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Impact of inhaled fluticasone propionate/salmeterol on health-related quality of life in asthma: a network meta-analysis

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Running head: Meta-analysis of Impact of asthma treatments on AQLQ

Keywords: Asthma Quality of Life questionnaire; ICS/LABA; Network meta-analysis; Systematic review
Abstract

Objective: This network meta-analysis (NMA) compared fixed-dose, twice daily fluticasone propionate/salmeterol (FP/Sal) vs. inhaled corticosteroid (ICS) and other ICS/long-acting beta-agonists (LABA) treatments, including when administered using maintenance and reliever therapy (MART) regimens, in terms of improvements in health-related quality of life (HRQoL). The relationship between changes in asthma control and HRQoL was assessed.

Methods: Articles published between 2001 and 2021, reporting change from baseline (CFB) in Asthma Quality of Life Questionnaire (AQLQ) in patients with moderate-severe asthma, were identified by a systematic review. Random effects Bayesian NMAs derived estimates of the mean difference in CFB in AQLQ vs. other interventions connected to the network (included 15 studies). Sensitivity analyses explored the impacts of differences in follow-up duration, baseline asthma control, the inclusion of observational studies, adjusting for baseline FEV₁, and low-medium ICS dose arms only. Linear regression analysis compared CFBs in AQLQ and Asthma Control Questionnaire (ACQ) score.

Results: Mean CFB in AQLQ with FP/Sal vs. comparators demonstrated expected ranked effects: mean difference 0.65 [95% credible interval: 0.54, 0.78] versus placebo, 0.58 [ 0.33, 0.84] versus LABA, 0.21 [ 0.13, 0.31] versus ICS alone, 0.06 [−0.04, 0.19] versus other ICS/LABA, and 0.00 [−0.13, 0.14] versus ICS/formoterol MART. Sensitivity analyses largely showed consistent results. Improvements in AQLQ and ACQ were strongly correlated (R=0.94).

Conclusions: This NMA demonstrates that HRQoL is responsive to treatment, is strongly related to asthma control and that it can be well-managed in patients with moderate-severe asthma using regular treatment with inhaled FP/Sal.
Introduction

Many patients with asthma experience persistent symptoms and have uncontrolled asthma, despite the availability of therapies aimed at achieving asthma control [1-3]. The reasons for patients remaining symptomatic may include, patients having an under-perception of their symptoms, a lack of adherence to asthma treatment, and the presence of comorbidities which contribute to patients’ symptom burden [2, 4-9]. Poor control may also be caused by inadequate treatment [4,10] or as a result of therapeutic inertia, defined as a failure to modify treatment according to evidence-based guidelines [11]. Patients with uncontrolled asthma symptoms are at increased risk of exacerbations and loss of lung function as well as significant impairments in their quality of life and functional abilities [1,2,12-14], representing a significant unmet need for patients as well as a considerable financial burden for society [15-18].

The efficacy of asthma treatments in clinical trials has often been assessed using lung function as a primary endpoint, although it is recognised that rates of exacerbations, measures of inflammation, patient-reported symptoms and rescue medication usage are also important [19,20]. There is often a poor correlation between lung function, inflammation and symptoms [21,22]. The recognition of the importance of how patients experience the disease and its impact on their daily lives [1,23,24] has led to the use of various endpoints based on patient-reported outcomes [19,20], including composite measures assessing asthma control (e.g., the Asthma Control Questionnaire (ACQ) [25] and the Asthma Control Test [26]) and health-related quality of life (HRQoL) (e.g., the Asthma Quality of Life Questionnaire (AQLQ) [27], and the Living with asthma Questionnaire [28]).

Several studies have assessed the HRQoL burden in patients with asthma, [29-31], but few have specifically focused on the comparative effects of asthma treatments on improvements in HRQoL. In a previous systematic review and network meta-analysis (NMA), mean differences in changes from baseline in AQLQ score following treatment with inhaled corticosteroids (ICS) or ICS plus a long-acting β-agonist (LABA) versus placebo, met the
criterion for minimal clinically important difference (MCID) [32]. Previous studies have demonstrated an association between better asthma control and improved HRQoL in adults with asthma, but these have been mainly non-interventional, observational, cross-sectional studies [12,16,33]. One study, using data from the TENOR longitudinal study, showed that the number of asthma control issues (measured by Asthma Therapy Assessment Questionnaire (ATAQ)) at baseline was significantly associated with worse HRQoL (measured by the mini-AQLQ) at 12 months [13].

The addition of a LABA to an ICS is a recommended step-up in treatment for asthma patients with persistent symptoms and/or risk of exacerbations [1], and this strategy has been shown to improve asthma symptom control and lung function as well as decrease the risk of exacerbations [34-36]. In the one-year Gaining Optimal Asthma controL (GOAL) study, significantly more patients achieved guideline-defined asthma control and a lower annual rate of severe exacerbations, following escalating treatment with fluticasone propionate/salmeterol combination (FP/Sal) than with fluticasone propionate alone [37], and this was associated with improvements in AQLQ scores [38]. The aim of this systematic literature review (SLR) and NMA, was to further assess the impact of inhaled FP/Sal on health-related quality of life in adults and adolescents with moderate to severe asthma by evaluating the relative efficacy of FP/Sal versus other inhaled ICS and ICS/LABA treatment regimens. The relationship between change in asthma control and change in HRQoL in patients treated with regular ICS/LABA regimens, was also investigated.

**Methods**

**Identification and selection of studies**

The SLR was conducted in accordance with the standards outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [39]. A final version of the approved protocol was registered in the PROSPERO database (ID: CRD42022300383) [40]. Systematic searches were conducted in Medline, EMBASE, and Cochrane CENTRAL to identify articles between January 2001 and December 2021. Search
terms and strategies were adapted to each database using the appropriate indexing terms (Medical Subject Headings in MEDLINE and Emtree terms in Embase). The search strategies are outlined in Supplementary Table S1. Additional studies were identified through searches of respiratory scientific conference proceedings (2019 to 2021) and by manual checking of reference lists of relevant review articles. English language articles only were included.

Identified articles were screened by two independent reviewers against the eligibility criteria outlined in Table 1. Any conflicts were resolved by a third independent reviewer. Included studies were randomized controlled trials (RCTs) and comparative observational studies that evaluated ICS/LABA combinations and regimens in adults and adolescents (≥ 12 years) with moderate-to-severe asthma, inadequately controlled with fixed low-medium dose ICS or as needed low-medium dose ICS+LABA or any other controller. The primary outcome of interest was the mean change from baseline in AQLQ (captured by either the original AQLQ [25] or the standardised AQLQ (AQLQ(s)) [41]). The secondary outcome of interest was the change from baseline in ACQ (included ACQ-5 and ACQ-6) [42]). The accepted MCID for both of these instruments is 0.5 [42,43].

For each included study, a standardized data extraction template was used to capture data on study design, patient characteristics and treatments, and were extracted by one reviewer, validated by a second reviewer, and any discrepancies were resolved by consensus or a third reviewer. The quality of studies was assessed using the Cochrane Risk of Bias Quality Assessment tool 2.0 for RCTs [44], or the Good ReseArch for Comparative Effectiveness (GRACE) checklist for observational studies [45].

Feasibility assessment

The feasibility of performing a valid NMA was conducted by assessing the compatibility of all studies identified by the SLR and to explore whether the basic assumptions of the NMA (homogeneity and transitivity) were met to allow indirect treatment comparisons. Clinical experts provided input on the assumptions required to perform the NMA.
Examination of clinical heterogeneity was assessed in terms of study design, treatment characteristics, patient characteristics and outcome definitions across the included studies. The following factors were identified a priori as potential treatment effect modifiers:

- **Study design**: phase, blinding, follow-up duration, run-in and post treatment phase, sample size, study region, eligibility criteria
- **Treatment**: dose frequency/schedule and route of administration, prior ICS use and dose, prior LABA use and dose, background therapies, reliever use, use of other asthma therapies
- **Baseline characteristics**: age, sex, weight/body mass index, asthma duration, severe exacerbation, forced expiratory volume in 1 sec (FEV₁), asthma control
- **Outcomes**: summary statistic, baseline risk, definition of AQLQ, definition of asthma control, timepoints, availability of subgroup data

**Network Meta-Analysis**

A random effects Bayesian model was used to simultaneously synthesize the results of the included RCTs and estimate the relative efficacy of FP/Sal/ versus comparators of interest. All analyses included a 100,000 run-in phase and a 100,000-iteration phase for parameter estimation, and calculations were performed using OpenBugs (version 3.2.3). Convergence was checked through inspection of the ratios of Monte Carlo error to the standard deviations of the posteriors; values greater than 5% are strong signs of convergence issues [46].

The mean difference in CFB in AQLQ observed across arms and corresponding standard errors (SEs) within each study were used as inputs for the base-case analysis. The analyses did not differentiate treatments on the basis of dose as the assessment of the impact of ICS dose as an effect modifier at the feasibility assessment stage led to the conclusion that treatment in the network would be categorized in the base-case analysis regardless of ICS dose. Multiple data for each treatment were mathematically pooled to calculate a treatment group, n-weighted mean and SDs for each treatment in the study.
Analyses were performed using the last period of follow-up reported during the randomized treatment phase of each trial. Results of the NMA are reported as a central estimate of the mean difference with 95% credible intervals, and the probability that the first treatment was better than the second treatment. Heterogeneity for each comparison on the mean difference was assessed by conducting a classical pairwise meta-analysis and calculating \( I^2 \), an estimate of the percentage of variability due to heterogeneity [47]. The Cochrane Collaboration have provided general guidance regarding the interpretation of \( I^2 \), stating that values ranging from 0%-40% represent low heterogeneity, while values ranging from 75%-100% represent considerable heterogeneity [48]. While \( I^2 \) represents the proportion of total heterogeneity that cannot be explained due to sampling error, a high value of \( I^2 \) does not necessarily represent clinically substantive heterogeneity. Global statistical heterogeneity was also assessed by considering the size of the \( \tau \) from the Bayesian NMA under the random effects model.

For the base case NMA, FP/Sal was compared to ICS monotherapy, ICS/LABA fixed dose regimens, and ICS/formoterol maintenance and reliever therapy (ICS/Form MART) at the treatment-class level. Sensitivity analyses were conducted to explore the impact on the NMA of differences in follow-up duration, baseline asthma control, when observational studies were included, adjusting for baseline FEV\(_1\), and the inclusion of low-medium ICS dose arms only (wherein fluticasone propionate ≤500 µg per day or equivalent was considered low-medium dose [1]). Based on clinical expert feedback during the feasibility assessment, it was also decided to perform a scenario analysis including only low-medium doses of ICS, as these were believed to represent a fairer comparison of the fixed dose and ICS/Form MART regimens in terms of total ICS exposure. These doses are also commonly used to treat moderate or moderate-severe asthma [1].

The planned NMA to evaluate the relationship between changes in HRQoL (AQLQ) and changes in asthma control (ACQ) could not be conducted due to insufficient data. This relationship was explored using linear regression analysis, weighting the inverse of
variances of mean differences for ACQ in one analysis and by inverse of the variances of mean differences of AQLQ in another analysis.

Results

Search results and study characteristics

The database searches yielded 1109 unique publications and six records were identified through other sources (Figure 1). Overall, 27 publications that described the results from 19 unique studies [37,38, 49-68] were included in the SLR, of which 15 studies [37,38, 49,50,52-55, 57-62, 55-68] were deemed suitable for inclusion in the base case NMA (Table 2).

Of the 19 studies included in the SLR, 18 were RCTs and one was an observational study; eleven studies evaluated FP/Sal, and eight evaluated other ICS/LABA combinations (Table 2). All studies were multicentre and most were multinational. Across studies, the treatment phase ranged between 8 and 52 weeks, and ranges for other baseline characteristics were: mean age (36.1 to 51.4 years old), sex (42% to 72.7% female), mean body mass index (BMI) (25.8 kg/m² to 30.2 kg/m²), mean asthma duration (10 to 24.2 years), mean FEV₁ (1.70 L to 3.06 L), mean % predicted FEV₁ (57.4% to 97.7%), mean total AQLQ (4.3 to 6.0), mean ACQ (0.5 to 2.1) (see Supplementary Table S2).

The included RCTs were deemed to have a low risk of bias overall, with the exception of eight trials which failed to report details regarding randomization, although baseline characteristics were mostly balanced in these studies (see Supplementary Figure S1). The observational study by Kardos et al. 2013 [63], was rated as having a low risk of bias as well (see Supplementary Table S3).

Network of evidence

Based on the findings of the feasibility assessment, four studies were excluded from the base case NMA. One study was excluded because it compared as-needed budesonide/formoterol (Bud/Form) vs. regular Bud/Form + short-acting beta-agonist, and therefore did not provide comparative evidence of interest for the analysis [64]; one was
excluded due to differences in the approach to the asthma therapy (dose was adjusted by the patients according to severity of their symptoms) [51]; one due to differences in the treatment that patients had to receive to enter the study (ICS/LABA) and due to ICS titration [56]; and one study due to a lack of clarity as to which treatments were included in the physician choice, and the fact that it was the only observational study [63].

Baseline % predicted FEV\textsubscript{1} was the only characteristic to show evidence of effect modification for AQLQ, with patients with FEV\textsubscript{1} ≤ 50% showing a significantly greater benefit in terms of AQLQ on high dose FP/Form vs. low dose FP/Form [60]. The range of mean % predicted FEV\textsubscript{1} across studies included in the NMA was 57.4% to 79.0%. No further evidence of effect modification was observed across the studies included in the NMA, and characteristics of potential effect modifiers were similar across the included trials.

The connected network of RCTs for the base case analyses is shown in Figure 2. It also flags the one observational study that was included in the relevant sensitivity analysis. The thickness of the lines corresponds to the number of trials included per treatment comparison.

**Change from baseline in AQLQ**

In the base case NMA, FP/Sal resulted in significantly greater improvements in mean change from baseline in AQLQ compared with placebo (mean between group difference [MD]: 0.65 [95% credible interval (CrI): 0.54-0.78]), LABA alone (MD: 0.58 [95% CrI: 0.33-0.84]) and ICS alone (MD: 0.21 [95% CrI: 0.13-0.31]) (Figure 3). The probability that FP/Sal is better than each of these treatments was 100%, and the difference between FP/Sal and either placebo or LABA exceeded the AQLQ MCID of 0.5. Change from baseline AQLQ between FP/Sal and other fixed dose ICS/LABA regimens (MD: 0.06 [95% CrI: -0.04-0.19]) or between FP/Sal and ICS/Form MART (MD: 0.00 [95% CrI: -0.13-0.14]), were similar. A forest plot of base case NMA results detailing all included studies is shown in Supplementary Figure S2.

Results for the sensitivity analyses, evaluating the impact of follow-up duration, baseline asthma control, observational studies inclusion, and adjustment for baseline FEV\textsubscript{1},
showed similar results to the base case NMA (Table 3). In the sensitivity analysis that included only low-medium ICS dose arms, FP/Sal was found to be numerically favourable compared with ICS/Form MART (MD: 0.11 [95% CrI: -0.08, 0.33]) (Figure S3).

Heterogeneity was high for the comparison of FP/Sal versus placebo ($I^2$ 88.6%, $\tau$ 0.3), which was the result of a single outlier study [58]. When this study was omitted from the analysis, heterogeneity was reduced ($I^2$ 36.5%, $\tau$ 0.07), with results that were consistent with the base case: MD 0.58 [95% CrI: 0.47, 0.68] versus placebo, 0.54 [95% CrI: 0.32, 0.76] versus LABA, 0.19 [95% CrI: 0.12, 0.27] versus ICS, 0.03 [95% CrI: −0.06, 0.11] versus other ICS/LABA, and −0.01 [95% CrI: −0.10, 0.08] versus MART. Heterogeneity was low for all other comparisons in the network ($I^2$ ranged from 0% to 40.7%).

**Relationship between asthma control and health-related quality of life**

Of the 19 studies identified in the systematic search, six reported data for change from baseline in both AQLQ and ACQ. The linear regression analysis showed that improved asthma control was strongly associated with improvement in AQLQ (Figure 4). The figure shows a very high coefficient of determination ($R^2$) of 0.88, representing an approximate correlation of $\sqrt{0.87} = 0.94$.

**Discussion**

The results of this Bayesian NMA show the benefits of regular treatment with FP/Sal in achieving clinically relevant improvements in HRQoL in adult patients with moderate to severe asthma. These improvements are significantly greater than those shown with placebo or ICS monotherapy. FP/Sal also caused similar improvements in AQLQ to other ICS/LABA treatments, including when administered using ICS/Form MART regimens. A data gap was identified in terms of the relationship between change in AQLQ and change in ACQ; we have now demonstrated a strong correlation between AQLQ and ACQ using linear regression analysis. These findings highlight the impact that worsening asthma control can have on patient quality of life.
Although NMAs have some inherent limitations, due to assumptions made on study similarities and the pooling of data, a feasibility assessment minimizes these effects whilst aiming to maximize the available evidence base. Results of the NMA sensitivity analyses were mostly consistent with the base case NMA and, together with the ranked treatment effects, suggest that the primary findings were robust. An additional NMA that compared FP/Sal with individual ICS/LABA combinations showed similar trends to the primary analysis (Figure S4), further supporting these findings. The effect size of FP/Sal in improving AQLQ vs. placebo was similar to that reported in a meta-analysis by Bateman et al in a comparison of ICS/LABA (pooled data) vs. placebo (MD 0.729 [95% CI 0.658, 0.799]), in a similar population of patients with uncontrolled asthma [32]. The NMA by Bateman et al assessed the effect size of various asthma treatments on change from baseline in HRQoL and reported the mean differences of active treatment versus placebo but did not compare the relative effects of active treatments. This study adds to these findings on HRQoL by comparing the effects of a specific ICS/LABA, FP/Sal, with other inhaled ICS and ICS/LABA treatment regimens.

The current NMA showed that FP/Sal was statistically significantly more effective than ICS monotherapy for improving AQLQ, although the difference between treatments did not exceed the MCID of 0.5. Other researchers have reported the challenges of using the MCID for comparisons between patient groups when evaluating two active treatments [32; 69]. Jones et al proposed the concept of a minimum worthwhile incremental advantage, defined as the percentage of patients who would experience improvement at or above the MCID on adding one treatment to another, or comparing two active treatments [69]. For certain patient groups with severe disease, this may be relatively small in order for them to perceive benefit.

This is the first NMA to consider the relative effects of asthma treatments with HRQoL as the primary focus. In NMAs with a primary focus on severe exacerbations, data for HRQoL has either not been reported [70, 71] or reported in too few studies to rank effects across treatments [72]. Similar to our findings, Sobieraj reported no difference between
MART and fixed dose ICS/LABA with respect to AQLQ but this included only one study [52,72]. Data for asthma control in these NMAs have also been limited in terms of study numbers or quality of data and generally show no differences between different ICS/LABA regimens [70,72]. It remains the case, that only the GOAL study has prospectively investigated whether, and in what proportion of patients, asthma control can be achieved by stepping-up treatment, and demonstrated that greater than 70% of patients receiving regular FP/Sal could achieve and maintain well-controlled asthma [37]]. In a re-analysis of the GOAL study, using the Global Initiative for Asthma (GINA) 2016 definition of asthma control [73], the proportion of patients who achieved/maintained control was > 85%. [74].

In a recent review article of efficacy versus systemic activity profiles for various dosing regimens of Bud/Form and FP/Sal, regular daily ICS/LABA dosing regimens (FP dose 250 to 500 µg or equivalent) had higher airway efficacy (in terms of bronchoprotective effects) but similar (and low) systemic activity compared with MART in moderate and moderate-severe asthma [75]. Interestingly, in the current NMA sensitivity analysis that included only low-medium ICS dose arms (FP dose ≤ 500 µg), a numerical trend in favour of FP/Sal over MART in improving AQLQ was seen, which is in line with the results from Singh et al, where regular dosing with medium dose FP/Sal in moderate asthma patients resulted in clinically significant bronchoprotection [75]. It’s possible that the exclusion of the high dose ICS arms led to the exclusion of patients with more difficult to control asthma, resulting in the improved HRQoL outcomes overall for FP/Sal. More data comparing different treatment strategies are required to fully understand comparative treatments effects on HRQoL.

In agreement with the current NMA, other NMAs highlight a significant gap with respect to asthma control data and its impact on HRQoL [70-72]. Despite the data limitations in this NMA, the logistic regression analysis demonstrated a strong association between changes in asthma control and HRQoL. This finding is consistent with previous reports in observational studies. In one study in patients with severe asthma, asthma control at baseline was significantly associated with worse HRQoL measured at 12 months follow-up (r= -0.49, p < .0001) and that an increase in asthma control issues over 12 months was a
significant predictor of worse asthma specific HRQoL at follow-up [13]. In a descriptive observational, cross-sectional study in patients with moderate to severe asthma, asthma control, measured by the ACT, was negatively correlated with HRQoL, measured by the St George’s Respiratory Questionnaire total score, \( r = -0.72; p < 0.01 \) [12]. In a retrospective analysis of 27 RCTS in patients with persistent asthma, a moderate correlation between patient daily symptoms and AQLQ was reported [76]. In this latter analysis, symptoms were based on patient reported symptoms via diary cards and the included studies covered a wider range of study designs and populations than included in the current study, which may explain the different findings. The high correlation coefficient demonstrated in the current analysis, based on change from baseline data measured by two validated questionnaires and derived from RCTs, provides robust evidence of the association between asthma control and HRQoL. This is important clinically, as it supports the targeting of asthma control as a treatment goal to improve patients’ experience of the disease. Treating patients to achieve and maintain asthma control in real life requires good communication between patients and healthcare professionals with regular monitoring to check suitability of and adherence to treatment, and implementation of a personalised asthma action plan [1,10].

This analysis has some limitations. The findings on comparisons with MART should be interpreted with caution given the limited evidence based on two trials – further studies to determine any differences between FP/Sal and MART regimens with respect to HRQoL are needed. The sensitivity analysis that included the one observational study resulted in consistent findings, but this required the assumption with regards to the physician choice arm that FP/Sal was not included in this arm. In addition, there was limited ability to adjust for factors that showed evidence of effect modification, namely FEV\(_1\), wherein the details regarding baseline values were incomplete. Lack of evidence of stratified or subgroup results for change in AQLQ limited our ability to identify evidence of effect modification across the included studies (i.e., flag characteristics that had an observed impact on relative effects). Similarly, inconsistent and lack of reporting for other potential effect modifiers across the included studies (e.g., comorbid conditions or measures of airway...
inflammation/hyperresponsiveness) may mean the differences in unobserved effect
modifiers could bias the results of this NMA. The reporting of change in ACQ for studies that
reported change in AQLQ in only six studies is another limitation. Future research is required
to verify the findings on the strong association shown between changes in AQLQ and ACQ,
and to examine the relationship between AQLQ and other outcomes including exacerbations
and lung function.

Conclusions
This network meta-analysis showed that fixed-dose, twice daily FP/Sal provides significant
improvements in HRQoL in moderate-severe patients with asthma. Comparative effects
across treatment classes demonstrated expected ranked effects. These data confirm the
importance of HRQoL as an outcome, and show that it is responsive to treatment, is strongly
related to asthma control and can be well managed using regular treatment with inhaled
FP/Sal.

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Declaration of interest statement
Kittipong Maneechotesuwan has received honoraria from Chiesi, GSK, Astra Zeneca,
Boehringer Ingelheim, Sanofi, Roche, and Novartis; and has acted as an advisory board
consultant for Chiesi, GSK, Astra Zeneca, Boehringer Ingelheim, and Sanofi. Dave Singh has
received personal fees from Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla,
CSL Behring, Epiendo, Genentech, GlaxoSmithKline, Glenmark, GossamerBio, Kinaset,
Menarini, Novartis, Pulmatrix, Sanofi, Synairgen, Teva, Theravance and Verona. Leandro
Fritscher and Neşe Dursunoğlu declare no conflicts of interest. Abhijit PG, Abhay
Phansalkar, Bhumika Aggarwal, Emilio Pizzichini are employees of GSK and hold stocks
and shares in GSK. Justyna Chorazy and Heather Burnett are employees of Evidera who conducted the systematic literature review and network meta-analysis, funded by GSK.

**Availability of data and materials**

Information on GSK’s data sharing commitments and requesting access can be found at: https://www.clinicalstudydatarequest.com.
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Table 1: Eligibility criteria for the systematic literature review

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<thead>
<tr>
<th>Domain</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tr>
<td>Population</td>
<td>• Adults (≥18 years) and adolescents (≥12 to &lt;18 years)</td>
<td>• Children &lt;12 years</td>
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<td>• Patients with moderate-to-severe asthma inadequately controlled with fixed low-medium dose ICS or as needed low-medium dose ICS (+LABA or any other controller)</td>
<td>• Patients with mild or mild-to-moderate asthma</td>
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<td>• Notes:</td>
<td>• Patients on LAMA, high-dose ICS-LABA, or biologic treatments</td>
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<td>o If the ICS dose is not reported at inclusion, studies with population described as having moderate-to-severe asthma will be included.</td>
<td>• Patients with OCS-dependent asthma</td>
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<td>• Key subgroups of interest:</td>
<td>• Studies with LABA as exclusion criteria</td>
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<td>Results by level of asthma control at baseline (based on ACQ or ACT, GINA definition)</td>
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<td>Intervention</td>
<td>• Fixed-dose, twice daily FP/Sal maintenance therapy ± SABA reliever</td>
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<td>• Budesonide/formoterol MART</td>
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<td>• Other fixed-dose, twice daily ICS/LABA combinations ± SABA reliever</td>
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<td>Comparator</td>
<td>• Any of the above interventions</td>
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<td>• ICS monotherapy/standard of care</td>
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<td>Outcomes</td>
<td>Primary: Mean change from baseline or least-squared mean change or mean differences in total HRQoL score based on AQLQ</td>
<td>Studies that do not report the outcomes of interest as noted under the inclusion criteria.</td>
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<td>Secondary (to be extracted only from outcomes reporting the primary outcome):</td>
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<td></td>
</tr>
<tr>
<td>Study Design</td>
<td>• RCTs (including comparative extension studies)</td>
<td>Uncontrolled observational studies (during design or analysis)</td>
</tr>
<tr>
<td></td>
<td>• Comparative observational studies with appropriate adjustment (e.g., propensity score matching or multivariate analysis) for confounding factors</td>
<td>Single-arm trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Narrative reviews</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Letters, editorials, comments, guidelines, erratum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In vitro, ex vivo studies</td>
</tr>
</tbody>
</table>
| **and possible effect modifiers (e.g., age, smoking status, FEV1, exacerbation history)** | • Pharmacodynamic/pharmacokinetic studies  
• Genetic studies  
• Case reports or case series  
• Protocols for RCTs or for other primary study types  
• SLR/NMA\(^b\) |

| **Time period** | January 1, 2001 to present | Studies published before 2001 |
| **Language** | English | Studies published in languages other than English |

\(^a\)Pooled RCTs analyses that reported HRQoL data were included.  
\(^b\)Publications of systematic reviews were used for citation chasing and were subsequently excluded at full-text level.

ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; AQLQ: Asthma Quality of Life Questionnaire; FEV\(_1\): forced expiratory volume in one second; FP/Sal: fluticasone propionate/salmeterol; GINA: Global Initiative for Asthma; HRQoL: health-related quality of life; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; MART: maintenance and reliver therapy; NMA: network meta-analysis; OCS: oral corticosteroids; RCT: randomized controlled trial; SABA: short-acting beta-agonist; SLR: systematic literature review
Table 2: Characteristics of studies identified in the systematic literature review

<table>
<thead>
<tr>
<th>Study name/Author, Year [Ref]</th>
<th>Study design</th>
<th>Intervention/Comparator</th>
<th>N (Total=17,647)</th>
<th>QoL Questionnaire</th>
<th>Included in network meta-analysis (Yes/no)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FP/Sal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bergmann KC, 2004 [48]</td>
<td>Multicentre, randomised, double-blind, parallel group, 12-week treatment period</td>
<td>FP/Sal</td>
<td>179</td>
<td>AQLQ</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FP</td>
<td>186</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00461500 [49]</td>
<td>Multicentre, randomised, double-blind, parallel group, 12-week treatment period</td>
<td>FP/Sal</td>
<td>37</td>
<td>AQLQ</td>
<td>Yes</td>
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<tr>
<td></td>
<td></td>
<td>FP</td>
<td>44</td>
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<tr>
<td>CONCEPT Price DB, 2007 [50]</td>
<td>Multicentre, randomised, double-blind, double-dummy, parallel group, 52-week treatment period</td>
<td>FP/Sal</td>
<td>344</td>
<td>AQLQ</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bud/Form</td>
<td>344</td>
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<td><strong>COMPASS</strong></td>
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<tr>
<td>Kuna P, 2007 [51]</td>
<td>Multicentre, randomised, double-blind, parallel group, 24-week treatment period</td>
<td>FP/Sal</td>
<td>1123</td>
<td>AQLQ(S)</td>
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<td>Kuna P, 2010 [52]</td>
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<td>Bud/Form</td>
<td>1105</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MART</td>
<td>1107</td>
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</tr>
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<td></td>
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<td>Bud/Form</td>
<td>947</td>
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<tr>
<td></td>
<td></td>
<td>MART</td>
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<td><strong>COSMOS</strong></td>
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<tr>
<td>Vogelmeier C, 2005 [53]</td>
<td>Multicentre, randomised, open label, parallel group, 52-week treatment period</td>
<td>FP/Sal</td>
<td>1076</td>
<td>AQLQ(S)</td>
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<tr>
<td></td>
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<td>Bud/Form</td>
<td>1067</td>
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<td><strong>GOAL</strong></td>
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<tr>
<td>Bateman ED, 2004 [37]</td>
<td>Multicentre, randomised, double-blind, parallel group, 52-week treatment period</td>
<td>FP/SAL</td>
<td>1709</td>
<td>AQLQ</td>
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<td>Bateman ED, 2007 [38]</td>
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<td>FP</td>
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<td></td>
<td></td>
<td>FP</td>
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<tr>
<td>Raphael G, 2017 [54]</td>
<td>Multicentre, randomised, double-blind, parallel group, 12-week treatment period</td>
<td>FP/Sal</td>
<td>258</td>
<td>AQLQ(S)</td>
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<td>FP</td>
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<td></td>
<td></td>
<td>Placebo</td>
<td>130</td>
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<tr>
<td>Study name/Author, Year [Ref]</td>
<td>Study design</td>
<td>Intervention/Comparator</td>
<td>N (Total=17,647)</td>
<td>QoL Questionnaire</td>
<td>Included in network meta-analysis (Yes/no)*</td>
</tr>
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<tr>
<td>SAM40031 Reddel HK, 2010 [55]</td>
<td>Multicentre, randomised, double-blind, parallel group, 52-week treatment period</td>
<td>FP/Sal</td>
<td>41</td>
<td>AQLQ</td>
<td>No</td>
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<tr>
<td>SAS40006 Juniper EF, 2002 [56]</td>
<td>Multicentre, randomised, double-blind, parallel group, 12-week treatment period</td>
<td>FP/Sal</td>
<td>55</td>
<td>AQLQ(S)</td>
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<td>SAS30004 Edin HM, 2009 [57]</td>
<td>Multicentre, randomised, double-blind, parallel group, 12-week treatment period</td>
<td>FP/Sal</td>
<td>186</td>
<td>AQLQ</td>
<td>Yes</td>
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<tr>
<td>Sher LD, 2017 [58]</td>
<td>Multicentre, randomised, double-blind, parallel group, 12-week treatment period</td>
<td>FP/Sal</td>
<td>291</td>
<td>AQLQ(S)</td>
<td>Yes</td>
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</tbody>
</table>

Other ICS/LABA

<p>| Bodzenta-Lukaszyk A, 2012 [61]| Multicentre, randomised, double-blind, double dummy, parallel group, 12-week treatment period | FP/Form vs. | 140 | AQLQ | Yes |
| Kardos P, 2013 [62]| Observational, real-life, 24 weeks | Bud/Form + | 139 | AQLQ(S) | No |
| Papi A, 2015 [63]| Multicentre, randomised, double-blind, parallel group, As-needed Bud/Form + placebo | 424 | AQLQ | No |</p>
<table>
<thead>
<tr>
<th>Study name/Author, Year [Ref]</th>
<th>Study design</th>
<th>Intervention/ Comparator</th>
<th>N (Total=17,647)</th>
<th>QoL Questionnaire</th>
<th>Included in network meta-analysis (Yes/no)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>P04073AM1 Meltzer EO, 2012 [64]</td>
<td>Multicentre, randomised, double-blind, double-dummy, parallel group, 26-week treatment period</td>
<td>MF/Form</td>
<td>182</td>
<td>Yes</td>
<td>AQLQ(S)</td>
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<tr>
<td></td>
<td></td>
<td>MF</td>
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<td></td>
<td></td>
<td>Form</td>
<td>188</td>
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<td>Placebo</td>
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<tr>
<td>P04334AM1 Nathan RA, 2010 [65]</td>
<td>Multicentre, randomised, double-blind, double-dummy, parallel group, 26-week treatment period</td>
<td>MF/Form</td>
<td>191</td>
<td>Yes</td>
<td>AQLQ(S)</td>
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<td>P04431AM2 Weinstein SF, 2010 [66]</td>
<td>Multicentre, randomised, double-blind, parallel group, 12-week treatment period</td>
<td>MF/Form</td>
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<td>Yes</td>
<td>AQLQ(S)</td>
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<td></td>
<td></td>
<td>MF</td>
<td>240</td>
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<tr>
<td>SD-039-0717 Chervinsky P, 2008 [67]</td>
<td>Multicentre, randomised, double-blind, double-dummy, parallel group, 12-week treatment period</td>
<td>Bud/Form</td>
<td>117</td>
<td>Yes</td>
<td>AQLQ(S)</td>
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<tr>
<td></td>
<td></td>
<td>Bud + Form</td>
<td>110</td>
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<td></td>
<td></td>
<td>Bud</td>
<td>102</td>
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<tr>
<td></td>
<td></td>
<td>Form</td>
<td>109</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>115</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Studies excluded from NMA base case based on feasibility assessment
AQLQ: Asthma Quality of Life Questionnaire; AQLQ (S): standardised AQLQ; Bud: budesonide; Bud/Form: budesonide/formoterol; FP/Form: fluticasone propionate/formoterol; FP/Sal: fluticasone propionate/salmeterol; MART: maintenance and reliver therapy; MF/Form: mometasone furoate/formoterol; Sal: salmeterol
**Table 3: Results of sensitivity analyses for comparison of FP/Sal vs. other treatment classes for mean change in AQLQ**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Placebo</th>
<th>LABA</th>
<th>ICS</th>
<th>Other ICS/LABA</th>
<th>ICS/Form MART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base Case</td>
<td>0.65 [0.54, 0.80]</td>
<td>0.58 [0.32, 0.87]</td>
<td>0.21 [0.12, 0.32]</td>
<td>0.07 [-0.05, 0.22]</td>
<td>0.00 [-0.14, 0.15]</td>
</tr>
<tr>
<td>Scenario: ≥24 week follow-up duration</td>
<td>0.53 [0.23, 0.82]</td>
<td>----</td>
<td>0.17 [-0.09, 0.42]</td>
<td>0.02 [-0.21, 0.25]</td>
<td>-0.01 [-0.19, 0.17]</td>
</tr>
<tr>
<td>Scenario: Include Kardos 2013 (observational study)</td>
<td>0.64 [0.52, 0.78]</td>
<td>0.57 [0.29, 0.85]</td>
<td>0.21 [0.11, 0.32]</td>
<td>0.04 [-0.08, 0.17]</td>
<td>0.04 [-0.09, 0.20]</td>
</tr>
<tr>
<td>Scenario: Low-Medium dose ICS only</td>
<td>0.62 [0.47, 0.78]</td>
<td>0.55 [0.24, 0.86]</td>
<td>0.17 [0.03, 0.32]</td>
<td>0.02 [-0.14, 0.20]</td>
<td>0.11 [-0.08, 0.33]</td>
</tr>
<tr>
<td>Meta-regression 1: baseline ACQ*</td>
<td>0.65 [0.53, 0.80]</td>
<td>0.59 [0.31, 0.87]</td>
<td>0.22 [0.12, 0.33]</td>
<td>0.07 [-0.06, 0.22]</td>
<td>0.01 [-0.16, 0.18]</td>
</tr>
<tr>
<td>Meta-regression 2a: follow-up duration*</td>
<td>0.65 [0.53, 0.78]</td>
<td>0.58 [0.32, 0.85]</td>
<td>0.22 [0.12, 0.32]</td>
<td>0.07 [-0.05, 0.2]</td>
<td>0.03 [-0.13, 0.2]</td>
</tr>
<tr>
<td>Meta-regression 3: baseline FEV₁ (percent predicted) *</td>
<td>0.67 [0.54, 0.82]</td>
<td>0.60 [0.32, 0.89]</td>
<td>0.24 [0.14, 0.37]</td>
<td>0.08 [-0.04, 0.24]</td>
<td>0.04 [-0.18, 0.28]</td>
</tr>
</tbody>
</table>

*Covariates were not significant

ACQ: Asthma Control Questionnaire; ICS: Inhaled corticosteroids; LABA: Long-acting beta-agonists; MART: Maintenance and reliever therapy
Figures legend

**Figure 1:** PRISMA flow diagram of study inclusion and exclusion
SLR: systematic literature review; NMA: network meta-analysis

**Figure 2:** Evidence network of included studies in the base case NMA
*Reports AQLQ(S). Italic underlined = scenario analysis only
ICS: inhaled corticosteroid; ICS/Form MART: inhaled corticosteroid/formoterol maintenance and reliever therapy; LABA: long-acting beta-agonist; SABA: short-acting beta-agonist;
FP/Sal: fluticasone propionate/salmeterol.
See Table 2 for study references

**Figure 3:** Base case NMA results showing difference in mean change from baseline in AQLQ for FP/Sal versus other interventions
AQLQ: Asthma Quality of Life Questionnaire; FP/Sal: fluticasone propionate/salmeterol; ICS: inhaled corticosteroid; ICS/Form MART: inhaled corticosteroid/formoterol maintenance and reliever therapy; LABA: long-acting beta-agonist; MART: maintenance and reliever therapy; Pbo: placebo

**Figure 4:** Logistic regression analysis of mean change in ACQ vs. mean change in AQLQ
ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; MD: mean difference; wt: weighted
Records identified from (n=1932):
- MEDLINE (n = 642)
- Embase (n = 780)
- CENTRAL (n = 510)

Duplicate records removed before screening (n = 823)

Records screened at title/abstract level (n = 1109)

Records excluded based on title/abstract screening (n = 1053)

Full-text records excluded (n = 35):
- Not a publication type of interest (n = 2)
- Not a study design of interest (n = 2)
- Not a population of interest (n = 6)
- Not an intervention/comparator of interest (n = 10)
- Not outcomes of interest (n = 14)
- Relevant SLR/NMA (n = 1)

Full-text records assessed for eligibility (n = 56)

Eligible records identified:
19 unique studies (27 publications)

Other sources: 6 publications
Impact of inhaled fluticasone propionate/salmeterol on health-related quality of life in asthma: a network meta-analysis

Kittipong Maneechotesuwan, Dave Singh, Leandro G Fritscher, Nese Dursunoglu, Abhijit PG, Abhay Phansalkar, Bhumika Aggarwal, Emilio Pizzichini, Justyna Chorazy, Heather Burnett

Highlights:
- Health-related quality of life (HRQoL) outcomes assess the impacts of asthma
- Fixed dose inhaled fluticasone propionate/salmeterol (FP/Sal) significantly improved HRQoL
- Comparative effects across ICS-containing regimens demonstrated expected ranked effects
- HRQoL is responsive to treatment and is strongly related to asthma control
- In moderate-severe asthma, HRQoL can be well-managed with regular FP/Sal