross-over trials will be excluded because the half-life of these agents is in the order of a month, and thus trialists are unlikely to implement a sufficient wash-out period for eliminating a carry-over effect (i.e. several times the half-life). We will include studies reported in full text, those published as an abstract only, and unpublished data. We will exclude non-randomised studies.

Types of participants

We will include adolescents and adults (aged 16 years or older) and children (younger than 16 years), with a diagnosis of asthma. We will exclude participants with other chronic respiratory comorbidities (e.g. COPD, bronchiectasis). If a study includes a mixture of patients with COPD and asthma, we will use or attempt to obtain data for the subgroup of patients with asthma; if this is not possible, the study will be excluded.

If studies in adolescent or adult populations include a proportion of individuals under 16, and data are not reported separately, we will include the study if the mean age in the intervention and comparator groups is 16 years or older.

Types of interventions

We will include studies of adolescents and adults (aged 16 years or older) and studies of children (younger than 16 years) in separate comparisons. In each main comparison we will include studies that compare the following:

1. Anti-interleukin-13 or -4 agents* with placebo.
2. Anti-interleukin-13 or -4 agents* with anti-Immunoglobulin E (IgE) agents.
3. Anti-interleukin-13 or -4 agents* with anti-interleukin-5 agents.

*Some agents may inhibit both interleukin-13 and -4, and we will also include studies of these agents.

We selected anti-interleukin-5 agents as active comparators, as they target the initiation and maintenance of eosinophilic airway inflammation (Ortega 2014). We selected anti-IgE agents as active comparators, as they target IgE-mediated immune response, thought to be involved in severe allergic asthma (Busse 2001).

We will include the following co-interventions, provided they are not part of the randomised treatment: individuals' usual short- or long-acting medications (e.g. inhaled corticosteroids, long-acting beta adrenoceptor agonists (LABA), long-acting muscarinic antagonists (LAMA), leukotriene receptor antagonists).

If a study evaluates more than one dose of an anti-interleukin-13 or -4 agent (in separate arms), we will consider the most clinically relevant dose. If the clinically relevant dose for a given agent is not clear, we will extract data for both doses, and use the most appropriate data set for the meta-analysis, based on the doses used in the majority of other included studies.

Types of outcome measures

Primary outcomes

1. Exacerbations requiring hospitalisation or emergency department visit (see section Unit of analysis issues for more details)
2. Quality of life (measured on a validated asthma scale, e.g. Asthma Quality of Life Questionnaire)
3. Serious adverse events (all causes)

Secondary outcomes

1. Exacerbations requiring oral corticosteroids
2. Lung function (e.g. change from baseline in forced expiratory volume in 1 second (FEV1; (L)); change from baseline in % predicted FEV1 (%); FEV1 bronchodilator reversibility (%); concentration of methacholine needed to produce a 20% fall in FEV1 from baseline (PC20 methacholine; (mg/mL)).
3. Asthma control (measured on a validated scale, e.g. Asthma Control Questionnaire or Asthma Control Test)
4. Time off work or study
5. Adverse events (all causes)
6. Measures of airway inflammation (e.g. blood eosinophil (count - absolute); sputum or bronchoalveolar lavage eosinophil (%); fraction of exhaled nitric oxide (FeNO; (ppb)).
7. Reduction in oral corticosteroid dose.

We will extract data for each outcome at the time point closest to the end of the treatment period. Where multiple outcomes are proposed (i.e. as for lung function and measures of airway inflammation), we will extract data for all available measures.

Reporting one or more of the outcomes listed here in the study is not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We will identify studies from the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group. The Cochrane Airways Trials Register contains studies identified from several sources:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (crso.cochrane.org);
2. weekly searches of MEDLINE Ovid SP 1946 to date;
3. weekly searches of Embase Ovid SP 1974 to date;
4. Monthly searches of PsycINFO Ovid SP 1967 to date;
5. Monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature) 1937 to date;
6. Monthly searches of AMED EBSCO (Allied and Complementary Medicine);
7. handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings are in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.

We will search the following trials registries:

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov)
2. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch)

We will search the Cochrane Airways Trials Register and additional sources from inception to present, with no restriction on language of publication.

Searching other resources

We will check the reference lists of all selected studies for additional references. We will search relevant manufacturers' websites for study information.

We will search for errata or retractions from included studies published in full text on PubMed, and report the date this was done in the review.

Data collection and analysis

Selection of studies

Three review authors (DE, AG, ME) will independently screen the titles and abstracts of the search results and code them as 'retrieve' (eligible, potentially eligible, or unclear) or 'do not retrieve'. We will retrieve the full-text study reports of all potentially eligible studies, and three review authors (DE, AV, ME) will independently screen them for inclusion, recording the reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion, or if required, we will consult a fourth review author (PM). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. One review author (DS) will extract the following study characteristics from included studies:

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, baseline measures of airway inflammation, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: intervention (including dose), comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for studies and notable conflicts of interest of trial authors.

Three review authors (DE, AG, ME) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus, or by involving a fourth review author (RS). One review author (DE) will transfer data into the Review Manager 5 file (RevMan 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (SD) will spot-check study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Three review authors (DE, AG, ME) will independently assess risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion, or by involving another author (PN/PM). We will assess the risk of bias according to the following domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting;
7. other bias.

We will judge each potential source of bias as high, low, or unclear, and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and justify any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as odds ratios (OR), and continuous data as risk ratios (RR), mean difference (MD), or standardised mean difference (SMD), which are presented with 95% confidence intervals (CI). If data from rating scales are combined in a meta-analysis, we will ensure they are entered with a consistent direction of effect (e.g. lower scores always indicate improvement).

We will undertake meta-analyses only when this is meaningful; that is, if the treatments, doses, participants, and the underlying clinical question are similar enough for pooling to make sense.

We will describe skewed data narratively (for example, as medians and interquartile ranges for each group).

Where multiple trial arms are reported in a single study, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will either combine the active arms or halve the control group to avoid double-counting.

If adjusted analyses are available (ANOVA or ANCOVA), we will use these as a preference in our meta-analyses. If both change from baseline and endpoint scores are available for continuous data, we will use change from baseline, unless there is a low correlation between measurements in individuals. If a study reports outcomes at multiple time points, we will use the latest available time point (i.e. corresponding to end of study) for studies with a duration of one year or less.

We will use intention-to-treat (ITT) or 'full analysis set' analyses when they are reported (i.e. when data have been imputed for participants who were randomly assigned but did not complete the study), instead of completer or per protocol analyses.

Unit of analysis issues

With the exception of outcomes relating to exacerbations, for dichotomous outcomes, we will use participants, rather than events, as the unit of analysis (i.e. number of children admitted to hospital, rather than number of admissions per child). However, if data were to permit the calculation of rate ratios, we will analyse them on this basis. We would expect the majority of patients enrolled in studies of anti-interleukin-13 and anti-interleukin-4 agents to have relatively severe or uncontrolled asthma, and to experience at least one exacerbation during the treatment period. Therefore, we will synthesise data relating to exacerbations based on the number of exacerbations per patient during the treatment period, using rate ratios. We will only meta-analyse data from cluster-RCTs if the available data have been adjusted (or can be adjusted), to account for the clustering.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data when possible (e.g. when a study is identified as an abstract only). When this is not possible, and the missing data are thought to introduce serious bias, we will take this into consideration in the GRADE rating for affected outcomes.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the studies in each analysis. If we identify substantial heterogeneity, we will report it and explore the possible causes by our prespecified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 studies, we will create and examine a funnel plot to explore possible small study and publication biases.

Data synthesis

We will use a random-effects model to allow for differences in the treatment effect from study to study, as multiple types of treatment will be grouped together. We will perform a sensitivity analysis with a fixed-effect model. Rate ratios will be combined using the generic inverse variance method.

'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes: exacerbations requiring hospitalisation or emergency department visit, quality of life, serious adverse events (all causes), exacerbations requiring oral corticosteroids, asthma control, time off work or study, adverse events (all causes). We will use the five considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data for the prespecified outcomes. We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software (GRADEpro GDT). We will justify all decisions to downgrade the quality of the evidence using footnotes, and we will make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses for the primary outcomes (for each of the main comparisons in children, and adolescents and adults, respectively):

1. Individual anti-interleukin-13 or anti-interleukin-4 agent (e.g. including but not limited to lebrikizumab, tralokinumab, IMA-026, GSK679586, anrukinzumab, pascolizumab, pitrakina, altrakincept, AMG-317, dupilumab).
2. Agent class (anti-interleukin-13 only versus anti-interleukin-4 only versus drugs that inhibit both interleukin-13 and -4 pathways).
3. Duration of therapy (up to 6 months versus longer than 6 months).
4. Severity of asthma as per Global Initiative for Asthma (GINA) or British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) definitions (mild or moderate versus severe).
5. Category of TH_2 inflammation (high versus low: e.g. as determined by serum IgE concentration (high: $\geq$ 300 kU/L%), exhaled nitric oxide (eNO; (high: $\geq$ 50 ppb)), airway eosinophil count (high: sputum eosinophilia $\geq$ 3%), serum periostin (high: $\geq$ 50 ng/ml), or direct assay of serum or sputum IL-13 (high: $\geq$10 pg/mL)). Rationale: TH_2 cells play a central role in asthma; interleukin-4 controls the development of TH_2 cells, and interleukin-13 functions during the effector phase of immunity, mediating the physiological response to TH_2 -induced inflammation. Patients with greater levels of TH_2 inflammation may respond better to anti-interleukin-13 or -4 therapies than patients with lower levels of TH_2 inflammation.
6. Dose of corticosteroids (including prednisone), at randomisation. Rationale: there is some overlap in the mechanism of action between corticosteroids and anti-interleukin agents; prior or concomitant corticosteroid use may potentially confound the results, with greater effects of the anti-interleukin agents observed when corticosteroid doses are low. Equally, some patients may not respond to even high doses of corticosteroids, but may respond to anti-interleukin-13 or -4 therapies.

We will use the formal test for subgroup interactions in Review Manager 5 (RevMan 2014).

Sensitivity analysis

We plan to carry out the following sensitivity analyses, removing the following from the primary outcome analyses:

1. Unpublished data.
2. Studies at high risk of bias for blinding of participants and personnel.
3. Studies at high risk for random sequence generation or allocation concealment.

We will compare the results from a fixed-effect model with the random-effects model.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Trials Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (the Cochrane Library)	Monthly
MEDLINE Ovid	Weekly
Embase Ovid	Weekly
PsycINFO Ovid	Monthly
CINAHL EBSCO	Monthly
AMED EBSCO	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.

8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11
The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search strategy to identify relevant studies from the Cochrane Airways Trials Register

1. AST:MISC1
2. MeSH DESCRIPTOR Asthma Explode All
3. asthma*:ti,ab
4. #1 or #2 or #3
5. Lebrikizumab:TI,AB,KW
6. MILR1444A
7. GSK679586
8. Tralokinumab:TI,AB,KW
9. CAT-354
10. Anrukinzumab:TI,AB,KW
11. IMA-638
12. IMA-026
13. Pascolizumab:ti,ab,kw
14. SB 240683
15. Altrakincept:ti,ab,kw
16. AMG-317
17. Dupilumab:ti,ab,kw
18. REGN668
19. pitrakinra:ti,ab,kw
20. aerovant:ti,ab,kw
21. AER 001
22. IL-13:ti,ab,kw
23 .anti-IL-13:ti,ab,kw
24. Interleukin 13:ti,ab,kw
25. anti-Interleukin-13:ti,ab,kw
26. IL-4:ti,ab,kw
27. anti-IL-4:ti,ab,kw
28. Interleukin 4:ti,ab,kw
29. anti-interleukin-4:ti,ab,kw
30. #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR # 20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
31. #30 AND #4

CONTRIBUTIONS OF AUTHORS

David JW Evans: Developed the protocol.

Michaela Edwards: Developed the protocol.

Andrew Gallagher: Developed the protocol.

Parameswaran Nair: Developed the protocol.

Aashish Vyas: Developed the protocol.

Rashmi Sharma: Developed the protocol.

Paul A Marsden: Developed the protocol.

DECLARATIONS OF INTEREST

David JW Evans: Provides freelance medical writing services to medical communications agencies.

Michaela Edwards: None.

Andrew Gallagher: None.

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