Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.
Design and Methods

From references to the systematic review and meta-analysis of the single inhaler combination inhaled corticosteroid (ICS)-formoterol maintenance and reliever therapy (SMART) regimen published in 2018, and further review of the literature and internal study databases at AstraZeneca and the Medical Research Institute of New Zealand, randomized controlled trials which compared budesonide-formoterol by SMART vs ICS-long-acting β₂-agonist (LABA) plus short-acting β₂-agonist (SABA) reliever were reviewed. The articles identified were reviewed by the authors, who were also involved in the conduct of the included studies, and had access to the individual patient data. Importantly, the individual patient data from the Patel et al study were provided to the statistical team for inclusion in the analysis. All studies in which individual patient data for ACQ were available were included.

The study selection criteria were prospectively specified and registered on PROSPERO in August 2018 (PROSPERO 2018 CRD42018107144). Since the document was published, two changes were made, as follows:

Firstly, in order to provide a more robust definition of uncontrolled asthma it was decided to only include patients who had an asthma control questionnaire (ACQ) score of ≥1.5 at baseline rather than additionally including patients who had used SABA on more than 5 occasions within 5 or more of the previous 7 days of a 2-week run in. This was because ACQ is a robust and validated tool, whereas SABA use alone could be open to interpretation. This meant that one study of budesonide-formoterol SMART vs budesonide-formoterol plus SABA (O’Byrne et al 2005) did not meet the prespecified criteria for inclusion, as it did not include a measure of asthma control status with ACQ.

Secondly, time-to-first severe exacerbation was chosen as the primary outcome variable for severe exacerbation risk, for the reason it was the primary endpoint in four of the five studies that were included in the meta-analysis.

In the study by O’Byrne et al (n=2,760) that was not included, budesonide-formoterol SMART prolonged time-to-first severe exacerbation, resulting in a 45% lower exacerbation risk versus budesonide-formoterol + SABA (HR 0.55; 95% CI, 0.44, 0.67; p<0.001; primary endpoint). This risk reduction was similar to those observed in the overall populations of the studies included in our submitted report, suggesting that if it had been included, it may not have significantly influenced the results.

Another study by Papi et al (n=1,714) evaluated the SMART regimen with a beclomethasone dipropionate-formoterol combination. Beclomethasone-formoterol maintenance and reliever therapy significantly prolonged time-to-first exacerbation, with a 36% reduction in risk (HR 0.64, 95% CI 0.49, 0.82; p=0.0005) compared with beclomethasone-formoterol plus salbutamol as needed. While the study did not fulfil our prespecified treatment of interest (budesonide-formoterol) as per the published PROSPERO protocol, the results from the subpopulation of patients with uncontrolled asthma treated with beclomethasone-formoterol would have been informative. However, as individual patient data from that subpopulation is not available in the public domain, there was no advantage in changing the registered protocol to expand the criteria to include studies of ICS-LABA combinations beyond budesonide-formoterol.

For each patient, the treatment before study entry was classified according to the Global Initiative for Asthma (GINA) report 2018, the current GINA version at the time of the relevant study search (https://ginasthma.org/wp-content/uploads/2019/01/2018-GINA.pdf). Briefly: Step 3: low-dose ICS + one of LABA/eukotriene receptor antagonist (LTRA)/xanthine, or medium/high-dose ICS, Step 4: medium- to high-dose ICS plus LABA or medium- to high-dose ICS with LTRA/xanthine. GINA 2018 also recommended
add on tiotropium (long-acting muscarinic antagonist or LAMA) for patients aged >12 years at Step 4, but tiotropium was not approved for asthma at the time the studies were conducted, so none of the patients included in the analysis were treated with a LAMA.
### eTable 1. Details of the studies that were included in the analysis and the studies that did not meet the prespecified criteria for inclusion.

| Study      | Study type                     | Randomized treatment* | Total number of patients randomized (SMART & Control groups) in the original studies | Time-to-first exacerbation in the overall study population |
|------------|--------------------------------|-----------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------|
|            | **Included studies**           |                       |                                                                                     |                                                          |
| AHEAD⁶     | Randomized, double-blind, parallel-group | BUD-FORM 160/4.5 µg x2 bid + as-needed BUD-FORM | 2309 (SMART: 1154, FLU-SAL: 1155)                                                  | SMART vs SAL-FLU + SABA (HR 0.82; 95% CI 0.63, 1.05, p=0.12) |
|            |                                | FLU-SAL 500/50 µg x1 bid + as-needed TERB 0.4 mg |                                                                                      |                                                          |
| COMPASS²   | Randomized, double-blind, double-dummy, parallel-group | BUD-FORM 160/4.5 µg x2 bid + as-needed BUD-FORM | 3335 (SMART: 1107, FLU-SAL: 1123, BUD-FORM: 1105)                                | SMART vs SAL-FLU + SABA (HR 0.67, 95% CI 0.52, 0.87, p=0.003) |
|            |                                | FLU-SAL 125/25 µg x2 bid + as-needed TERB 0.4 mg |                                                                                      | SMART vs BUD-FORM + SABA (HR 0.74, 95% CI 0.56, 0.96, p=0.026) |
|            |                                | BUD-FORM 320/9 µg x1 bid + as-needed TERB 0.4 mg |                                                                                      |                                                          |
| PATEL²     | Randomized, open-label, parallel-group | SMART – BUD-FORM 200/6 µg x2 bid + as-needed BUD-FORM | 303 (SMART: 151, BUD-FORM: 152)                                                   | SMART vs BUD-FORM + SABA (HR 0.53, 95% CI 0.33, 0.84, p=0.008) |
|            |                                | Control – BUD-FORM 200/6 µg x2 bid + as-needed SALB 100 µg |                                                                               |                                                          |
| SAKURA⁸    | Randomized, double-blind, parallel-group | SMART – BUD-FORM 160/4.5 µg x1 bid + as-needed BUD-FORM | 2091 (SMART: 1049, BUD-FORM: 1042)                                               | SMART vs BUD-FORM + SABA (HR 0.70, 95% CI 0.57, 0.85, p=0.0003) |
|            |                                | Control – BUD-FORM 160/4.5 µg x1 bid + as-needed TERB 0.4 mg |                                                                                     |                                                          |
| SMILE³     | Randomized, double-blind, parallel-group | SMART – BUD-FORM 160/4.5 µg x1 bid + as-needed BUD-FORM | 3394 (SMART: 1113, BUD-FORM: 1141)                                               | SMART vs BUD-FORM + SABA (HR 0.55, 95% CI 0.45, 0.68, p<0.0001) |
|            |                                | Control – BUD-FORM 160/4.5 µg x1 bid + as-needed TERB 0.4 mg |                                                                                     |                                                          |

### Studies not meeting the prespecified criteria for inclusion

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| Study | Design | Treatment 1 | Treatment 2 | Control | HR (95% CI, p-value) |
|-------|--------|-------------|-------------|---------|---------------------|
| PAPI 4 | Randomized, double-blind, parallel group | SMART – BECLO-FORM 100/6 µg* bid + as-needed BECLO-FORM 100/6 µg | 1714 (SMART: 852, BECLO-FORM + SABA: 849) | BECLO-FORM + BECLO-FORM as needed vs BECLO-FORM + SABA (HR 0.64, 95% CI 0.49, 0.82, p=0.0005) |
| Control - BECLO-FORM 100/6 µg* bid + as-needed albuterol 100 µg | Control - BUD 160 µg x 2 bid + as-needed TERB 0.4 mg |
| STAY 3 | Randomized, double-blind, parallel-group | SMART – BUD-FORM 80/4.5 µg bid + as-needed BUD-FORM 80/4.5 µg | 2760 (SMART: 925, BUD-FORM + SABA: 909) | BUD/FORM + BUD-FORM as needed vs BUD-FORM + TERB (HR 0.55, 95% CI 0.44, 0.67, p<0.001) |
| Control – BUD-FORM 80/4.5 µg bid + as-needed TERB 0.4 mg |

Albuterol, US name for salbutamol; BECLO-FORM, beclometasone-formoterol; bid, twice daily; BUD-FORM, budesonide-formoterol; CI, confidence interval; GINA, Global Initiative for Asthma; HR, hazard ratio; ICS, inhaled corticosteroid; SABA, short-acting β₂-agonist; SALB, salbutamol. SMART, single maintenance and reliever therapy; TERB, terbutaline.

*In the Papi et al study, doses of beclometasone-formoterol are given as metered doses. In all other studies, they are given as delivered doses.
### eTable 2. *Post hoc* comparison of the two treatment arms included in the pooled data from COMPASS

| Variable                  | GINA Step at entry | Comparators                                                                 | Hazard ratio (95% CI) | P value |
|---------------------------|--------------------|-----------------------------------------------------------------------------|-----------------------|---------|
| Time-to-first exacerbation| GINA 3 (Step up)   | BUD-FORM 320/9 µg 1 inh bid + TERB 0.4 mg vs                               | 0.84 (0.55, 1.29)     | p=0.43  |
|                           | GINA 4 (same Step) | FLU-SAL 125/25 µg 2 inh bid + TERB 0.4 mg                                  | 0.83 (0.57, 1.20)     | p=0.32  |
| Number of exacerbations   | GINA 3 (Step up)   | BUD-FORM 320/9 µg 1 inh bid + TERB 0.4 mg vs                               | 0.83 (0.53, 1.29)     | p=0.40  |
|                           | GINA 4 (same Step) | FLU-SAL 125/25 µg 2 inh bid + TERB 0.4 mg                                  | 0.76 (0.46, 1.25)     | p=0.28  |

BUD-FORM, budesonide-formoterol; CI, confidence interval; FLU-SAL, fluticasone-salmeterol; GINA, Global Initiative for Asthma; inh, inhalation; TERB, terbutaline.
eTable 3. Summary of demographic variables and baseline characteristics for pooled population and by study (patients with ACQ-5 ≥1.5 included in this analysis)

| Variable                              | AHEAD<sup>*</sup> (n=1419) | COMPASS<sup>7</sup> (n=2160) | PATEL<sup>2</sup> (n=154) | SAKURA<sup>8</sup> (n=466) | SMILE<sup>9</sup> (n=664) | Total (n=4863) |
|---------------------------------------|-----------------------------|-------------------------------|---------------------------|---------------------------|---------------------------|----------------|
| GINA step at entry, n (%)             |                             |                               |                           |                           |                           |                |
| 3                                     | 744 (52.4)                  | 1146 (53.1)                   | 60 (39.0)                 | 466 (100.0)               | 664 (100.0)               | 3080 (63.3)    |
| 4                                     | 675 (47.6)                  | 1014 (46.9)                   | 94 (61.0)                 | 0 (0.0)                   | 0 (0.0)                   | 1783 (36.7)    |
| Sex, female, n (%)                    | 901 (63.5)                  | 1299 (60.1)                   | 112 (72.7)                | 311 (66.7)                | 411 (61.9)                | 3034 (62.4)    |
| Age, years, mean (SD)                 | 39.2 (16.3)                 | 38.4 (16.5)                   | 40.1 (14.2)               | 46.1 (14.7)               | 41.3 (16.2)               | 39.8 (16.3)    |
| FEV<sub>1</sub>, % of predicted normal, mean (SD) | 69.63 (13.35) | 72.37 (13.72) | 78.03 (19.20) | 70.65 (14.63) | 72.07 (12.83) | 71.55 (13.89) |
| Reversibility, %, mean (SD)           | 24.36 (11.74)               | 24.64 (12.78)                 | 7.73 (19.43)              | 23.58 (12.19)             | 23.96 (12.76)             | 23.84 (13.01)  |
| ACQ (0–5), mean (SD)                  | 2.43 (0.68)                 | 2.51 (0.70)                   | 2.59 (0.85)               | 2.40 (0.68)               | 2.37 (0.61)               | 2.46 (0.69)    |
| Smoking status, n (%)                 |                             |                               |                           |                           |                           |                |
| Never                                 | 1169 (82.4)                 | 1684 (78.0)                   | 63 (40.9)                 | 417 (89.5)                | 534 (80.4)                | 3867 (79.5)    |
| Previous                              | 191 (13.5)                  | 354 (16.4)                    | 45 (29.2)                 | 13 (2.8)                  | 88 (13.3)                 | 691 (14.2)     |
| Current/Habitual                      | 59 (4.2)                    | 122 (5.7)                     | 46 (29.9)                 | 36 (7.7)                  | 42 (6.3)                  | 305 (6.3)      |
| Pack-years, n, mean (SD)              | 4.2 (3.4)                   | 4.5 (2.9)                     | 9.3 (9.7)                 | 4.0 (2.6)                 | 4.8 (3.4)                 | 4.9 (4.4)      |

Smoking status given as occasional smoker has been reclassified to the Current category.

Note that for SMILE and SAKURA patients on GINA Step 4 at entry are not included since this corresponds to a step down on the GINA treatment step.

ACQ, asthma control questionnaire; FEV<sub>1</sub>, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; SD, standard deviation.
eTable 4. Summary of demographic variables and baseline characteristics for pooled population and by study (all patients)

| Variable                          | AHEAD<sup>6</sup> (n=2304) | COMPASS<sup>7</sup> (n=3319) | PATEL<sup>2</sup> (n=303) | SAKURA<sup>8</sup> (n=2091) | SMILE<sup>9</sup> (n=2245) | Total (n=10262) |
|----------------------------------|-----------------------------|-----------------------------|---------------------------|----------------------------|---------------------------|-----------------|
| **GINA step at entry, n (%)**    | 3 1244 (54.0)               | 1735 (52.3)                 | 108 (35.6)                | 719 (34.4)                 | 1154 (51.4)               | 4960 (48.3)     |
|                                  | 4 1057 (45.9)               | 1580 (47.6)                 | 163 (53.8)                | 1333 (63.7)                | 1071 (47.7)               | 5204 (50.7)     |
| **Sex, female, n (%)**           | 1419 (61.6)                 | 1918 (57.8)                 | 209 (69.0)                | 1414 (67.6)                | 1363 (60.7)               | 6323 (61.6)     |
| **Age, years, mean (SD)**        | 39.5 (16.7)                 | 38.0 (16.9)                 | 42.0 (14.1)               | 45.6 (14.5)                | 42.1 (16.2)               | 40.9 (16.4)     |
| **FEV<sub>1</sub>, % of predicted normal, mean (SD)** | 70.55 (14.10)               | 72.61 (13.78)               | 81.00 (19.70)             | 69.91 (14.21)              | 71.87 (13.03)             | 71.68 (14.12)   |
| **Reversibility, %, mean (SD)**  | 23.88 (11.66)               | 23.90 (12.53)               | 5.46 (16.14)              | 22.82 (11.67)              | 23.77 (11.92)             | 23.11 (12.54)   |
| **ACQ (0–5), mean (SD)**         | 1.86 (0.95)                 | 1.98 (0.98)                 | 1.78 (1.12)               | 1.85 (0.90)                | 1.91 (0.88)               | 1.91 (0.94)     |
| **Smoking status, n (%)**        | Never 1897 (82.3)           | 2627 (79.2)                 | 147 (48.5)                | 1780 (85.1)                | 1750 (78.0)               | 8201 (79.9)     |
|                                  | Previous 305 (13.2)         | 512 (15.4)                  | 97 (32.0)                 | 82 (3.9)                   | 351 (15.6)                | 1347 (13.1)     |
|                                  | Current/Habitual 102 (4.4)  | 180 (5.4)                   | 59 (19.5)                 | 229 (11.0)                 | 144 (6.4)                 | 714 (7.0)       |
| **Pack-years, n, mean (SD)**     | 4.4 (3.6)                   | 4.5 (2.9)                   | 9.2 (9.8)                 | 4.8 (2.8)                  | 5.0 (3.0)                 | 5.0 (4.2)       |

Smoking status given as occasional smoker has been reclassified to the Current category.

Note that for SMILE and SAKURA patients on GINA Step 4 at entry are not included since this corresponds to a step down on the GINA treatment step.

ACQ, asthma control questionnaire; FEV<sub>1</sub>, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; SD, standard deviation.

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eFigure 1. Pooled analysis (without the Patel\(^2\) study) of SMART vs ICS-LABA maintenance plus SABA therapy (step up to GINA 4) for a) time to first severe exacerbation by study; b) number (rate) of exacerbations by study; c) difference in ACQ (0–5); d) difference in FEV\(_1\) (L)

| Study     | SMART  | GINA 4 | HR (95% CI) | P Value |
|-----------|--------|--------|-------------|---------|
| AHEAD     | 29/371 (7.8) | 38/373 (10.2) | 0.77 (0.48, 1.25) | 0.30    |
| COMPASS   | 29/372 (7.8) | 84/774 (10.9) | 0.71 (0.46, 1.08) | 0.11    |
| Pooled    | 58/743 (7.8) | 122/1147 (10.6) | 0.73 (0.53, 1.01) | 0.06    |

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| Study   | SMART | GINA 4 | RR (95% CI) | P Value |
|---------|-------|--------|-------------|---------|
| AHEAD   | 371 (0.22) | 373 (0.27) | 0.81 (0.48, 1.37) | 0.43    |
| COMPASS | 372 (0.26) | 774 (0.33) | 0.78 (0.50, 1.24) | 0.30    |
| Pooled  | 743 (0.24) | 1147 (0.30) | 0.79 (0.56, 1.12) | 0.19    |

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c)

![Graph showing the difference in ACQ (0-5) for SMART vs step up to GINA 4 over months since randomization.]

- Y-axis: Difference in ACQ (0-5)
- X-axis: Months since randomization

The graph shows a downward trend in the difference in ACQ score over time.

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d)

![Graph showing the difference in FEV1 (L) for SMART vs step up to GINA 4 over months since randomization.]

- Y-axis: Difference in FEV1 (L)
- X-axis: Months since randomization

The graph shows an upward trend in the difference in FEV1 score over time.

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ACQ, Asthma Control Questionnaire; CI, confidence intervals; FEV₁, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; HR, hazard ratio; RR, rate ratio; SMART, single inhaler combination ICS-formoterol maintenance and reliever therapy.

ACQ-5 and FEV₁ are shown as means +/- 95% CI. The dotted line represents the minimal clinically important differences.
eFigure 2. Kaplan-Meier survival curves for the pooled analysis of SMART vs ICS-LABA maintenance plus SABA therapy for a) step up to GINA 4); b) same step GINA 3 or 4

a)

b)

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GINA, Global Initiative for Asthma; SMART, single inhaler combination ICS-formoterol maintenance and reliever therapy.
**eFigure 3.** Pooled analysis of SMART vs ICS-LABA maintenance plus SABA therapy for number (rate) of exacerbations by study for a) step up to GINA 4; b) same step GINA 3 or 4

| Study | SMART N (rate per year) | GINA 4 N (rate per year) | RR (95% CI) | P Value |
|-------|-------------------------|--------------------------|-------------|---------|
| AHEAD | 371 (0.22)              | 373 (0.27)               | 0.81 (0.48, 1.37) | 0.43    |
| COMPASS | 372 (0.26)          | 774 (0.33)               | 0.78 (0.50, 1.24) | 0.30    |
| PATEL | 38 (0.45)              | 22 (0.77)                | 0.58 (0.16, 2.08) | 0.40    |
| Pooled | 781 (0.31)            | 1169 (0.40)              | 0.78 (0.56, 1.10) | 0.16    |
CI, confidence intervals; GINA, Global Initiative for Asthma; RR, rate ratio; SMART, single inhaler combination ICS-formoterol maintenance and reliever therapy.
eFigure 4. Pooled analysis (without the Patel² study) of SMART vs ICS-LABA maintenance plus SABA therapy (same step GINA 3 or 4) for a) time to first severe exacerbation by study; b) number (rate) of exacerbations by study; c) difference in ACQ (0–5); d) difference in FEV₁ (L)

a)

| Study   | SMART | GINA 3 or 4 | HR (95% CI) | P Value |
|---------|-------|-------------|-------------|---------|
|         |       |             |             |         |
|         |       | No exa./N (%)| No exa./N (%)|         |
| AHEAD   | 40/327 (12.2) | 61/348 (17.5) | 0.67 (0.45, 1.00) | 0.05 |
| COMPASS | 41/333 (12.3) | 108/681 (15.9) | 0.77 (0.53, 1.10) | 0.15 |
| SAKURA  | 35/251 (13.9) | 38/215 (17.7) | 0.77 (0.49, 1.22) | 0.26 |
| SMILE   | 42/339 (12.4) | 58/325 (17.8) | 0.64 (0.43, 0.96) | 0.03 |
| Pooled  | 158/1250 (12.6) | 265/1569 (16.9) | 0.71 (0.58, 0.87) | <0.001 |

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b)

| Study    | SMART N (rate per year) | GINA 3 or 4 N (rate per year) | RR (95% CI) | P Value |
|----------|-------------------------|-------------------------------|-------------|---------|
| AHEAD    | 327 (0.34)              | 348 (0.53)                    | 0.64 (0.42, 0.99) | 0.04    |
| COMPASS  | 333 (0.33)              | 681 (0.62)                    | 0.53 (0.35, 0.81) | 0.004   |
| SAKURA   | 251 (0.19)              | 215 (0.27)                    | 0.72 (0.44, 1.17) | 0.19    |
| SMILE    | 339 (0.17)              | 325 (0.31)                    | 0.55 (0.36, 0.86) | 0.008   |
| Pooled   | 1250 (0.25)             | 1569 (0.41)                   | 0.60 (0.48, 0.75) | <0.001  |
ACQ, Asthma Control Questionnaire; CI, confidence intervals; FEV₁, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; HR, hazard ratio; RR, rate ratio; SMART, single inhaler combination ICS-formoterol maintenance and reliever therapy.

ACQ-5 and FEV₁ are shown as means +/- 95% CI. The dotted line represents the minimal clinically important differences.
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