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Pairwise indirect treatment comparison of dupilumab versus other biologics in patients with uncontrolled persistent asthma

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ABSTRACT

Background: Currently, five biologic treatment options are available for use in patients with uncontrolled persistent asthma: three interleukin (IL)-5 antagonists, which either bind to the anti-IL-5 ligand (mepolizumab, reslizumab) or to the IL-5 receptor (benralizumab); one anti-immunoglobulin E (anti-IgE) therapy (omalizumab); and one anti-IL-4/IL-13 therapy (dupilumab). To date, no comparative data from head-to-head clinical trials are available for these biologics.

Objective: An indirect treatment comparison (ITC) of dupilumab versus each of the anti-IL-5 and anti-IgE therapies using the endpoints of annualized severe asthma exacerbation rates and change in pre-bronchodilator forced expiratory volume in 1 s (FEV_1).

Methods: Embase®, MEDLINE®, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for studies published between January 1, 1980 and March 25, 2019. Eligible articles included randomized controlled trials (RCTs) in patients aged $\geq$ 12 years with persistent/uncontrolled asthma using at least medium-to-high dose inhaled corticosteroid plus long-acting β_2-agonist with add-on biologic therapy. Bucher ITCs were performed to compare subgroups of dupilumab patients with the anti-IL-5s and anti-IgE trial populations.

Results: Fourteen RCTs were included in the analyses. The matched dupilumab subgroups were associated with greater reductions in annualized severe exacerbation rates compared with benralizumab, mepolizumab, reslizumab, and omalizumab (54%, 28%, 38%, and 26% greater reduction, respectively). A greater improvement in FEV_1 was also observed for dupilumab at week 12 and/or week 24/52 than for the other biologics (0.06–0.14 L).

Conclusion: In this ITC, dupilumab was associated with lower severe asthma exacerbation rates and greater improvements in lung function than anti-IL-5s and omalizumab.

1. Introduction

Asthma affects approximately 339 million people worldwide [1]. It is a complex disease characterized by airway inflammation, variable airway obstruction, and hyperresponsiveness [2]. The underlying pathogenesis varies across endotypes, but is associated with type 2 inflammatory responses in the majority of patients [3]. Type 2 responses include recruitment of eosinophils, mast cells, and basophils to the airway, the production of immunoglobulin E (IgE) [4], and the release of several pro-inflammatory cytokines, including interleukin (IL)-4 and IL-13. The latter mediate pathophysiologic changes (such as mucus hypersecretion barrier dysfunction and airway remodeling) that account for the major clinical features of the disease. IL-4 and IL-13 also play a central role in comorbid conditions caused by type 2 inflammation (such as nasal polyposis, atopic dermatitis, and allergic rhinitis), commonly encountered in patients with asthma [5]. The presence of these comorbid conditions is associated with worse asthma control, greater use

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Abbreviations

ATS	American Thoracic Society
CI	confidence interval
CSR	clinical study report
EAACI	European Academy of Allergy and Clinical Immunology
EMA	European Medicines Agency
EOS	eosinophil
FDA	US Food and Drug Administration
FEV_1	forced expiratory volume in 1 s
GINA	Global Initiative for Asthma
ICS	inhaled corticosteroid
IgE	immunoglobulin E
IL	interleukin
ITC	indirect treatment comparison
ITT	intent-to-treat
LABA	long-acting β_2-agonist
NICE	National Institute for Health and Care Excellence
NR	not reported
OCS	oral corticosteroid
PICOS	Population, Intervention, Comparison, Outcome, Study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
SD	standard deviation
SLR	systematic literature review

of healthcare resources, and decreased health-related quality of life [6].

Approximately 5–10% of patients with asthma have severe disease, i.e. disease that remains uncontrolled despite Global Initiative for Asthma (GINA) Steps 4 to 5 medications [7]. All currently approved biologic add-on treatments for uncontrolled moderate-to-severe asthma target components of the type 2 inflammatory pathway [8].

Therapies that antagonize IL-5 either bind directly to the anti-IL-5 ligand (anti-IL-5s; mepolizumab, reslizumab) or to the IL-5 receptor (IL-5Rα; benralizumab) [9–11], whereas anti-immunoglobulin E (anti-IgE; omalizumab) works by binding to IgE, and down-regulates FcεRI on mast cells and basophils, making them less responsive to allergen stimulation [12].

Dupilumab is a fully human monoclonal VelocImmune®-derived antibody [13,14], which blocks the shared receptor component for IL-4 and IL-13, key drivers of type 2 inflammation in multiple diseases [15]. Thus, dupilumab is the first-in-class anti-IL-4/IL-13 biologic that targets type-2 inflammation more broadly [15].

Approved indications for use of biologics in asthma are largely based on the phenotypic features of the patients recruited in the pivotal clinical trials with each biologic treatment. These features were to some extent determined by the putative mechanism of action of each biologic treatment. Thus, anti-IL-5 and IL-5Rα therapies are approved for treatment of severe asthma with an eosinophilic phenotype [16–18], and omalizumab for moderate-to-severe allergic asthma [19]. The indications for dupilumab are somewhat broader but differ in different jurisdictions. In the USA, dupilumab is approved as an add-on maintenance treatment for patients aged ≥12 years with moderate-to-severe asthma with an eosinophilic phenotype or who have oral corticosteroid-dependent asthma [20]. In Japan, the Pharmaceuticals and Medical Devices Agency has approved dupilumab for use in patients with severe or refractory asthma whose symptoms are inadequately controlled with existing therapy [21]. In the EU, dupilumab is approved for severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised fractional exhaled nitric oxide, which is inadequately controlled with high-dose inhaled corticosteroid (ICS) plus another medicinal product for maintenance treatment [22]. The 2019 GINA pocket guide recommends dupilumab as add-on treatment for patients (≥12 years of age) with severe eosinophilic or type 2 asthma that is uncontrolled on high-dose ICS plus long acting β_2-agonist (LABA) or requires maintenance oral corticosteroids (OCS) [23]. Dupilumab is also approved for the treatment of patients with inadequately controlled, moderate-to-severe atopic dermatitis, aged ≥12 years in the USA [20], and for adults in the EU [22] and other countries [24–26]. In the USA, dupilumab is additionally approved as an add-on maintenance treatment for adults with inadequately controlled chronic rhinosinusitis with nasal polyps [20].

Although each biologic treatment has been shown to be efficacious versus standard of care, including ICS plus additional controllers, the absence of head-to-head comparative trials, and the diversity of approved indications complicates the selection of treatment for individual patients. The mode of action of each treatment alone is not a sufficient basis on which to make this choice. An alternative approach is to consider the results of indirect treatment comparisons (ITCs) that examine the comparative efficacy of each treatment for selected key endpoints in cohorts of patients with the same well-defined selected clinical and inflammatory phenotypes. Such ITCs can provide useful comparative evidence [27], which is required by some policymakers [28].

The aim of the ITCs performed in this study was to compare annualized severe asthma exacerbation rates and pre-bronchodilator forced expiratory volume in 1 s (FEV_1) or percent predicted FEV_1, as applicable, for dupilumab versus anti-IL-5s (benralizumab, mepolizumab, reslizumab) and anti-IgE (omalizumab) biologics among patients with uncontrolled, persistent asthma and similar inflammatory phenotypes.

2. Methods

2.1. Evidence base

A systematic literature review (SLR) was conducted following recommended methods described in the *Cochrane Handbook for Systematic Reviews of Intervention* [29], the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [30], and the National Institute for Health and Care Excellence (NICE) guidelines manual [31].

Searches were conducted in Embase® (via OvidSP), MEDLINE® (via OvidSP), and Cochrane Central Register of Controlled Trials (CENTRAL; via Wiley) for articles in English published from January 1, 1980 to March 25, 2019. Searches were also conducted for recent (2015–2019, inclusive) conference proceedings published by the American Thoracic Society (ATS) and the European Academy of Allergy and Clinical Immunology (EAACI). Additional searches of trial registries, journals, reference lists, and industry submissions were conducted.

The PICOS (Population, Intervention, Comparison, Outcome, Study design) criteria were used to establish the evidence base for the analyses; randomized controlled trials (RCTs), conducted in patients (age ≥ 12 years) with persistent/uncontrolled asthma using at least medium-to-high dose ICS plus LABA with add-on biologic treatment that reported annualized severe exacerbation rates and/or lung function were included.

Risk of bias was assessed for all publications identified in the SLR.

2.2. Feasibility assessment of conducting ITC

All available studies identified during the SLR were examined for comparability of study design, patient populations, outcomes of interest, and durations of follow-up. Additionally, key treatment effect modifiers

were assessed to identify the studies and subgroups relevant for inclusion in the ITC. Clinical expert opinion was sought to confirm that the selected effect modifiers were appropriate and comprehensive. Finally, the findings from the feasibility assessment were used to determine which statistical approach (Bayesian network meta-analysis, Bucher ITC, matching adjusted, or simulated treatment comparison) would be the most appropriate and efficient methodology for conducting a valid analysis. In order to facilitate the ITCs, dupilumab subgroups were created to match the patient inclusion criteria used in the comparator biologic trials.

To make these ITCs applicable to clinical practice, all dupilumab subgroups selected for the ITCs were required to be within the scope of dupilumab's United States Food and Drug Administration (US FDA) or European Medicines Agency (EMA) indication in asthma. For this reason, in the comparison of dupilumab versus omalizumab, the eosinophilic subgroups of dupilumab with ≥1 perennial aeroallergen-specific IgE ≥0.35 kU/L and IgE 30–700 IU/mL was considered and compared with omalizumab's eosinophilic subgroup. The skin-prick test, used for the diagnosis of allergic asthma, was not administered in the dupilumab trials. The criteria of ≥1 perennial aeroallergen-specific (*Alternaria tenuis/alternata, Cladosporium herbarum* (*Hormodendrum*), *Aspergillus fumigatus*, cat dander, *Dermatophagoides farinae, Dermatophagoides pteronyssinus*, dog dander, German cockroach, and Oriental cockroach) IgE ≥ 0.35 kU/L and IgE 30–700 IU/mL was used as a proxy to identify the subgroup of dupilumab patients for comparison with omalizumab (Table 1 summarizes the criteria used to identify dupilumab subgroups which were comparable to the comparator biologics of interest).

2.3. ITC methods

Bucher ITCs were performed using the *Metafor* package in R 3.3.0. Using frequentist meta-analysis, a pooled treatment effect was estimated for each biologic by pooling the estimates of treatment effects from all studies of the same biologic. Next, treatment effects were compared between biologic treatments by using estimates of the relative effects derived from the pairwise comparisons through a common comparator (e.g. placebo) [32].

When more than one study was available for comparison, analyses were based on random effect models, while fixed effect models were used in cases where pairwise meta-analysis was not possible (i.e. if only a single study was available per comparison).

Results of the Bucher ITCs were presented as the mean estimate of the relative effect (rate ratio for annualized severe exacerbation, mean difference for change in FEV_1 (at weeks 12 and 24), or change in percent predicted FEV_1 (at weeks 24 and 52), along with 95% confidence intervals (CIs). Statistical heterogeneity between the same comparisons was evaluated using the I^2 statistic, and sensitivity analyses were conducted, when applicable.

3. Results

3.1. SLR and feasibility assessment results

The SLR identified 6646 records (excluding duplicates). After title/abstract and full-text screening, and feasibility assessment, 14 RCTs were deemed eligible for inclusion in the ITC (Fig. 1).

Findings from the feasibility assessment illustrated that the intent-to-treat (ITT) trial population of dupilumab was broader than that of the anti-IL-5 and IL-5Ra therapies and included patients with ≥1 perennial aeroallergen-specific IgE ≥ 0.35 kU/L and total IgE > 30 IU/mL (see Table E1 in the online repository). Due to differences across the biologic therapies with regard to study design and ITT population characteristics, it was determined that using the "pairwise" Bucher ITC would be the most appropriate analytical approach. To adjust for the differences in population characteristics, the pairwise ITCs used subgroups of patients from the dupilumab ITT trial population which were comparable to patients treated with corresponding biologic treatments in terms of key treatment-effect modifiers.

Table E1 in the online repository summarizes the trials included in the ITCs, while Table E2 in the online repository outlines the definitions of severe exacerbations across the trials. Table E3A–D in the online repository presents the baseline characteristics of dupilumab subgroups and patients included in the corresponding comparator biologic trials in terms of key treatment effect modifiers, including age, eosinophil (EOS)/IgE level, prior exacerbations, ICS dose, and FEV_1 reversibility.

A qualitative assessment of the baseline characteristics of dupilumab subgroups and patients treated with the corresponding comparator biologics suggests that the study data used in the ITCs were balanced for the key treatment effect modifiers.

3.2. Results of the efficacy analyses

3.2.1. Comparisons of annualized severe asthma exacerbations

Table E4A-D in the online repository presents the severe exacerbation rates by individual dupilumab subgroups and comparator arms.

Table 1
Identification of dupilumab subgroups for indirect treatment comparisons.

Dupilumab subgroup	ICS + LABA baseline concentration	Baseline blood eosinophil count or serum total IgE level at baseline	Severe exacerbations in previous year, n	Age, years	% of asthma phase 2b study (DRI) or QUEST ITT population, n/N (%)
Compared with benralizumab	Medium/high	Blood eosinophils ≥ 300 cells/μL	≥2	≥12	QUEST: 439/1902 (23.1) DRI: 100/465 (21.5)
Compared with reslizumab	Medium/high	Blood eosinophils ≥ 400 cells/μL	≥1	≥18	QUEST: 556/1902 (29.2) DRI: 128/465 (27.5)
Compared with mepolizumab	High	Blood eosinophils ≥ 150 cells/μL	≥2	≥12	QUEST: 406/1902 (21.3) DRI: 112/465 (24.0)
Compared with omalizumab[a]	Medium/high	Allergic asthma (serum total IgE level 30–700 IU/mL and ≥1 perennial aeroallergen-specific IgE [≥ 0.35 kU/L]) and baseline blood eosinophils ≥ 300 cells/μL	≥1	≥12	QUEST: 300/1902 (15.8) DRI: 84/465 (18.1)

ICS, inhaled corticosteroid; IgE, immunoglobulin E; ITT, intent-to-treat; LABA, long-acting β_2-agonist.

[a] Skin-prick test not conducted in dupilumab trials. Total IgE and aeroallergen-specific IgE were used as a proxy for allergic asthma. Aeroallergen-specific IgE included *Alternaria tenuis/alternata* IgE; *Cladosporium herbarum/Hormodendrum* IgE; *Aspergillus fumigatus* IgE; cat dander IgE; *Dermatophagoides farinae* IgE; *Dermatophagoides pteronyssinus* IgE; dog dander IgE; German cockroach IgE; and Oriental cockroach IgE. Sensitivity analysis also presented for allergic subgroups (IgE 30–700 IU/mL and ≥1 perennial aeroallergen-specific IgE ≥ 0.35 kU/L) without eosinophil restriction.

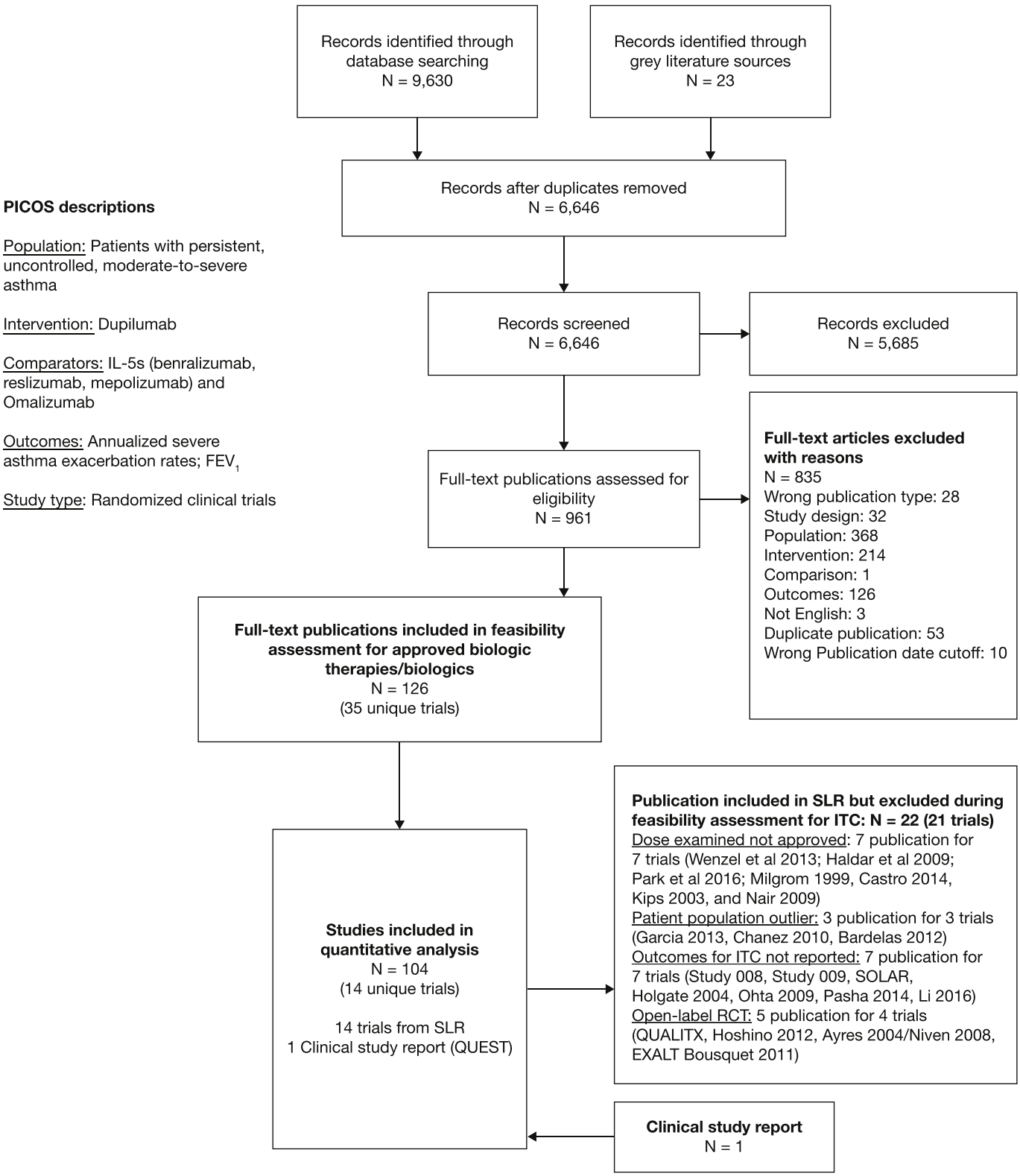

Fig. 1. PICOS criteria and flow diagram of articles for inclusion in the SLR and ITC.
CSR, clinical study report; FEV $_1$, forced expiratory volume in 1 s; IL, interleukin; ITC, indirect treatment comparison; PICOS, Population, Intervention, Comparison, Outcome, Study design; RCT, randomized controlled trial; SLR, systemic literature review.

3.2.1.1. Dupilumab subgroup versus benralizumab. Dupilumab (200 mg and/or 300 mg) was associated with a significantly lower severe exacerbation rate compared with benralizumab (exacerbation rate ratio 0.46; 95% CI 0.32–0.67) (Fig. 2A).

3.2.1.2. Dupilumab subgroup versus mepolizumab. Dupilumab (200 mg and/or 300 mg) was associated with a significantly lower severe exacerbation rate compared with mepolizumab (exacerbation rate ratio 0.72; 95% CI 0.57–0.92) (Fig. 2B).

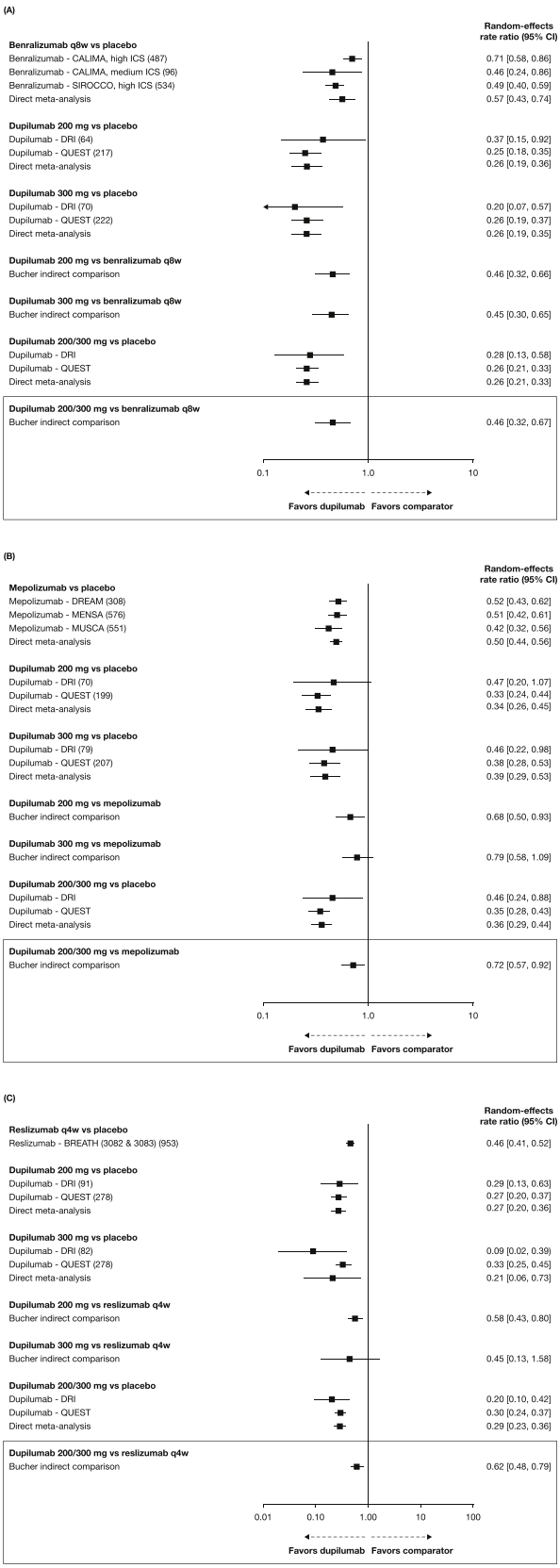

Fig. 2. Annualized severe exacerbation rate: (A) dupilumab (200 mg and/or 300 mg) vs benralizumab q8w; (B) dupilumab (200 mg and/or 300 mg) vs mepolizumab; and (C) dupilumab (200 mg and/or 300 mg) vs reslizumab q4w.

3.2.1.3. Dupilumab subgroup versus reslizumab. Dupilumab (200 mg and/or 300 mg) was associated with a significantly lower severe exacerbation rate compared with reslizumab (exacerbation rate ratio 0.62; 95% CI 0.48–0.79) (Fig. 2C).

Sample sizes of subgroups used in analysis are given in parentheses. Lower bound of confidence interval (CI) for DRI dupilumab 300 mg vs placebo goes beyond the range of the x-axis in part A and is denoted by a left arrow. q4w, every 4 weeks; q8w, every 8 weeks.

3.2.1.4. Dupilumab subgroup versus omalizumab. The severe exacerbation rate in the dupilumab (200 mg and/or 300 mg) eosinophilic subgroup with ≥1 perennial aeroallergen-specific IgE ≥ 0.35 kU/L and total IgE 30–700 IU/mL was not statistically significantly lower than in the omalizumab's eosinophilic subgroup (exacerbation rate ratio 0.74; 95% CI 0.50–1.10) (Fig. 3). Since omalizumab's label population is broader than its eosinophilic subgroup, a sensitivity analysis was performed by comparing omalizumab's ITT population with the dupilumab subgroup without eosinophil criteria, that is, with only ≥1 perennial aeroallergen-specific IgE ≥0.35 kU/L and total IgE 30–700 IU/mL criteria. In this sensitivity analysis, the dupilumab (200 mg and/or 300 mg) subgroup was not statistically significantly lower than omalizumab (exacerbation rate ratio 0.73; 95% CI 0.38–1.42).

Sample sizes of subgroups used in analysis are given in parentheses. Allergic: total immunoglobulin E (IgE) 30–700 IU/mL and ≥1 perennial aeroallergen-specific IgE ≥ 0.35 kU/L. Lower bound of confidence interval (CI) for DRI dupilumab 300 mg vs placebo goes beyond the range of the x-axis and is denoted by a left arrow.

3.2.2. Comparisons of pre-bronchodilator FEV_1 or percent predicted FEV_1

Table 5A-H in the online repository presents the changes in FEV_1 (L) from baseline by individual treatment arms for the subgroup comparisons.

3.2.2.1. Dupilumab subgroup versus benralizumab. Dupilumab (200 mg and/or 300 mg) was associated with a statistically significantly greater improvement in FEV_1 compared with benralizumab at week 12 (mean difference 0.12 L; 95% CI 0.02–0.22) and week 24 (mean difference 0.11 L; 95% CI 0.01–0.21) (Fig. 4A).

3.2.2.2. Dupilumab subgroup versus mepolizumab. The improvement in FEV_1 with dupilumab (200 mg and/or 300 mg) at week 12 and at week 24 were not statistically significantly greater compared with mepolizumab (0.08 L; 95% CI −0.08 to 0.24; and 0.09 L; 95% CI −0.05 to 0.24) respectively (Fig. 4B).

3.2.2.3. Dupilumab subgroup versus reslizumab. At week 12, improvement in FEV_1 with dupilumab (200 mg and/or 300 mg) was not statistically significantly greater compared with reslizumab (0.08 L; 95% CI −0.02 to 0.18). However, at week 24 improvement in FEV_1 was statistically significantly greater with dupilumab versus reslizumab (0.14 L; 95% CI 0.04–0.24) (Fig. 4C).

3.2.2.4. Dupilumab subgroup versus omalizumab. The improvement in percent predicted FEV_1 with dupilumab (200 mg and/or 300 mg) eosinophilic subgroup with ≥1 perennial aeroallergen-specific IgE ≥ 0.35 kU/L and total IgE 30–700 IU/mL compared with omalizumab's eosinophilic subgroups was not statistically significantly greater at week 24 (mean difference 2.91%; 95% CI −0.83 to 6.64), but was statistically significantly greater at week 52 (mean difference 6.83%; 95% CI 2.86–10.81) compared with omalizumab's eosinophilic subgroups (Fig. 5). Similar to the sensitivity analysis performed for the outcome of annualized exacerbation rates, improvement in FEV_1 from BL to week 24 in the omalizumab's ITT population was compared with dupilumab's subgroup without the eosinophil criteria. In this sensitivity analysis, improvement in FEV_1 for dupilumab was not statistically significantly

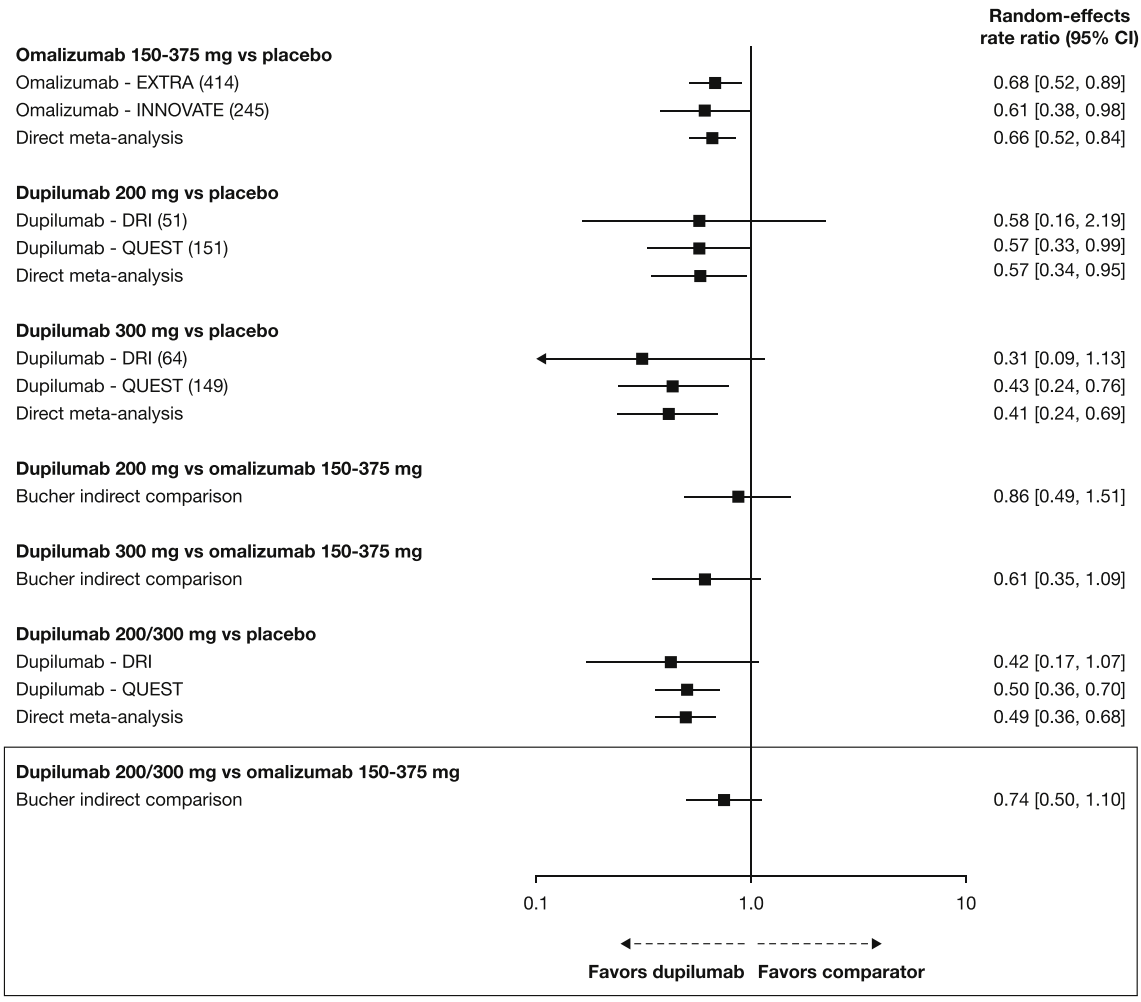

Fig. 3. Annualized severe exacerbation rate in allergic and eosinophilic subgroup: dupilumab (200 mg and/or 300 mg) vs omalizumab's eosinophilic subgroup.

greater at week 24 (mean difference 0.06 L; 95% CI −0.04 to 0.17) compared with omalizumab.

4. Discussion

This is the first pairwise ITC that comprehensively evaluates the RCTs of biologics for uncontrolled persistent asthma with respect to study design, trial populations, and specified outcomes in order to identify which RCTs should be included in the comparative analysis. Previously reported ITCs [33–37] had several methodologic limitations, some of which were acknowledged by their authors. In our analysis, we attempted to address these limitations. In the ITC reported by Busse et al., one landmark trial (i.e. the DREAM trial for mepolizumab) with a 52-week follow-up period was excluded [37]. The inclusion of RCTs with longer follow-up is especially important for the exacerbation-related outcomes. Annualizing exacerbation data from short-term trials is less accurate than using exacerbation data collected over the entire year, which accounts for seasonal variations in exacerbations [38]. Cockle et al. did not include the DREAM and MUSCA trials in their analysis [34]. In the study conducted by Iftikhar et al. [36], only limited data were included for dupilumab since the pivotal phase 3 trial data [39] were not available at the time. In addition, Iftikhar et al. applied network meta-analysis to compare heterogeneous trial populations [36], a limitation that we addressed by using a pairwise ITC approach.

This is the first ITC that includes all relevant RCT data for dupilumab and other biologics. Our ITC included data for mepolizumab 75 mg administered intravenously, evaluated in the DREAM and MENSA studies, since this dose of mepolizumab is considered to be bioequivalent to the 100 mg administered subcutaneously [40]. Results from our ITC are consistent with findings from the Institute of Clinical and Economic Review, an independent non-partisan research organization, which used network meta-analysis to compare all biologics in an eosinophilic subgroup and showed a greater exacerbation rate reduction and greater lung function improvement for dupilumab versus all the comparators [41].

Although some biologic treatments have demonstrated improvements in lung function, our systematic literature review ascertained that not all RCTs of omalizumab [42], reslizumab [43,44], and mepolizumab [45,46] demonstrated a consistent and clinically meaningful effect of these drugs on lung function. In contrast, treatment with dupilumab has consistently shown improvements in lung function across phase 2 and 3 studies. The effect of dupilumab on lung function is observed as early as week 2, is sustained over the entire duration of the trials, and tends to increase over time (up to 52 weeks in the study by Castro et al.) [39,47].

As presented in the results, dupilumab's allergic and eosinophilic subgroup was compared with omalizumab's eosinophilic subgroup to ensure that all data presented in this analysis were within the scope of dupilumab's US FDA and EMA indications. Although this approach limits the breadth of omalizumab data that could be included in the ITC, it should be noted that the 2019 GINA guidelines specify that omalizumab may have greater efficacy in a high eosinophil count subgroup [8]. Therefore, selection of omalizumab's eosinophilic subgroup is not expected to introduce any bias against omalizumab.

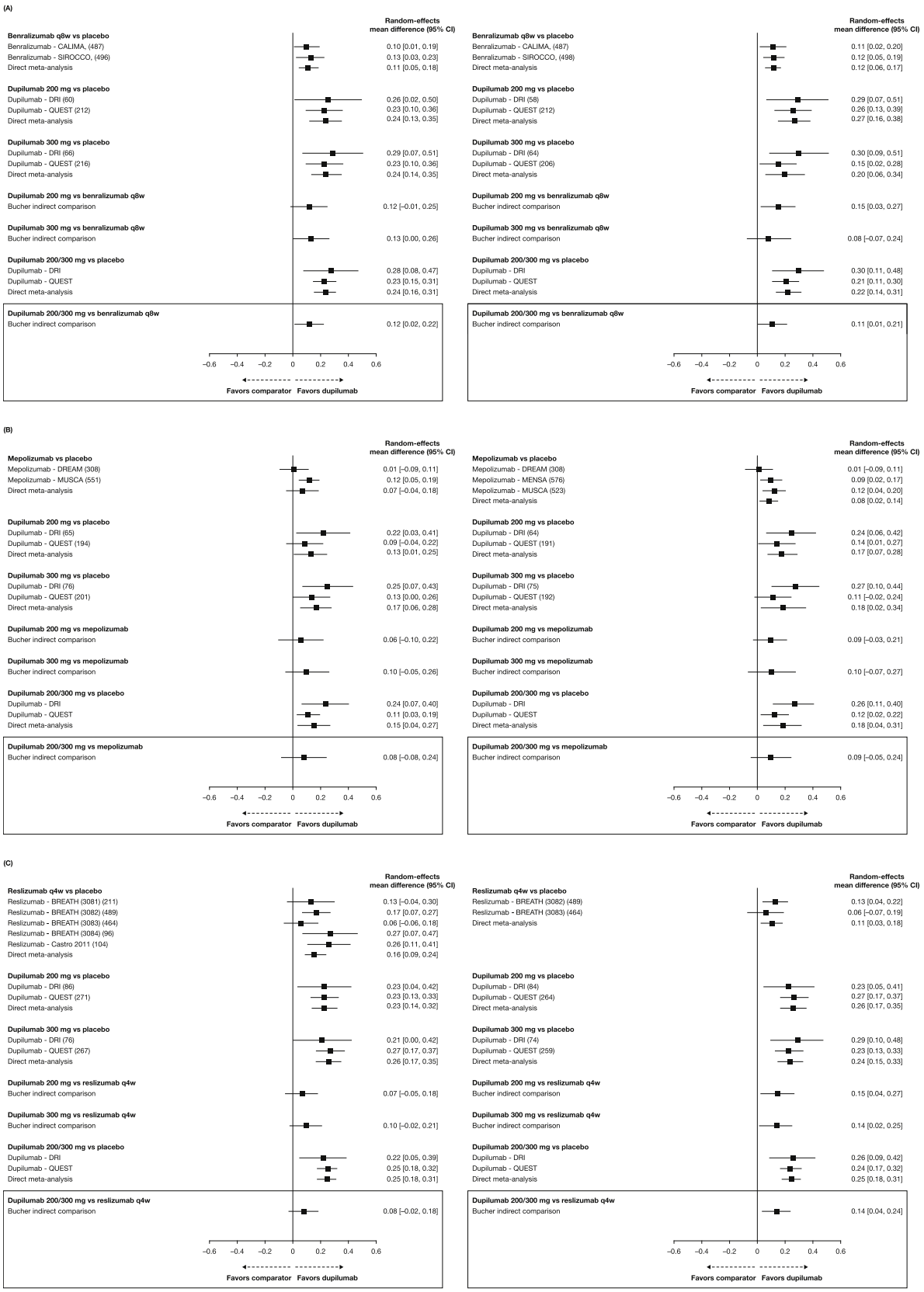

Fig. 4. Change in FEV_1 (L) from baseline: (A) dupilumab (200 mg and/or 300 mg) vs benralizumab at weeks 12 and 24; (B) dupilumab (200 mg and/or 300 mg) vs mepolizumab at weeks 12 and 24; and (C) dupilumab (200 mg and/or 300 mg) vs reslizumab at weeks 12 and 24. Left shows data for week 12 and on the right data for week 24.

CI, confidence interval; FEV_1, forced expiratory volume in 1 s; q4w, every 4 weeks; q8w, every 8 weeks.

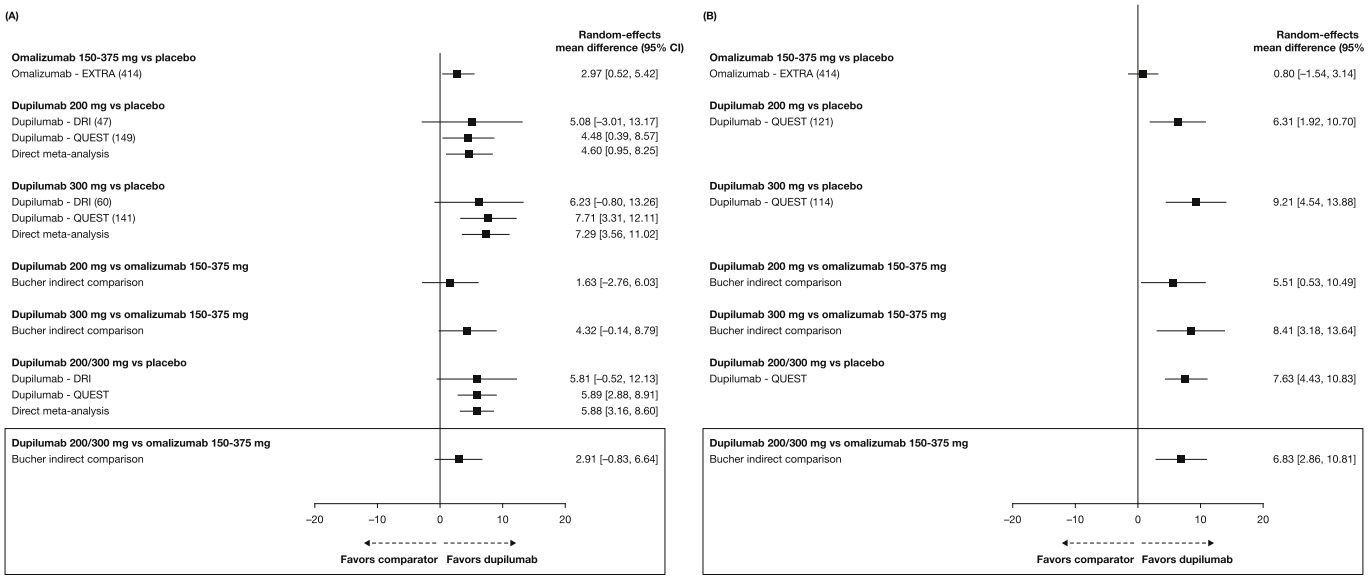

Fig. 5. Change in percent predicted FEV_1 from baseline: the allergic and eosinophilic subgroup dupilumab (200 mg and/or 300 mg) vs omalizumab's eosinophilic subgroup (A) at week 24 and (B) week 52.
Allergic: total immunoglobulin E (IgE) 30–700 IU/mL and ≥1 perennial aeroallergen-specific IgE ≥ 0.35 kU/L. CI, confidence interval; FEV_1, forced expiratory volume in 1 s.

Dupilumab reduces asthma exacerbations, and improves asthma control, lung function, and asthma-related quality of life, even in the allergic subgroup of patients with IgE ≥700 IU/mL [48]. This subgroup is currently not included in omalizumab's label, and no corresponding data exist for omalizumab to support an ITC versus dupilumab in this subgroup.

Finally, the consistency of exacerbation and lung function results observed in the dupilumab subgroups used in the ITC might be related to the mechanism of action of dupilumab. The broader impact of dupilumab on type 2 inflammation by targeting IL-4 and IL-13 seems to improve efficacy across the allergic and eosinophilic phenotypes. Inhibition of IL-4/IL-13 reduces IgE production, as well as reducing IL-5, eotaxin-3, tissue eosinophilia, and production of inflammatory mediators by mast cells, thereby impacting many facets of the type 2 response [49,50].

Although this ITC assesses efficacy outcomes of exacerbations and lung function to inform decision-makers, it should be noted that several additional factors may contribute to treatment related decision-making. These factors include, but are not limited to, mode of administration (e.g. subcutaneous or intravenous), place of treatment administration (at home or in the physician's office), frequency of administration, and presence of type 2 comorbidities. Additionally, although the comparability of clinical studies of biologics was evaluated with respect to their study designs, trial populations, and specified outcomes in order to identify which trials should be included in the ITC, this analysis has a number of limitations. First, although we attempted to match the key inclusion criteria of all comparator trials when identifying dupilumab subgroups, some differences in trial populations still remained. For example, no maintenance OCS treatment use was allowed in the trial populations of QUEST and DRI, whereas trials of all other biologics allowed use of maintenance OCS at baseline. However, exacerbation reduction and FEV_1 improvement observed in the OCS-dependent patient population study of dupilumab (i.e. VENTURE [51]) were consistent with QUEST, and there was no difference in the efficacy of mepolizumab between patients who did and did not use OCS in either DREAM or MENSA. The definition of asthma exacerbation in clinical trials of anti-IL-5/IL-5Rs and dupilumab was generally consistent and included worsening of asthma symptoms that required use of systemic corticosteroids for 3 days or more or an emergency department/urgent care visit, or inpatient admission. However, in the EXTRA and INNOVATE trial of omalizumab, asthma exacerbation was defined as worsening of asthma symptoms requiring treatment with systemic corticosteroids, without any clarification on the duration of OCS use or place of treatment. Secondly in identifying dupilumab's allergic subgroup, the presence of ≥1 perennial aeroallergen-specific IgE to common inhaled allergens was used as a proxy, since skin-prick testing was not performed in any of the dupilumab trials. Furthermore, we were unable to exactly match dupilumab subgroups to the populations from the mepolizumab studies, since different time periods were used for the evaluation of baseline eosinophil counts. It should also be noted that data from anti-IL, anti-IL-5R, and omalizumab studies were mostly available for their ITT populations; hence, a comparison of sub-groups of comparator biologics (rather than the ITT populations) versus dupilumab was not feasible due to lack of comprehensive published information on such sub-groups of the comparator biologics.

Patient-reported outcomes, such as asthma control and health status, are important in assessing the impact of treatments in asthma. We were unable to include these outcomes in our analysis due to the lack of data or lack of consistency in the patient-reported outcome questionnaires used in trials of the different biologic treatments. Similarly, comparisons of safety outcomes were not feasible due to differences in definitions of adverse events and serious adverse events across the trials.

This analysis did not compare the biologics in the OCS-dependent patient population. This was mainly because only a single trial with limited sample size exists for each of the three biologics (dupilumab, benralizumab, and mepolizumab). Additionally, matching the key inclusion criteria to identify comparable dupilumab subgroups would further reduce the sample size and the ability to conduct a robust analysis.

Finally, it should be noted that the data included in this analysis comes from randomized clinical trials and may not be generalizable to real-life clinical practice. Further research is needed to analyze the differences among treatments in a real-world situation.

5. Conclusions

The results of this ITC suggest that among comparable patient populations, dupilumab was associated with statistically significantly lower

annualized severe asthma exacerbation rates compared with benralizumab, mepolizumab, and reslizumab. Additionally, dupilumab was associated with statistically significantly greater improvement in lung function compared with benralizumab and reslizumab (at week 24) and omalizumab (at week 52). However, reduction in annualized severe asthma exacerbation rates and improvements in lung function for dupilumab were not statistically significant versus omalizumab and mepolizumab, respectively.

In the absence of any head-to-head trials, our analysis may be useful to clinicians and decision-makers considering these treatments for patients with uncontrolled persistent asthma.

Data sharing statement

Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient level data will be anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: http://www.clinicalstudydatarequest.com/

Originality and clinical relevance of paper

Currently, five biologic treatment options are available for use in patients with uncontrolled persistent asthma: three interleukin (IL)-5 antagonists, which either bind to the anti-IL-5 ligand (mepolizumab, reslizumab) or to the IL-5 receptor (benralizumab); one anti-immunoglobulin E (anti-IgE) therapy (omalizumab); and one anti-IL-4/IL-13 therapy (dupilumab). To date, no comparative data from head-to-head clinical trials are available for these biologics. There is also no indirect treatment comparison study for all five biologics to guide the selection of treatment for individual patients. The inclusion criteria of different biologics differed widely, which could lead to false conclusions if compared without adjusting for these. This study compares the outcomes of five products in comparable populations. In the absence of the head-head clinical trials, the results of the study may provide useful additional information for practitioners in deciding on treatment.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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CRediT authorship contribution statement

Eric D. Bateman: Conceptualization, Formal analysis, Investigation, Writing - review & editing, Supervision. **Asif H. Khan:** Conceptualization, Formal analysis, Investigation, Writing - review & editing, Supervision, Project administration, Validation. **Yingxin Xu:** Conceptualization, Formal analysis, Investigation, Writing - review & editing, Supervision. **Patricia Guyot:** Conceptualization, Investigation, Writing - review & editing. **Jingdong Chao:** Conceptualization, Investigation, Writing - review & editing. **Siddhesh Kamat:** Conceptualization, Formal analysis, Investigation, Writing - review & editing, Supervision, Project administration, Validation. **Paul Rowe:** Conceptualization, Investigation, Writing - review & editing. **Heather Burnett:** Conceptualization, Investigation, Writing - review & editing. **Jerome Msihid:** Conceptualization, Formal analysis, Investigation, Writing - review & editing. **David Weinreich:** Conceptualization, Investigation, Writing - review & editing. **Ian D. Pavord:** Conceptualization, Formal analysis, Investigation, Writing - review & editing, Supervision.

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Appendix A. Supplementary data

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References

[1] Global Asthma Network, The global asthma report, Available from: http://www.globalasthmareport.org, 2018. Accessed July 2019.
[2] Lung National Heart, Blood Institute (US), Expert panel report 3: guidelines for the diagnosis and management of asthma, in: National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma, 2007. Bethesda, MD.
[3] L. Pembrey, M.L. Barreto, J. Douwes, et al., Understanding asthma phenotypes: the World Asthma Phenotypes (WASP) international collaboration, ERJ Open Res 4 (2018), 00013-2018.
[4] M. Caminati, D.L. Pham, D. Bagnasco, G.W. Canonica, Type 2 immunity in asthma, World Allergy Organ J 11 (2018) 13.
[5] L.P. Boulet, Influence of comorbid conditions on asthma, Eur. Respir. J. 33 (2009) 897–906.
[6] A.S. Gershon, J. Guan, C. Wang, et al., Describing and quantifying asthma comorbidity [corrected]: a population study, PloS One 7 (2012), e34967.
[7] K.F. Chung, S.E. Wenzel, J.L. Brozek, et al., International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma, Eur. Respir. J. 43 (2014) 343–373.
[8] Global Initiative for Asthma, Global strategy for asthma prevention, Updated Available from, https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf, 2019. Accessed July 2019.
[9] L. Fala, Nucala (mepolizumab): first IL-5 antagonist monoclonal antibody FDA approved for maintenance treatment of patients with severe asthma, Am Health Drug Benefits 9 (Spec Feature) (2016) 106–110.
[10] S. Hom, M. Pisano, Reslizumab (Cinqair): an interleukin-5 antagonist for severe asthma of the eosinophilic phenotype, P T 42 (2017) 564–568.
[11] F. Menzella, M. Lusuardi, C. Galeone, et al., The clinical profile of benralizumab in the management of severe eosinophilic asthma, Ther. Adv. Respir. Dis. 10 (2016) 534–548.

[12] Genentech. Xolair® (omalizumab) prescribing information, Available from, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103976s5225lbl.pdf, 2013. Accessed October 2019.

[13] L.E. Macdonald, M. Karow, S. Stevens, et al., Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 5147–5152.

[14] A.J. Murphy, L.E. Macdonald, S. Stevens, et al., Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 5153–5158.

[15] N.A. Gandhi, G. Pirozzi, N.M.H. Graham, Commonality of the IL-4/IL-13 pathway in atopic diseases, Expet Rev. Clin. Immunol. 13 (2017) 425–437.

[16] FDA approval of Cinqair® (reslizumab) to treat severe asthma, Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-cinqair-treat-severe-asthma. Accessed October 2019.

[17] FDA approval of Fasenra® (benralizumab), Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761070Orig1s000TOC.cfm. Accessed October 2019.

[18] FDA approval of Nucala® (mepolizumab), Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761122Orig1s000TOC.cfmhttps://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761122Orig1s000TOC.cfm. Accessed October 2019.

[19] FDA approval of Xolair® (omalizumab), Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/omalgen062003LB.pdf. Accessed April 2019.

[20] FDA supplementary approval of Dupixent® (dupilumab), Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761055s014lbl.pdf. Accessed October 2019.

[21] Pharmaceuticals and medical Devices agency (Japan), Available from: http://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/780069_4490405G1024_1_04. Accessed October 2019.

[22] European Medicines agency approval of Duxipent® (dupilumab), Available from: http://ec.europa.eu/health/documents/community-register/2019/20190506144541/anx_144541_en.pdf. Accessed October 2019.

[23] Global Initiative for Asthma, Pocket guide for asthma management and prevention (for adults and children older than 5 years), Available from: https://ginasthma.org/wp-content/uploads/2019/04/GINA-2019-main-Pocket-Guide-wms.pdf, 2019. Accessed October 2019.

[24] A. Blauvelt, M. de Bruin-Weller, M. Gooderham, et al., Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial, Lancet 389 (2017) 2287–2303.

[25] E.L. Simpson, T. Bieber, E. Guttman-Yassky, et al., SOLO 1 and SOLO 2 Investigators. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis, N. Engl. J. Med. 375 (2016) 2335–2348.

[26] D. Thaçi, E.L. Simpson, L.A. Beck, et al., Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial, Lancet 387 (2016) 40–52.

[27] D.C. Hoaglin, N. Hawkins, J.P. Jansen, et al., Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on indirect treatment comparisons good research practices: part 2, Value Health 14 (2011) 429–437.

[28] I.J. Es-Skali, J. Spoors, Analysis of indirect treatment comparisons in national health technology assessment assessments and requirements for industry submissions, J Comp Eff Res (2018 Mar 28), https://doi.org/10.2217/cer-2017-0092 [Epub ahead of print].

[29] Version 5.1.0 [updated March 2011]J.P.T. Higgins, S. Green (Eds.), Cochrane Handbook for Systematic Reviews of Interventions, The Cochrane Collaboration, 2011. Available from: http://handbook.cochrane.org. Accessed October 2019.

[30] B. Hutton, G. Salanti, D.M. Caldwell, et al., The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations, Ann. Intern. Med. 162 (2015) 777–784.

[31] National Institute for Health and Clinical Excellence, Developing NICE Guidelines: the Manual, National Institute for Health and Clinical Excellence, London, 2018. Available from: https://www.nice.org.uk/process/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869. Accessed October 2019.

[32] H.C. Bucher, G.H. Guyatt, L.E. Griffith, S.D. Walter, The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials, J. Clin. Epidemiol. 50 (1997) 683–691.

[33] Y. Cabon, N. Molinari, G. Marin, et al., Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo-controlled trials, Clin. Exp. Allergy 47 (2017) 129–138.

[34] S.M. Cockle, G. Stynes, N.B. Gunsoy, et al., Comparative effectiveness of mepolizumab and omalizumab in severe asthma: an indirect treatment comparison, Respir. Med. 123 (2017) 140–148.

[35] L.-L. He, L. Zhang, L. Jiang, et al., Efficacy and safety of anti-interleukin-5 therapy in patients with asthma: a pairwise and Bayesian network meta-analysis, Int. Immunopharm. 64 (2018) 223–231.

[36] I.H. Iftikhar, M. Schimmel, W. Bender, et al., Comparative efficacy of anti IL-4, IL-5 and IL-13 drugs for treatment of eosinophilic asthma: a network meta-analysis, Lung 196 (2018) 517–530.

[37] W. Busse, G. Chupp, H. Nagase, et al., Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: indirect treatment comparison, J. Allergy Clin. Immunol. 143 (2019) 190–200.

[38] M. Gerhardsson de Verdier, P. Gustafson, C. McCrae, et al., Seasonal and geographic variations in the incidence of asthma exacerbations in the United States, J. Asthma 54 (2017) 818–824.

[39] M. Castro, J. Corren, I.D. Pavord, et al., Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma, N. Engl. J. Med. 378 (2018) 2486–2496.

[40] Nucala (mepolizumab), An Overview of Nucala and Why it Is Authorised in the EU. European Public Assessment Report (EPAR), EMA, London, 2015. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003860/WC500198039.pdf. Accessed July 2019.

[41] ICER (Institute for Clinical and Economic Review), Biologic therapies for treatment of asthma associated with type 2 Inflammation: effectiveness, value, and value-based price benchmarks. Final evidence report. December 20, Available from: https://icer-review.org/wp-content/uploads/2018/04/ICER_Asthma_Final_Report_122018-1.pdf, 2018. Accessed July 2019.

[42] N.A. Hanania, S. Wenzel, K. Rosén, et al., Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study, Am. J. Respir. Crit. Care Med. 187 (2013) 804–811.

[43] M. Castro, J. Zangrilli, M.E. Wechsler, et al., Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials, Lancet Respir Med 3 (2015) 355–366.

[44] L. Bjermer, C. Lemiere, J. Maspero, et al., Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study, Chest 150 (2016) 789–798.

[45] H.G. Ortega, M.C. Liu, I.D. Pavord, et al., MENSA Investigators. Mepolizumab treatment in patients with severe eosinophilic asthma, N. Engl. J. Med. 371 (2014) 1198–1207.

[46] I.D. Pavord, S. Korn, P. Howarth, et al., Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial, Lancet 380 (2012) 651–659.

[47] S. Wenzel, M. Castro, J. Corren, et al., Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial, Lancet 388 (2016) 31–44.

[48] J. Corren, M. Castro, T. O'Riordan, et al., Dupilumab efficacy in patients with uncontrolled, moderate-to-severe allergic asthma, J Allergy Clin Immunol Pract (2019 Sep 12), https://doi.org/10.1016/j.jaip.2019.08.050 [Epub ahead of print].

[49] C. Hahn, M. Teufel, U. Herz, et al., Inhibition of the IL-4/IL-13 receptor system prevents allergic sensitization without affecting established allergy in a mouse model for allergic asthma, J. Allergy Clin. Immunol. 111 (2003) 1361–1369.

[50] J. Allinne, G. Scott, D. Birchard, et al., Broader impact of IL-4Rα blockade than IL-5 blockade on mediators of type 2 inflammation and lung pathology in a house dust mite-induced asthma mouse model, Am. J. Respir. Crit. Care Med. 199 (2019) A5555.

[51] K.F. Rabe, P. Nair, G. Brusselle, et al., Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma, N. Engl. J. Med. 378 (2018) 2475–2485.