Supplementary data

Materials and methods

Search strategy and study eligibility

This quantitative synthesis has been registered to the international prospective register of systematic reviews (PROSPERO, Protocol ID: CRD42020211870), and performed in agreement with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [1]. The relative flow diagram and network nodes are shown in Figure 1A and B. This study satisfied all the recommended items reported by the PRISMA-P checklist (Table S1) [1].

A comprehensive literature search was performed for Phase III randomized controlled trials (RCTs) written in English and evaluating the efficacy and safety of triple combination therapies for the treatment of asthma. In this regard, the PICO (Patient problem, Intervention, Comparison, and Outcome) framework was applied to develop the literature search strategy, as previously reported [2]. Namely, the "Patient problem" included patients suffering from asthma; the “Intervention” regarded the administration of different triple combination therapies; the “Comparison” was performed across active combination treatments; the assessed “Outcomes” were the risk of moderate to severe asthma exacerbation, lung function, level of asthma control, and risk of serious adverse events (SAEs), specifically with respect to pneumonia and serious cardiovascular adverse events (AEs).

The search was performed in ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, EU Clinical Trials Register, MEDLINE, Scopus, and Web of Science, in order to provide for relevant studies lasting ≥24 weeks, and published up to September 23rd, 2020. The research string was as follows: (((Beclomethasone formoterol glycopyrronium) OR (CHF 5993) OR (CHF5993)) OR (fluticasone furoate vilanterol umeclidinium) OR (mometasone indacaterol glycopyrronium OR (QVM149) OR (QVM 149)) OR ((fluticasone propionate salmeterol tiotropium) OR (ICS LABA tiotropium)) OR triple) AND asthma. Citations of previous published reviews were checked to select further pertinent RCTs, if any.

Literature search results were uploaded to Eppi-Reviewer 4 (EPPI-Centre Software. London, UK), a web-based software program for managing and
Supplementary data

analysing data in literature reviews that facilitates collaboration among reviewers during the study selection process.

Study selection

Phase III RCTs that enrolled asthmatic patients, lasting ≥24 weeks, and that included at least one arm assessing the impact of any triple combination therapy in asthma were included in the network meta-analysis. Three reviewers independently examined the studies, and any difference in opinion concerning the selection of relevant Phase III RCTs from literature searches and databases was resolved by consensus.

Data extraction

Data from the RCTs included in this quantitative synthesis were extracted from published papers, and/or supplementary files, and/or the public database ClinicalTrials.gov and/or publically available pharmaceutical companies’ clinical databases. Data were checked for study characteristics and duration, number of analysed patients, treatments with doses of medications and regimen of administration, asthma severity and main inclusion criteria, age, gender, asthma duration; forced expiratory volume in the 1st second (FEV₁); level of FEV₁ reversibility; blood eosinophil count at baseline; smoking habit, Asthma Control Questionnaire (ACQ), primary outcomes analysed in every study, Jadad Score [3], and the Cochrane risk of bias [4].

The level of inhaled corticosteroid (ICS) doses (medium-dose [MD] and high-dose [HD]) included in the combinations was ranked in agreement with the current Global Initiative for asthma (GINA) recommendations [5] and the National Institute for Health and Care Excellence (NICE) guidelines [6].

Data were extracted in agreement with Data Extraction for Complex Meta-anALysis (DECiMAL) recommendations [7]. The inter- and intra-rater reliability for data abstraction was assessed via the Cohen’s Kappa score, as previously described [8]. Briefly, Cohen’s Kappa ≥0.80 indicated excellent agreement, coefficients between 0.61 and 0.80 represented substantial agreement, coefficients between 0.41 and 0.61 moderate agreement and <0.41 fair to poor agreement.

Endpoints
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The co-primary endpoints of this network meta-analysis were the comparison across the different triple combination therapies and comparators with respect to the risk of moderate to severe exacerbation in asthmatic patients and the change from baseline in trough FEV₁.

The secondary efficacy endpoint was the comparison across the different triple combination therapies and comparators with respect to the change from baseline in ACQ score. The safety endpoint was the risk of SAEs, namely pneumonia and serious cardiovascular AEs.

Quality of studies, risk bias, and evidence profile

The summary of the risk of bias for each included Phase III RCT was analyzed via the Cochrane Risk of Bias 2 (RoB 2) [4] and Jadad score [3]. The Jadad score ranges from 1 to 5 (score of 5 being the best score), and the quality of studies was ranked as follows: score ≤2, low quality; score =3, medium quality; score ≥4 high quality. The weighted assessment of the risk of bias was analyzed via the Cochrane RoB 2 [4].

The risk of bias was performed for the co-primary endpoints and it was checked via the normalized consistency/inconsistency analysis, a procedure that allows assessing whether the outcomes resulting from the consistency and inconsistency models fit adequately with the line of equality, as previously described [9]. The inconsistency of evidence was also investigated by quantifying the inconsistency factor, that indicates whether one of the treatments had a different effect when it was compared with the others.

The quality of the evidence was assessed for the co-primary endpoints in agreement with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, indicating ++++ for high-quality of evidence, +++ for moderate-quality of evidence, ++ for low-quality of evidence, and + for very low-quality of evidence [10].

Three reviewers independently assessed the quality of studies, risk bias, and evidence profile, and any difference in opinion was resolved by consensus.

Data synthesis and analysis

A network meta-analysis was performed to indirectly compare the impact of the different triple combination therapies and active comparators in asthmatic patients.
A full Bayesian evidence network was used in the network meta-analysis (chains: 4; initial values scaling: 2.5; tuning iterations: 20,000; simulation iterations: 50,000; tuning interval: 10). The convergence diagnostics for consistency and inconsistency were assessed via the Brooks-Gelman-Rubin method, as previously described [11]. Due to the characteristics of parameters besides the available data, the just proper non-informative distributions specified the prior densities, in agreement with the Bayesian Approaches to Clinical Trials and Health-Care Evaluation [12, 13]. Since the distributions were sufficiently vague, the reference treatment, study baseline effects, and heterogeneity variance were unlikely to have a noticeable impact on model results. In this condition, GeMTC software automatically generates and runs the required Bayesian hierarchical model and selects the prior distributions and starting values as well, via heuristically determining a value for the outcome scale parameter (i.e. outcome scale S) [14, 15]. The posterior mean deviance of data points in the unrelated mean effects model was plotted against their posterior mean deviance in the consistency model in order to provide information for identifying the loops in the treatment network where evidence was inconsistent [16]. Results of the network meta-analysis are expressed as relative effect (RE) and 95% credible interval (95%CrI). The analysis of the number needed to treat (NNT) was performed on the risk of moderate to severe exacerbations. NNT is the reciprocal of the absolute risk reduction associated with an intervention over a fixed period of time [17-19]. The values of NNT are reported in this study as person-based per year and calculated by analysing the Kaplan-Meyer curves or the Cox proportional hazards model, as previously described [20, 21]. The relative weight of each study resulting from the network meta-analysis was used to calculate the weighted average rate of the investigated treatment arms and to correctly provide NNT values. Sensitivity analysis was performed in agreement with the patients' characteristics at baseline of each study. Subset analyses were performed on both moderate or severe exacerbations, and with respect to the different doses of umeclidinium included in the fixed-dose combination (FDC).
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The probability that each intervention arm was the most effective/safe was calculated by counting the proportion of iterations of the chain in which each intervention arm had the best relative effect, and the surface under the cumulative ranking curve analysis (SUCRA), representing the summary of these probabilities [22]. The SUCRA is 1 when a treatment is considered to be the best, and 0 when a treatment is considered to be the worst [9].

Software and statistical significance

ImageJ was used to extract data from the figures, when necessary [23], GeMTC [24] software was used to perform the network meta-analysis, GraphPad Prism (CA, US) software to graph the data, GRADEpro GDT to assess the quality of evidence [10], and the robvis visualization software to perform the RoB 2 tool [25, 26]. The statistical significance of the effect estimates resulting from the network meta-analysis was assessed for P<0.05.

Results

Study characteristics

Data obtained from 9535 asthmatic patients (MD ICS/LABA/LAMA FDC: 26.02%; HD ICS/LABA/LAMA FDC: 25.99%; HD ICS/LABA FDC: 23.23%; MD ICS/LABA FDC: 16.76%; HD ICS/LABA FDC + TIO: 8.00%) were selected from 5 Phase III RCTs published between 2019 and 2020.

The inter-rater reliability for data abstraction was excellent before and after the learning process (Cohen’s Kappa >0.90). The intra-rater reliability produced a Cohen’s Kappa of 1.00 after the learning process.

All the studies included in the network meta-analysis were Phase III RCTs published as full-text papers, with a period of treatment between 24 weeks and 52 weeks.
### Supplementary data

**Supplementary Tables**

**Table S1. PRISMA-P Checklist**

<table>
<thead>
<tr>
<th>Section/topic</th>
<th>#</th>
<th>Checklist item</th>
<th>Reported on page #</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TITLE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
<td>1 main MS</td>
</tr>
<tr>
<td><strong>ABSTRACT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structured summary</td>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
<td>2 main MS</td>
</tr>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
<td>3 main MS</td>
</tr>
<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
<td>3 main MS</td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol and registration</td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
<td>3-4 main MS; 1 suppl. file</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
<td>3-4 main MS; 1 suppl. file</td>
</tr>
<tr>
<td>Information sources</td>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
<td>1 suppl. file</td>
</tr>
<tr>
<td>Search</td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
<td>1 suppl. File; Table S2; Appendix 1</td>
</tr>
<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
<td>4 main MS; 2 suppl. file</td>
</tr>
<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
<td>4 main MS; 2 suppl. file</td>
</tr>
</tbody>
</table>
### Supplementary data

<table>
<thead>
<tr>
<th>Data items</th>
<th>11</th>
<th>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</th>
<th>4 main MS; 3 suppl. file</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of bias in individual studies</td>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
<td>4 main MS; 3 suppl. file</td>
</tr>
<tr>
<td>Summary measures</td>
<td>13</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
<td>5 main MS; 4 suppl. file</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>14</td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis.</td>
<td>5 main MS; 4-5 suppl. file</td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
<td>5 main MS; 3 suppl. file</td>
</tr>
<tr>
<td>Additional analyses</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
<td>4 suppl. file</td>
</tr>
</tbody>
</table>

### RESULTS

| Study selection                                | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 5 main MS, Figure 1; 5 suppl. file |
| Study characteristics                          | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 5 main MS; Table S3; 5 suppl. file |
| Risk of bias within studies                   | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 8 main MS; Figure S1 |
| Results of individual studies                 | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 6-8 main MS; Figure 2 |
| Synthesis of results                           | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 8 main MS; Table 1; Figure 3; Figure S2 |
| Risk of bias across studies                   | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 8 main MS; Figure 4 |
| Additional analysis                            | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 8 main MS; Table 2, Table 3 |
### DISCUSSION

<table>
<thead>
<tr>
<th>Category</th>
<th>Page</th>
<th>Description</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>24</td>
<td>Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).</td>
<td>9-10 MS</td>
</tr>
<tr>
<td>Limitations</td>
<td>25</td>
<td>Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).</td>
<td>11 MS</td>
</tr>
<tr>
<td>Conclusions</td>
<td>26</td>
<td>Provide a general interpretation of the results in the context of other evidence, and implications for future research.</td>
<td>11 MS</td>
</tr>
</tbody>
</table>

### FUNDING

<table>
<thead>
<tr>
<th>Category</th>
<th>Page</th>
<th>Description</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funding</td>
<td>27</td>
<td>Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.</td>
<td>12 MS</td>
</tr>
</tbody>
</table>

Supplementary data

Table S2. Literature search terms used for OVID MEDLINE. The final search strategy applied to conduct this network meta-analysis is reported at step #30. The summary text of the identified records is shown in Appendix 1.

<table>
<thead>
<tr>
<th>#</th>
<th>Search strategy</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Beclomethasone*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
</tr>
<tr>
<td>2</td>
<td>Formoterol*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
</tr>
<tr>
<td>3</td>
<td>Glycopyrronium*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
</tr>
<tr>
<td>4</td>
<td>CHF 5993.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
</tr>
<tr>
<td>5</td>
<td>CHF5993.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
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<td>6</td>
<td>Fluticasone furoate*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
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<td>7</td>
<td>Vilanterol*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
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<td>8</td>
<td>Umeclidinium*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
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<td>9</td>
<td>Mometasone*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
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<tr>
<td>10</td>
<td>Indacaterol*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
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<td>11</td>
<td>QVM149.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
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<tr>
<td>12</td>
<td>QVM 149.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
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<td>Fluticasone propionate*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
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<td>14</td>
<td>Salmeterol*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
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<td>15</td>
<td>Tiotropium*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
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<td>16</td>
<td>ICS*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
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<td>17</td>
<td>LABA*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
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<td>18</td>
<td>Triple*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
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<td>19</td>
<td>Asthma*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]</td>
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<td>20</td>
<td>1 and 2 and 3</td>
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<tr>
<td>21</td>
<td>4 or 5</td>
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<td>22</td>
<td>6 and 7 and 8</td>
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<tr>
<td>30</td>
<td>19 and 29</td>
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## Supplementary data

### Table S3. Patient demographics, baseline, study characteristics, and Jadad score.

<table>
<thead>
<tr>
<th>Study and year and reference</th>
<th>Trial number identifier</th>
<th>Study characteristics</th>
<th>Study duration (months)</th>
<th>Number of analyzed patients</th>
<th>Triple FDC therapy (doses and regimen of administration)</th>
<th>Comparator (doses and regimen of administration)</th>
<th>Inhaler device (brand)</th>
<th>Patients characteristics</th>
<th>Age (years)</th>
<th>Male (%)</th>
<th>Duration of asthma (years)</th>
<th>Pred. bronchodilator FEV₁ (% predicted)</th>
<th>Reversibility (%)</th>
<th>Rate of exacerbation in the previous year</th>
<th>Blood eosinophil count (cells per µL)</th>
<th>Current smokers (%)</th>
<th>ACQ at baseline (score)</th>
<th>Primary outcome</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al., 2020, CAPTAIN [27]</td>
<td>NCT02504688</td>
<td>Phase III, multicentre, randomized, double-blind, active-controlled, parallel-group</td>
<td>12.0</td>
<td>2436</td>
<td>FFVI/UMEC (100/25/31.25 µg q.d.), FFVI/UMEC (100/25/62.5 µg q.d.), FFVI/UMEC (200/25/31.25 µg q.d.), FFVI/UMEC (200/25/62.5 µg q.d.)</td>
<td>FFVI (100/25 µg q.d.), FFVI (200/25 µg q.d.)</td>
<td>FFVI/UMEC; DPI (Diskhaler®); FFVI; DPI (DPIx®)</td>
<td>Inadequately controlled asthma (pre-bronchodilator FEV₁ &lt;80% predicted; airway reversibility at screening defined as an increase in FEV₁ ≥12% and ≥200 mL after four inhalations of albuterol or salbutamol; ICS stable use ≥250 µg per day for 26 weeks prior to pre-screening)</td>
<td>53.2</td>
<td>38.0</td>
<td>21.2</td>
<td>58.5</td>
<td>29.9</td>
<td>0.8</td>
<td>228</td>
<td>0.0</td>
<td>2.8</td>
<td>Change in trough FEV₁: at week 24</td>
<td>5</td>
</tr>
<tr>
<td>Karelj et al., 2020, IRDIUM [28]</td>
<td>NCT02571777</td>
<td>Phase III, multicentre, randomized, double-blind, active-controlled, parallel-group</td>
<td>12.0</td>
<td>3092</td>
<td>MF/IND/GLY (80/150/50 µg q.d.), MF/IND/GLY (160/150/50 µg q.d.)</td>
<td>MF/IND (80/150 µg q.d.), MF/IND (160/150 µg q.d.), FP/SAL (100/50 µg b.i.d.)</td>
<td>MF/IND; DPI (Breezhaler®); MF/IND; DPI (Dialux®)</td>
<td>Symptomatic asthma (pre-bronchodilator FEV₁ &lt;80% predicted; ≥1 asthma exacerbation requiring medical care from a physician, ER visit, hospitalization, and systemic corticosteroid treatment for at least 3 days in the year prior to screening; airway reversibility defined as an increase in FEV₁ ≥12% and ≥200 mL after inhalation of albuterol or salbutamol; use of ICS/LABA medium- or high-dose for ≥3 months and at stable dose for ≥1 month prior to screening)</td>
<td>52.2</td>
<td>38.0</td>
<td>18.1</td>
<td>54.8</td>
<td>27.7</td>
<td>1.3</td>
<td>NA</td>
<td>NA</td>
<td>2.5</td>
<td>Change in trough FEV₁: at week 26</td>
<td>5</td>
</tr>
<tr>
<td>Grassner et al., 2020, ARGON [29]</td>
<td>NCT03158311</td>
<td>Phase III, multicentre, randomized, double-blind, active-controlled, parallel-group</td>
<td>5.5</td>
<td>1426</td>
<td>MF/IND/GLY (80/150/50 µg q.d.), MF/IND/GLY (160/150/50 µg q.d.)</td>
<td>MF/IND (80/150 µg q.d.), MF/IND (160/150 µg q.d.), FP/SAL (100/50 µg b.i.d.)</td>
<td>MF/IND; DPI (Breezhaler®); DPI (Accuhaler®); TIO: soft mist inhaler (Respimat®)</td>
<td>Symptomatic asthma (pre-bronchodilator FEV₁ &lt;80% predicted; ≥1 severe asthma exacerbation requiring medical care from a physician, ER visit or hospitalization and systemic corticosteroid treatment for at least 3 days in the year prior to study entry; airway reversibility defined as an increase in FEV₁ ≥12% and ≥200 mL, or historical evidence within the past 5 years of reversibility or positive bronchial provocation test; use of ICS/LABA stable medium- or high-dose prior to screening)</td>
<td>52.5</td>
<td>36.7</td>
<td>20.7</td>
<td>62.9</td>
<td>28.1</td>
<td>1.2</td>
<td>NA</td>
<td>2.2</td>
<td>2.6</td>
<td>Change in AQoL total score</td>
<td>3</td>
</tr>
<tr>
<td>Vincze et al., 2019, TRIBULUM [30]</td>
<td>NCT02676076</td>
<td>Phase III, multicentre, randomized, double-blind, active-controlled, parallel-group</td>
<td>12.0</td>
<td>1150</td>
<td>BDP/FOR/GLY (200/122.5 µg b.i.d.)</td>
<td>BDP/FOR (200/12 µg b.i.d.)</td>
<td>BDP/FOR/GLY (200/122.5 µg b.i.d.); BDP/FOR (200/12 µg b.i.d.); pMDI (NA)</td>
<td>Uncontrolled asthma (pre-bronchodilator FEV₁ &lt;80% predicted; ≥1 asthma exacerbation requiring an ER visit or hospitalization or systemic corticosteroid treatment in the year prior to study entry; airway reversibility defined as an increase in FEV₁ ≥12% and ≥200 mL at ≥15–16 min after inhalation of salbutamol 400 µg; use of ICS/LABA medium-dose for ≥1 month prior to study entry)</td>
<td>52.6</td>
<td>38.5</td>
<td>25.0</td>
<td>55.5</td>
<td>31.7</td>
<td>1.2</td>
<td>NA</td>
<td>0.0</td>
<td>2.3</td>
<td>Change in trough FEV₁: at week 26, rate of moderate and severe exacerbations</td>
<td>5</td>
</tr>
</tbody>
</table>
**Supplementary data**

| Virchow et al., 2019 TRIGGER [30] | NCT02876089 | Phase III, multicentre, randomized, double-blind (BDP/FOR + TIO group was open-label), active-controlled, parallel-group | 12.0 | 1431 | BDP/FOR/GLY (400/12/20 µg b.i.d.) | BDP/FOR (400/12 µg b.i.d.) + TIO (5 µg q.d.) | BDP/FOR/GLY (pMDI (NA); BDP/FOR: pMDI (NA); TIO: soft mist inhaler (Respimat®)) | Uncontrolled asthma (pre-bronchodilator FEV<sub>1</sub>=80% predicted; ≥1 asthma exacerbation requiring an ER visit or hospitalization or systemic corticosteroid treatment in the year prior to study entry; airway reversibility defined as an increase in FEV<sub>1</sub>≥12% and ≥200 mL at 10–15 min after inhalation of salbutamol 400 µg; use of ICS/LABA high-dose for ≥1 month prior to study entry) | 52.9 | 38.7 | 25.2 | 51.9 | 34.0 | 1.2 | NA | 0.0 | 2.4 | Change in trough FEV<sub>1</sub>, rate of moderate and severe exacerbations | 5 |

ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire; BDP: beclomethasone dipropionate; b.i.d.: *bis in die*, twice-daily; DPI: dry powder inhaler; ER: emergency room; FDC: fixed-dose combination; FEV<sub>1</sub>: forced expiratory volume in the 1<sup>st</sup> second; FF: fluticasone furoate; FOR: formoterol fumarate; FP: fluticasone propionate; GLY: glycopyrronium; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting β<sub>2</sub>-adrenoceptor agonist; q.d.: *quaque die*, once daily; MF: momethasone furoate; NA: not available; pMDI: pressurized metered dose inhaler; RCT: randomized controlled trial; SAL: salmeterol; TIO: tiotropium bromide; UMEC: umeclidinium bromide; VI: vilanterol.
### Table S4. Definition of moderate and severe asthma exacerbations as reported by the studies included in the network meta-analysis.

<table>
<thead>
<tr>
<th>Study, year and reference</th>
<th>Study identifier</th>
<th>Definition of asthma exacerbation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al., 2020, CAPTAIN [27]</td>
<td>NCT02924688</td>
<td>Moderate asthma exacerbation: “deterioration in either asthma symptoms or lung function, or increased rescue bronchodilator use, that required a physician-directed temporary change in maintenance treatment to prevent the exacerbation from becoming a severe exacerbation”. Severe asthma exacerbation: “an exacerbation requiring admission to hospital or a visit to an emergency department due to the need for SCSs, or asthma deterioration requiring SCS use (or doubling of the current maintenance SCS dose) for at least 3 days”.</td>
</tr>
<tr>
<td>Kerstjens et al., 2020 IRIDIUM [28]</td>
<td>NCT02571777</td>
<td>Moderate asthma exacerbation: “the occurrence of two or more of the following: progressive increase of at least one asthma symptom; increased use of rescue medication; or deterioration in lung function lasting for 2 days or more that is usually not severe enough to warrant SCSs for more than 2 days or hospitalization”. Severe asthma exacerbation: “an aggravation of asthma symptoms (such as shortness of breath, cough, wheezing, or chest tightness) that requires SCSs for at least 3 consecutive days or a need for an ER visit, hospitalisation owing to asthma, or death due to asthma”.</td>
</tr>
</tbody>
</table>
| Gessner et al., 2020 ARGON [29] | NCT03158311 | Moderate asthma exacerbation: “the occurrence of two or more of the following: 1. progressive increase of at least one of the asthma symptoms like shortness of breath, cough, wheezing, or chest tightness. The symptoms were outside the patient’s usual range of day-to-day asthma and lasted at least two consecutive days. 2. increased use of “rescue” inhaled bronchodilators defined by: ≥50% increase in SABA use and ≥8 puffs on 2 out of any 3 consecutive days compared to baseline captured or night time awakenings requiring SABA use on at least 2 out of any 3 consecutive nights. 3. deterioration in lung function, which lasted for two days or more but usually not severe enough to warrant SCSs for more than 2 days or hospitalisation. This deterioration was defined by: ≥20% decrease in FEV\textsubscript{1} from baseline value or ≥20% decrease in morning or evening PEF from baseline on 2 out of any 3 consecutive days compared to baseline or <60% of predicted PEF compared to baseline”. Severe asthma exacerbation: “an aggravation of asthma symptoms (like shortness of breath, cough, wheezing, or chest tightness) that required SCS for at least three consecutive days and/or a need for an ER visit (or local equivalent structure), hospitalisation due to asthma or death due to asthma”.

| Virchow et al., 2019 TRIMARAN [30] | NCT02676076 | Moderate asthma exacerbation: “nocturnal awakenings due to asthma requiring a SABA for 2 consecutive nights or an increase of 0.75 or more from baseline in daily symptom score on 2 consecutive days; increase from baseline in use of SABA on 2 consecutive days (minimum increase 4 puffs per day); 20% or more decrease in PEF from baseline on at least 2 consecutive mornings or evenings; or 20% or more decrease in FEV\textsubscript{1} from baseline; or a visit to an emergency department or a study site for asthma treatment not requiring SCSs” (definition in accordance with the ATS and ERS joint statement [31]). Severe asthma exacerbation: “worsening of asthma that required treatment with SCSs for at least 3 days (with any associated emergency department visit or admission to hospital documented)”. |
| Virchow et al., 2019 TRIGGER [30] | NCT02676089 | Moderate asthma exacerbation: “nocturnal awakenings due to asthma requiring a SABA for 2 consecutive nights or an increase of 0.75 or more from baseline in daily symptom score on 2 consecutive days; increase from baseline in use of SABA on 2 consecutive days (minimum increase 4 puffs per day); 20% or more decrease in PEF from baseline on at least 2 consecutive mornings or evenings; or 20% or more decrease in FEV\textsubscript{1} from baseline; or a visit to an emergency department or a study site for asthma treatment not requiring SCSs” (definition in accordance with the ATS and ERS joint statement [31]). Severe asthma exacerbation: “worsening of asthma that required treatment with SCSs for at least 3 days (with any associated emergency department visit or admission to hospital documented)”. |

ATS: American Thoracic Society; ER: emergency room; ERS: European Respiratory Society; FEV\textsubscript{1}: forced expiratory flow in the 1\textsuperscript{st} second; PEF: peak expiratory flow; SABA: short-acting $\beta_2$-adrenoceptor agonist; SCS: systemic corticosteroid.
**Supplementary data**

Table S5. Level of ICS doses in agreement with the daily doses of medications in adults in the Phase III RCTs included in the network meta-analysis as reported by current GINA recommendations [5] and NICE guidelines [6].

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Regimen of administration</th>
<th>Daily dose</th>
<th>Level of ICS dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDP</td>
<td>200 µg b.i.d.</td>
<td>400 µg</td>
<td>MD</td>
</tr>
<tr>
<td></td>
<td>400 µg b.i.d.</td>
<td>800 µg</td>
<td>HD</td>
</tr>
<tr>
<td>FF</td>
<td>100 µg q.d.</td>
<td>100 µg</td>
<td>MD*</td>
</tr>
<tr>
<td></td>
<td>200 µg q.d.</td>
<td>200 µg</td>
<td>HD*</td>
</tr>
<tr>
<td>FP</td>
<td>500 µg b.i.d.</td>
<td>1000 µg</td>
<td>HD</td>
</tr>
<tr>
<td>MF</td>
<td>80 µg q.d.</td>
<td>80 µg</td>
<td>MD**</td>
</tr>
<tr>
<td></td>
<td>160 µg q.d.</td>
<td>160 µg</td>
<td>HD**</td>
</tr>
<tr>
<td></td>
<td>320 µg q.d.</td>
<td>320 µg</td>
<td>HD**</td>
</tr>
</tbody>
</table>

*The dose levels refer to those reported in the NICE guidelines [32].
*The MD 80 µg and the HD 160 µg of MF delivered via Breezhaler® device correspond to the MD 400 µg and the HD 800 µg of MF delivered via the approved Twisthaler® formulation [28, 29].

Supplementary data

Table S6. Sensitivity analysis performed by excluding the CAPTAIN study [27] from the Bayesian network concerning the relative effects with 95%CrI of the co-primary endpoints.

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Sensitivity analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>References for direct comparisons</td>
</tr>
<tr>
<td>HD ICS/LABA FDC + TIO vs. MD ICS/LABA/LAMA FDC</td>
<td>[29, 30]</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA/LAMA FDC</td>
<td>[28, 29]</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>[28, 30]</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>[28]</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA/LAMA FDC</td>
<td>[29]</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>[30]</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>IC</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>[28]</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>[27, 28, 30]</td>
</tr>
<tr>
<td>HD ICS/LABA FDC vs. MD ICS/LABA FDC</td>
<td>IC</td>
</tr>
</tbody>
</table>

*P<0.05.
CrI: credible interval; CV: cardiovascular; FDC: fixed-dose combination; FEV₁: forced expiratory volume in the 1st second; HD: high-dose; IC: indirect comparison; ICS: inhaled corticosteroid; LABA, long-acting β₂-adrenoceptor agonist; MD: medium-dose; RR: relative risk; TIO: tiotropium bromide.
### Supplementary data

**Table S7.** Sensitivity analysis performed by excluding the CAPTAIN study [27] from the Bayesian network with respect to the moderate or severe asthma exacerbations.

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Moderate asthma exacerbation (RR)</th>
<th>Severe asthma exacerbation (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD ICS/LABA FDC + TIO</td>
<td>0.86 (0.61 - 1.14)</td>
<td>1.39 (0.85 - 2.36)</td>
</tr>
<tr>
<td>MD ICS/LABA/LAMA FDC</td>
<td>0.95 (0.73 - 1.23)</td>
<td>0.72 (0.48 - 1.09)</td>
</tr>
<tr>
<td>HD ICS/LABA FDC</td>
<td>0.79 (0.60 - 1.01)</td>
<td>0.65 (0.42 - 0.98) *</td>
</tr>
<tr>
<td>MD ICS/LABA FDC</td>
<td>0.74 (0.55 - 0.98) *</td>
<td>0.57 (0.36 - 0.90) *</td>
</tr>
<tr>
<td>HD ICS/LABA/LAMA FDC vs. HD ICS/LABA FDC + TIO</td>
<td>1.10 (0.80 - 1.58)</td>
<td>0.52 (0.29 - 0.89) *</td>
</tr>
<tr>
<td>HD ICS/LABA FDC</td>
<td>0.92 (0.67 - 1.32)</td>
<td>0.46 (0.26 - 0.80) *</td>
</tr>
<tr>
<td>MD ICS/LABA FDC</td>
<td>0.85 (0.60 - 1.28)</td>
<td>0.41 (0.22 - 0.75) *</td>
</tr>
<tr>
<td>HD ICS/LABA FDC</td>
<td>0.83 (0.63 - 1.10)</td>
<td>0.89 (0.57 - 1.40)</td>
</tr>
<tr>
<td>MD ICS/LABA FDC</td>
<td>0.77 (0.60 - 1.00) *</td>
<td>0.79 (0.52 - 1.20)</td>
</tr>
<tr>
<td>MD ICS/LABA FDC</td>
<td>0.93 (0.69 - 1.26)</td>
<td>0.88 (0.55 - 1.42)</td>
</tr>
</tbody>
</table>

*P<0.05, *P=0.05.

CrI: credible interval; FDC: fixed-dose combination; HD: high-dose; ICS: inhaled corticosteroid; LABA: long-acting β₂-adrenoceptor agonist; LAMA: long-acting muscarinic antagonist; MD: medium-dose; RR: relative risk; SUCRA: surface under the cumulative ranking curve; TIO: tiotropium bromide.
**Figure S1.** Weighted plot for the assessment of the overall risk of bias via the Cochrane RoB 2 tool (n=5 Phase III RCTs). RCT: randomized controlled trial; RoB 2: Risk of Bias 2.
**Figure S2.** Traffic light plot for assessment of the risk of bias of each included Phase III RCT via the Cochrane RoB 2 tool. D1: bias arising from the randomization process; D2: bias due to deviations from intended intervention; D3: bias due to missing outcome data; D4: bias in measurement of the outcome; D5: bias in selection of the reported result; RCT: randomized controlled trial; RoB: risk of bias; robvis: risk of bias visualization tool. Yellow circle indicates some concerns on the risk of bias and green circle represents low risk of bias.
Figure S3. Publication bias assessment via the normalized consistency/inconsistency plot (linear regression and 95% prediction bands) of different triple combination therapies and active comparators with respect to the risk of moderate to severe asthma exacerbation (A) and change from baseline in trough FEV$_1$ (B). FEV$_1$: forced expiratory volume in the 1$^{st}$ second.
References

Supplementary data

**Appendix 1**. Summary text of the identified records.


14: Virchow JC. Assessing the benefits of triple versus dual fixed-dose


Supplementary data

32302698.


50: FitzGerald JM, Sadatsafavi M. Triple therapy in a single inhaler: a new


Supplementary data


Supplementary data


109: Mesonzhnik NV, Moskaleva NE, Shestakova RM, Kuryinina KO, Baranov PA, Gretsakaya NM, Serkov IV, Lyubimov II, Bezuglov VV, Appolonova SA. LC-MS/MS


Supplementary data


Supplementary data


166: Lichtveld M, Kennedy S, Krouse RZ, Grimsley F, El-Dahr J, Bordelon K,
Supplementary data


Supplementary data


Supplementary data


220: Suikerbuijk AW, de Wit GA, Wijga AH, Heijmans M, Hoogendoorn M, Rutten-van Molen M, Maurits EN, Hoogenveen RT, Feenstra TL. Maatschappelijke kosten van astma, COPD en respiratoire allergie [Societal costs of asthma, COPD and...
Supplementary data


Supplementary data


Supplementary data


Supplementary data


Supplementary data


