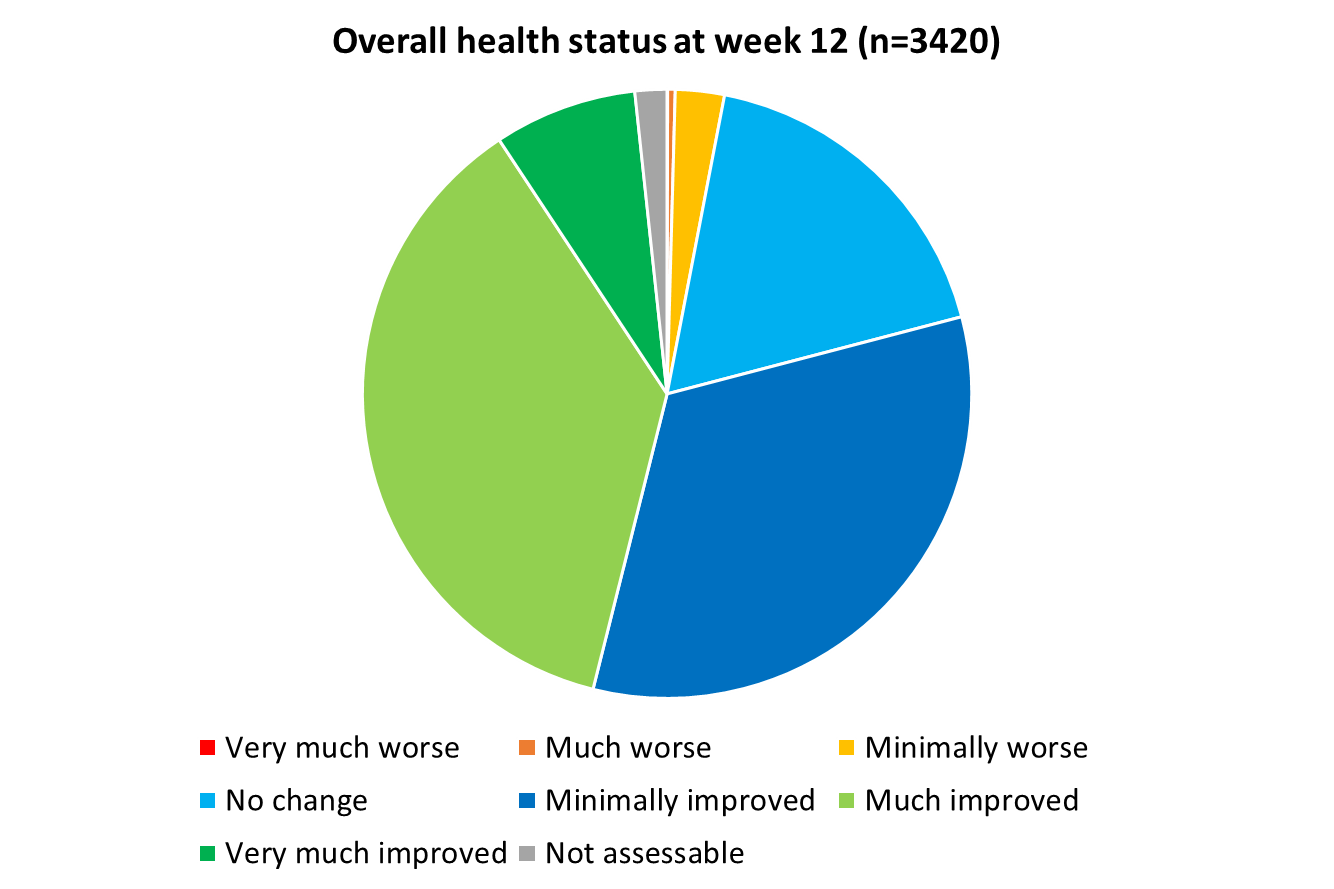
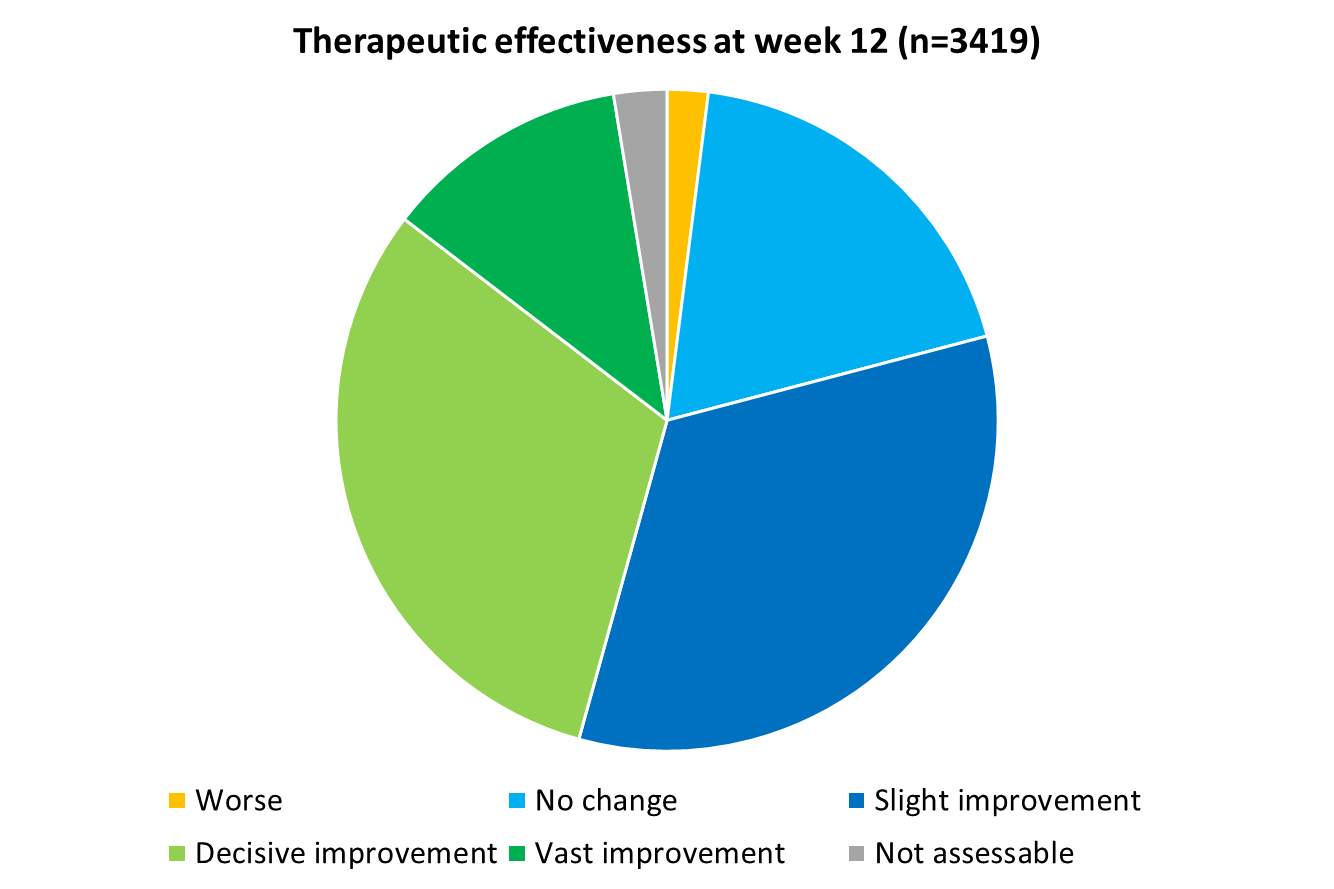
**ONLINE SUPPLEMENT**

**Supplemental Figure S1.** Change from baseline in CGI-assessed overall health status **(A)**, therapeutic effectiveness **(B)**, and therapeutic risks **(C)** at week 12.

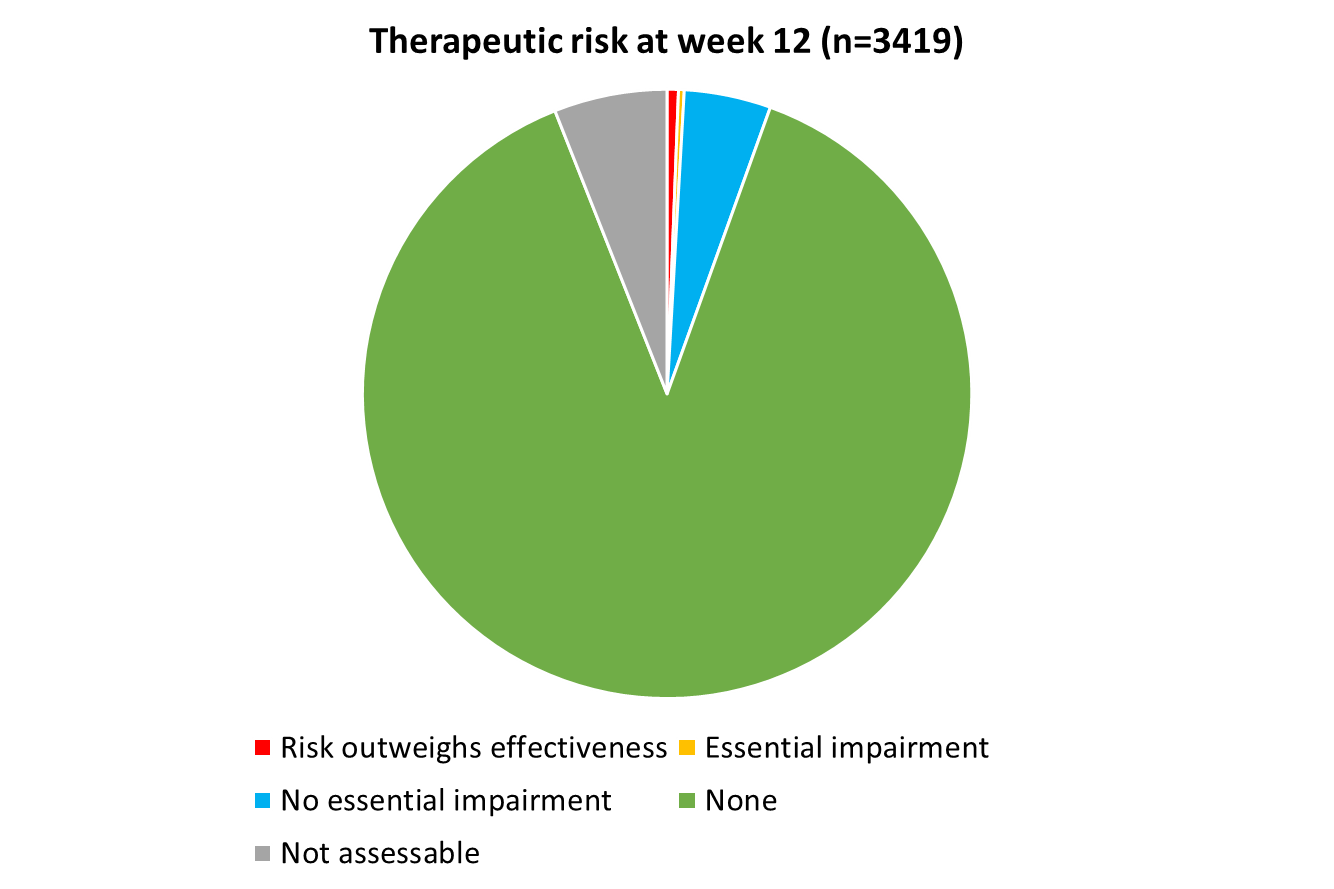
**(A)**

****

**(B)**



**(C)**

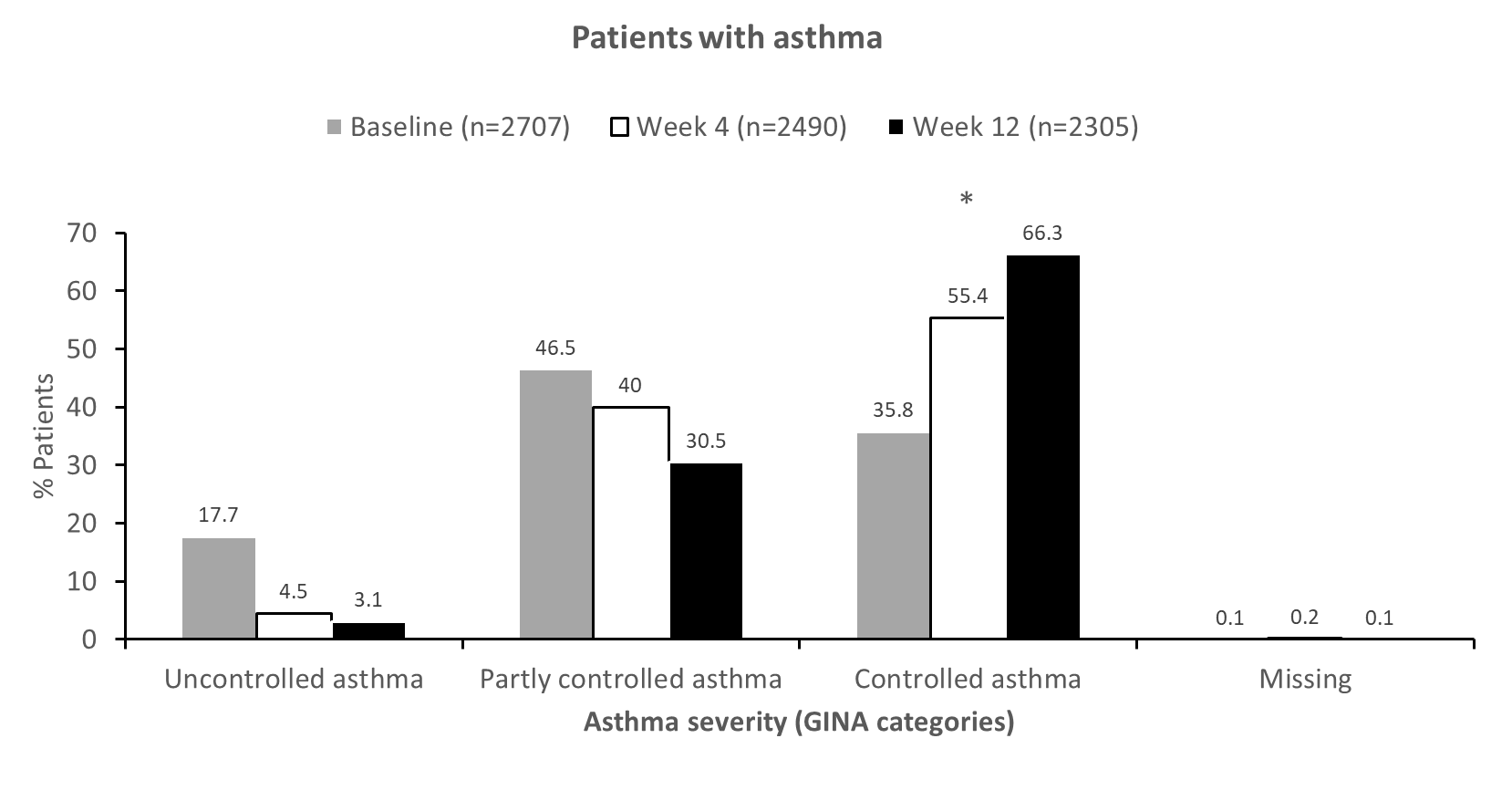


CGI, Clinical Global Impression Scale.

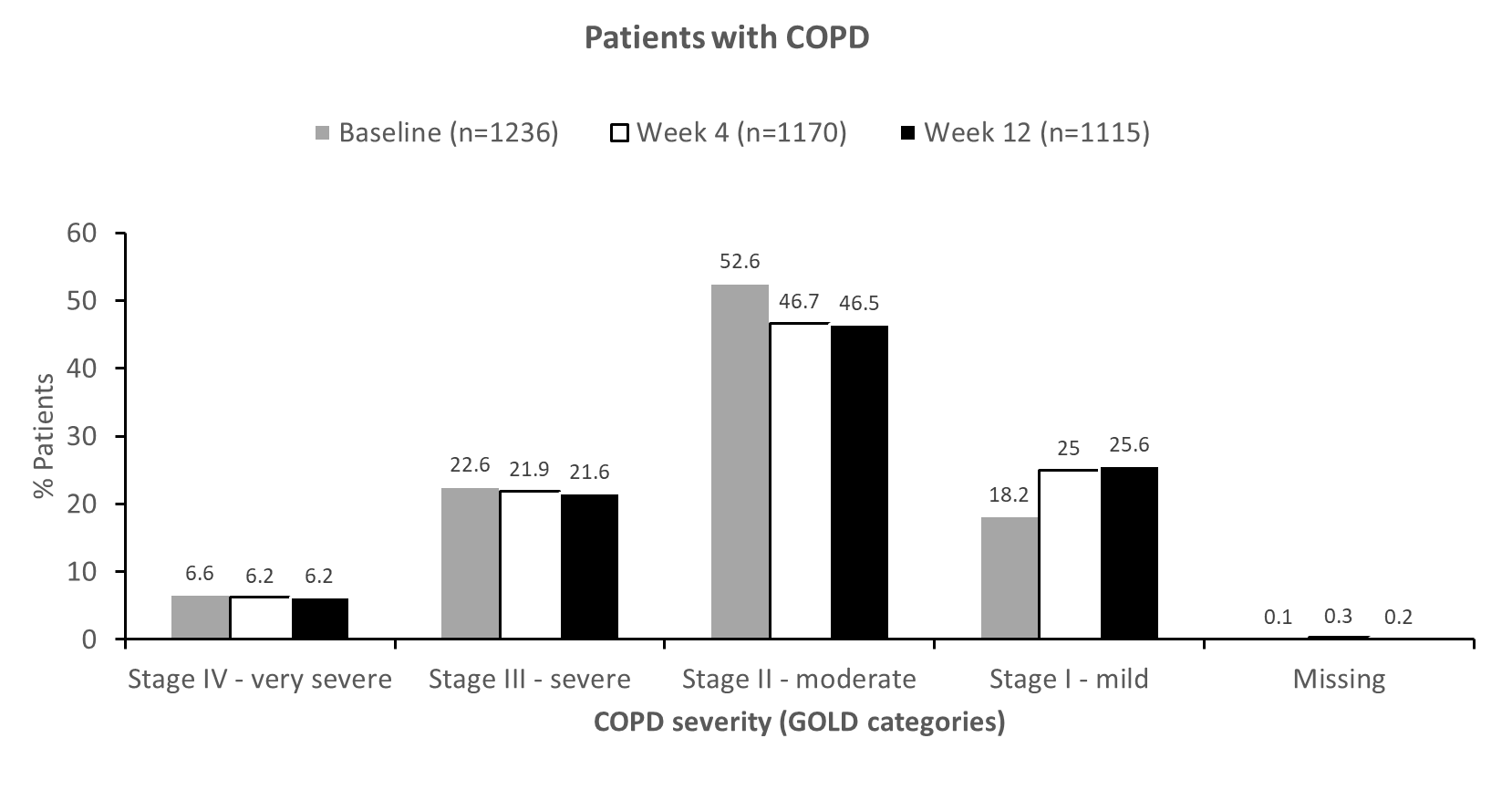
Essential impairment denotes significant interference with the patient’s functioning.

**Supplemental Figure S2.** Guideline-defined asthma control **(A)** and COPD disease severity **(B)** (as rated by physicians) at baseline, week 4, and week 12.

**(A)**



**(B)**



\* *p* < 0.0001 for the proportion of patients with controlled asthma and valid documentation at each visit.

COPD, chronic obstructive pulmonary disease; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

**Supplemental Table S1.** Frequency of inhalation (inhalations in the morning–evening) in the FAS at baseline, second visit, and last documentation.

| **Inhalations: mornings-evenings** | **Baseline** | | **Week 4** | | **Week 12** | |
| --- | --- | --- | --- | --- | --- | --- |
| ***N*** | **%** | ***N*** | **%** | ***N*** | **%** |
| **Total** | 3,943 | 100.0 | 3,660 | 100.0 | 3,420 | 100.0 |
| 0–0 | 2 | 0.1 | 12 | 0.3 | 7 | 0.2 |
| 0–1 | 6 | 0.2 | 10 | 0.3 | 9 | 0.3 |
| 0–2 | 1 | <0.1 | 0 | - | 0 | - |
| 1–0 | 96 | 2.4 | 84 | 2.3 | 80 | 2.3 |
| 1–1 | 3,082 | 78.2 | 2,898 | 79.2 | 2,710 | 79.2 |
| 1–2 | 7 | 0.2 | 8 | 0.2 | 6 | 0.2 |
| 2–0 | 14 | 0.4 | 11 | 0.3 | 8 | 0.2 |
| 2–1 | 50 | 1.3 | 48 | 1.3 | 48 | 1.4 |
| 2–2 | 632 | 16.0 | 547 | 14.9 | 514 | 15.0 |
| 4–4 | 1 | <0.1 | 0 | - | 0 | - |
| Missing | 52 | 1.3 | 42 | 1.1 | 38 | 1.1 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Supplemental Table S2.** Severity of illness, as assessed by the Clinical Global Impression Scale, in the FAS | | | | | | |
| Severity of disease | Baseline | | Week 4 | | Week 12 | |
| *n* | % | *n* | % | *n* | % |
| Total | 3,943 | 100.0 | 3,660 | 100.0 | 3,420 | 100.0 |
| Missing | 2 | 0.1 | 1 | <0.1 | 1 | <0.1 |
| Not assessable | 56 | 1.4 | 41 | 1.1 | 41 | 1.2 |
| Normal, not at all ill | 31 | 0.8 | 52 | 1.4 | 67 | 2.0 |
| Borderline mentally ill | 94 | 2.4 | 171 | 4.7 | 203 | 5.9 |
| Mildly ill | 1057 | 26.8 | 1397 | 38.2 | 1422 | 41.6 |
| Moderately ill | 1740 | 44.1 | 1408 | 38.5 | 1168 | 34.2 |
| Markedly ill | 796 | 20.2 | 466 | 12.7 | 406 | 11.9 |
| Severely ill | 151 | 3.8 | 111 | 3.0 | 99 | 2.9 |
| Among the most extremely ill patients | 16 | 0.4 | 13 | 0.4 | 13 | 0.4 |

FAS, full analysis set.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Supplemental Table S3.** Patient-reported asthma control (as assessed by ACT). | | | | | | |
|  | Baseline | | Week 4 | | Week 12 | |
| *n* | % | *n* | % | *n* | % |
| Total | 2,200 | 100.0 | 2,033 | 100.0 | 1,886 | 100.0 |
| Question 1 (impairment)\* |  |  |  |  |  |  |
| All of the time | 99 | 4.5 | 23 | 1.1 | 20 | 1.1 |
| Most of the time | 388 | 17.6 | 119 | 5.9 | 81 | 4.3 |
| Some of the time | 829 | 37.7 | 624 | 30.7 | 404 | 21.4 |
| A little of the time | 462 | 21.0 | 668 | 32.9 | 718 | 38.1 |
| None of the time | 378 | 17.2 | 517 | 25.4 | 595 | 31.5 |
| Question 2 (shortness of breath)\* |  |  |  |  |  |  |
| More than once a day | 426 | 19.4 | 162 | 8.0 | 89 | 4.7 |
| Once a day | 339 | 15.4 | 199 | 9.8 | 148 | 7.8 |
| 3 to 6 times a week | 512 | 23.3 | 356 | 17.5 | 242 | 12.8 |
| Once or twice a week | 639 | 29.0 | 837 | 41.2 | 850 | 45.1 |
| Not at all | 240 | 10.9 | 395 | 19.4 | 490 | 26.0 |
| Question 3 (night-time symptoms)\* |  |  |  |  |  |  |
| 4 or more nights a week | 286 | 13.0 | 75 | 3.7 | 49 | 2.6 |
| 2 to 3 nights a week | 465 | 21.1 | 211 | 10.4 | 139 | 7.4 |
| Once a week | 364 | 16.5 | 331 | 16.3 | 215 | 11.4 |
| Once or twice in the previous 4 weeks | 435 | 19.8 | 553 | 27.2 | 547 | 29.0 |
| Not at all | 607 | 27.6 | 780 | 38.4 | 871 | 46.2 |
| Question 4 (rescue medication use)\* |  |  |  |  |  |  |
| 3 or more times per day | 160 | 7.3 | 35 | 1.7 | 26 | 1.4 |
| 1 or 2 times per day | 427 | 19.4 | 232 | 11.4 | 145 | 7.7 |
| 2 or 3 times per week | 398 | 18.1 | 363 | 17.9 | 237 | 12.6 |
| Once a week or less | 410 | 18.6 | 579 | 28.5 | 639 | 33.9 |
| Not at all | 741 | 33.7 | 735 | 36.2 | 771 | 40.9 |
| Question 5 (asthma control)\* |  |  |  |  |  |  |
| Not controlled at all | 131 | 6.0 | 13 | 0.6 | 12 | 0.6 |
| Poorly controlled | 401 | 18.2 | 76 | 3.7 | 42 | 2.2 |
| Somewhat controlled | 769 | 35.0 | 550 | 27.1 | 341 | 18.1 |
| Well controlled | 630 | 28.6 | 919 | 45.2 | 924 | 49.0 |
| Completely controlled | 220 | 10.0 | 389 | 19.1 | 502 | 26.6 |

\*Questionnaire was not available or data were missing in <5% of patients. Question 1: In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home? Question 2: During the past 4 weeks, how often have you had shortness of breath? Question 3: During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning? Question 4: During the past 4 weeks, how often have you used your rescue inhaler or nebuliser medication (such as albuterol) Question 5: How would you rate your asthma control during the past 4 weeks?

ACT, Asthma Control Test.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Supplemental Table S4.** Patient-reported COPD symptom control (as assessed by CAT). | | | | | | | | |
|  | *n* | Mean | SD | Min | Q1 | Median | Q3 | Max |
| Cough | | | | | | | | |
| Baseline | 921 | 2.7 | 1.3 | 0.0 | 2.0 | 3.0 | 4.0 | 5.0 |
| Week 4 | 870 | 2.1 | 1.1 | 0.0 | 1.0 | 2.0 | 3.0 | 5.0 |
| Week 12 | 821 | 2.0 | 1.1 | 0.0 | 1.0 | 2.0 | 3.0 | 5.0 |
| Phlegm in chest | | | | | | | | |
| Baseline | 922 | 2.6 | 1.3 | 0.0 | 2.0 | 3.0 | 4.0 | 5.0 |
| Week 4 | 870 | 2.0 | 1.2 | 0.0 | 1.0 | 2.0 | 3.0 | 5.0 |
| Week 12 | 823 | 1.9 | 1.2 | 0.0 | 1.0 | 2.0 | 3.0 | 5.0 |
| Chest tightness | | | | | | | | |
| Baseline | 922 | 2.0 | 1.4 | 0.0 | 1.0 | 2.0 | 3.0 | 5.0 |
| Week 4 | 867 | 1.6 | 1.3 | 0.0 | 0.0 | 2.0 | 2.0 | 5.0 |
| Week 12 | 821 | 1.5 | 1.2 | 0.0 | 0.0 | 1.0 | 2.0 | 5.0 |
| Shortness of breath while climbing one flight of stairs | | | | | | | | |
| Baseline | 922 | 3.4 | 1.3 | 0.0 | 3.0 | 4.0 | 5.0 | 5.0 |
| Week 4 | 870 | 2.9 | 1.4 | 0.0 | 2.0 | 3.0 | 4.0 | 5.0 |
| Week 12 | 823 | 2.7 | 1.5 | 0.0 | 2.0 | 3.0 | 4.0 | 5.0 |
| Limited activities at home | | | | | | | | |
| Baseline | 921 | 2.4 | 1.5 | 0.0 | 1.0 | 3.0 | 4.0 | 5.0 |
| Week 4 | 866 | 1.9 | 1.4 | 0.0 | 1.0 | 2.0 | 3.0 | 5.0 |
| Week 12 | 823 | 1.8 | 1.4 | 0.0 | 1.0 | 2.0 | 3.0 | 5.0 |
| Confidence leaving home despite lung condition | | | | | | | | |
| Baseline | 921 | 1.4 | 1.4 | 0.0 | 0.0 | 1.0 | 3.0 | 5.0 |
| Week 4 | 869 | 1.2 | 1.3 | 0.0 | 0.0 | 1.0 | 2.0 | 5.0 |
| Week 12 | 821 | 1.1 | 1.2 | 0.0 | 0.0 | 1.0 | 2.0 | 5.0 |
| Sleep quality | | | | | | | | |
| Baseline | 921 | 2.1 | 1.5 | 0.0 | 1.0 | 2.0 | 3.0 | 5.0 |
| Week 4 | 869 | 1.8 | 1.3 | 0.0 | 1.0 | 2.0 | 3.0 | 5.0 |
| Week 12 | 823 | 1.6 | 1.3 | 0.0 | 0.0 | 2.0 | 3.0 | 5.0 |
| Energy level | | | | | | | | |
| Baseline | 920 | 2.6 | 1.4 | 0.0 | 2.0 | 3.0 | 4.0 | 5.0 |
| Week 4 | 868 | 2.2 | 1.3 | 0.0 | 1.0 | 2.0 | 3.0 | 5.0 |
| Week 12 | 821 | 2.2 | 1.3 | 0.0 | 1.0 | 2.0 | 3.0 | 5.0 |
| CAT parameter | Change from baseline at week 12 | | | | | | | |
| *N* | Mean difference | 95% CI | SD | 95% CL of the SD | Max | Min | *p*-value |
| Cough | 775 | –0.75 | –0.84, –0.66 | 1.25 | 1.19, 1.31 | –5.0 | +5.0 | <0.0001 |
| Phlegm in chest | 778 | –0.69 | –0.77, –0.60 | 1.25 | 1.19, 1.31 | –5.0 | +4.0 | <0.0001 |
| Chest tightness | 776 | –0.55 | –0.64, –0.46 | 1.23 | 1.69, 1.29 | –5.0 | +5.0 | <0.0001 |
| Shortness of breath while climbing a flight of stairs | 777 | –0.74 | –0.82, –0.66 | 1.13 | 1.07, 1.19 | –5.0 | +4.0 | <0.0001 |
| Limited daily activities | 777 | –0.61 | –0.70, –0.52 | 1.26 | 1.20, 1.33 | –5.0 | +5.0 | <0.0001 |
| Confidence leaving home | 776 | –0.35 | –0.43, –0.27 | 1.16 | 1.11, 1.22 | –5.0 | +5.0 | <0.0001 |
| Sleep quality | 777 | –0.49 | –0.58, –0.40 | 1.29 | 1.12, 1.36 | –5.0 | +5.0 | <0.0001 |
| Energy level | 775 | –0.47 | –0.55, –0.39 | 1.15 | 1.09, 1.21 | –5.0 | +4.0 | <0.0001 |

CAT, COPD assessment test; CI, confidence intervals; CL, confidence limits; COPD, chronic obstructive pulmonary disease; Max, maximum; Min, minimum; Q, quartile; SD, standard deviation

**Supplemental** **Table S5.** Improvements in lung function with B/F Spiromax.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Measure | Baseline | | Week 4 | | Week 12 | | P-value\* |
| *n* | Mean (SD) | *n* | Mean (SD) | *n* | Mean (SD) |
| Vital capacity (% predicted)  Overall population  Asthma  COPD | 3,527  2,473  1,054 | 81.7 (17.5)  85.7 (15.8)  72.3 (17.7) | 2,218  1,516  702 | 84.1 (17.3)  88.5 (15.4)  74.7 (17.3) | 2,508  1,749  759 | 85.3 (17.6)  89.8 (15.3)  75.0 (18.1) | <0.0001  <0.0001  <0.0001 |
| FEV1 pre-bronchodilation (% predicted)  Overall population  Asthma  COPD | 3,209  2,267  942 | 74.4 (19.8)  79.8 (17.4)  61.5 (19.1) | 1,920  1,328  592 | 78.0 (19.7)  84.0 (16.7)  64.6 (19.3) | 2,050  1,446  604 | 79.0 (20.0)  85.1 (16.9)  64.4 (19.3) | <0.0001  <0.0001  <0.0001 |
| FEV1 post-bronchodilation (% predicted)  Overall population  Asthma  COPD | 1,607  1,066  541 | 78.6 (19.0)  84.1 (16.1)  67.7 (19.8) | 938  611  327 | 81.4 (18.0)  86.6 (14.9)  71.8 (19.4) | 1,045  675  370 | 81.3 (19.2)  87.9 (15.1)  69.3 (20.2) | <0.0001  <0.0001  <0.0001 |

\*Two-tailed t-test for comparison between baseline and week 12.

COPD, chronic obstructive pulmonary disease; FAS, full analysis set; FEV1, forced expiratory volume in 1 second; SD, standard deviation.

**Supplemental Table S6.** Incidence of adverse events and adverse drug reactions among the FAS, and in patients with asthma and COPD.

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristic | Overall population (*N* = 3943) | Asthma  (*n* = 2707) | COPD  (*n* = 1236) |
| Non-serious AEs, *n* (%) | 115 (2.9) | 82 (3.0) | 33 (2.7) |
| Serious AEs, *n* (%) | 33 (0.8) | 14 (0.5) | 19 (1.5) |
| Non-serious ADRs, *n* (%) | 113 (2.9) | 88 (3.3) | 25 (2.0) |
| Serious ADRs, *n* (%) | 4 (0.1) | 3 (0.1) | 1 (0.1) |
| Specific non-serious AEs reported in ≥0.2% patients, *n* (%)  Nasopharyngitis  Bronchitis  Asthma  Condition aggravated | 13 (0.33)  10 (0.25)  10 (0.25)  8 (0.20) | 11 (0.41)  6 (0.22)  9 (0.33)  6 (0.22) | 2 (0.16)  4 (0.32)  1 (0.08)  2 (0.16) |
| Specific non-serious ADRs reported in ≥0.2% patients, *n* (%)  Dysphonia  Headache  Cough  Dyspnoea  Muscle spasms | 12 (0.30)  11 (0.28)  10 (0.25)  9 (0.23)  9 (0.23) | 12 (0.44)  11 (0.41)  9 (0.33)  6 (0.22)  8 (0.30) | 0 (0)  0 (0)  1 (0.08)  3 (0.24)  1 (0.08) |
| Specific serious AEs reported in ≥2 patients, *n* (%)\*  COPD  Pneumonia | 3 (0.08)  3 (0.08) | 0 (0)  1 (0.04) | 3 (0.24)  2 (0.16) |

\* No individual serious ADRs were reported in ≥2 patients.

ADR; adverse drug reaction; AE, adverse event; COPD, chronic obstructive pulmonary disease; FAS, full analysis set.