**SUPPLEMENTARY APPENDIX**

**Model inputs**

***Additional drug costs***

Costs of drug treatments for moderate exacerbations and use of salbutamol rescue medication were also included in the analysis. In IMPACT, the majority of patients who experienced a moderate exacerbation received oral corticosteroids and antibiotics, which was estimated to cost C$7.59 per event using costs from the ODB Formulary.19 Rescue medication use was assumed to cost C$0.0250 per inhalation.19

**Table S1. Values for 6MWT equation – ITT population**

The same criteria as the equation for fibrinogen prediction were used to select a version of the regression model to predict 6MWT. The equation with FEV1% predicted was selected over the version with FEV1 volume based on a higher r2 value, and variables that tested at p>0.005 were omitted after the initial test. The final coefficients included in the final model for baseline 6MWT are presented in Table S1.

|  | **Coefficient (βi)** | **Variable (xi) input for ITT** |
| --- | --- | --- |
| β0 | 326.6785 | 1 |
| Age, years | −2.29716 | 65.3 |
| Fibrinogen, μg/dL | −0.07836 | 477.5# |
| FEV1% predicted | 2.0078 | 45.5 |
| Height, cm | 1.11649 | 167.5 |
| Female | −21.2676 | 34% |
| CVD comorbidity | −15.832 | 44% |
| mMRC dyspnea score ≥2 | −72.8311 | 37% |
| BMI category high (>30) | −42.7528 | 25% |
|  | **Estimated mean 6MWT, m** | **365.8** |

#Estimated value based on previous baseline prediction for fibrinogen.

**Abbreviations:** 6MWT, 6-min walk test; BMI, body mass index; CVD, cardiovascular disease; FEV1, forced expiratory volume in 1 s; ITT, intent to treat; mMRC, modified Medical Research Council.

**Table S2. Values for fibrinogen regression equation – ITT population**

To predict baseline fibrinogen concentration, a linear model was developed from a *post hoc* analysis of the ECLIPSE sample baseline data. The model was originally tested using all available concurrent GALAXY baseline variables, including baseline FEV1 in mL or FEV1% predicted. The equation based on the FEV1 volume estimate was selected as the better fitting model (greater value of r2), and baseline values that did not meet p<0.05 in the first fitting were dropped from the final model. The final version of the fibrinogen prediction model is presented in Table S2 and shows the corresponding values used to estimate fibrinogen for the average patient from the IMPACT trial population.

|  |  |  |
| --- | --- | --- |
|  | **Coefficient (βi)** | **Variable (xi) input for ITT** |
| β0 | 408.8547 | 1 |
| Age | 1.5589 | 65.3 |
| FEV1 (volume, L) | −46.8247 | 1.215 |
| Smoking status (1 = current smoker) | 11.0953 | 35% |
| Prior exacerbations (≥1 in previous year) | 14.6866 | 99.9% |
| BMI category high (>30) | 37.6358 | 25% |
| BMI category low (<20) | −25.0056 | 17% |
| **Estimated mean fibrinogen (μg/dL)** | | **477.5** |

**Abbreviations:** BMI, body mass index; FEV1, forced expiratory volume in 1 s; ITT, intent to treat.

**Table S3. Subsequent treatment costs after discontinuation of IMPACT treatment**

|  |  |  |
| --- | --- | --- |
| **Treatment class** | **Renormalized % of patients**  **receiving treatment in IMPACT** | **Average cost weighted by Canadian prescription utilization in regimen class (based on IMS data)** |
| ICS/LAMA/LABA | 57.9% | C$5.2527 |
| ICS/LABA | 25.1% | C$3.5116 |
| LAMA/LABA | 10.3% | C$2.4717 |
| LAMA | 6.7% | C$1.7317 |
| Average weighted cost | 100% | C$4.2944 |

Canadian prescription utilization data were obtained from IMS.20

**Abbreviations:** C$, Canadian dollars; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist.

**Table S4. Sensitivity and scenario analyses: incremental outcomes for FF/UMEC/VI versus FF/VI**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Input value** | **LYs** | | **QALYs** | | **Costs** | | **ICER/QALY gained** | | **Change from base case, %** |
|  | **SA value** | **PA mean**  **(95% CI)** | | **PA mean**  **(95% CI)** | | **PA mean**  **(95% CI)** | | **PA mean**  **(95% CI)** | |  |
| Base-case lifetime |  | *0.1388* | *(0.07, 0.21)* | *0.1371* | *(0.09, 0.18)* | *C$2604* | *(C$1980, C$3285)* | *C$18,989* | *(C$14,665, C$25,753)* | – |
| **Sensitivity analyses** |  |  |  |  |  |  |  |  |  |  |
| Baseline fibrinogen lower CI | 472.83 | 0.1394 | (0.07, 0.21) | 0.1379 | (0.10, 0.18) | C$2602 | (C$2002, C$3267) | C$18,862 | (C$14,691, C$25,358) | −1 |
| Baseline fibrinogen upper CI | 482.10 | 0.1401 | (0.07, 0.21) | 0.1378 | (0.09, 0.18) | C$2602 | (C$1984, C$3278) | C$18,876 | (C$14,633, C$25,739) | −1 |
| Baseline 6MWT lower CI | 360.42 | 0.1381 | (0.07, 0.21) | 0.1369 | (0.09, 0.18) | C$2593 | (C$1981, C$3272) | C$18,937 | (C$14,678, C$25,845) | 0 |
| Baseline 6MWT upper CI | 371.17 | 0.1401 | (0.07, 0.21) | 0.1380 | (0.09, 0.18) | C$2617 | (C$2025, C$3306) | C$18,964 | (C$14,790, C$26,075) | 0 |
| Baseline mMRC dyspnea score ≥2 −25% | 0.278 | 0.1390 | (0.07, 0.21) | 0.1377 | (0.10, 0.18) | C$2623 | (C$2019, C$3307) | C$19,045 | (C$14,814, C$26,018) | 0 |
| Baseline mMRC dyspnea score ≥2 +25% | 0.463 | 0.1388 | (0.07, 0.21) | 0.1371 | (0.09, 0.18) | C$2583 | (C$1985, C$3223) | C$18,834 | (C$14,740, C$25,827) | −1 |
| All hospital costs −25% |  | 0.1391 | (0.07, 0.21) | 0.1374 | (0.09, 0.18) | C$2432 | (C$1956, C$2966) | C$17,693 | (C$13,945, C$23,814) | −7 |
| All hospital costs +25% |  | 0.1392 | (0.07, 0.21) | 0.1376 | (0.09, 0.18) | C$2772 | (C$2043, C$3615) | C$20,141 | (C$15,492, C$27,733) | 6 |
| All physician visits −25% |  | 0.1395 | (0.07, 0.21) | 0.1380 | (010, 0.18) | C$2601 | (C$2005, C$3286) | C$18,842 | (C$14,649, C$25,430) | −1 |
| All physician visits +25% |  | 0.1392 | (0.07, 0.21) | 0.1373 | (0.09, 0.18) | C$2600 | (C$2007, C$3293) | C$18,941 | (C$14,693, C$25,664) | 0 |
| Predicted utility value in each cycle increased by 10% |  | 0.1393 | (0.07, 0.21) | 0.1513 | (0.10, 0.20) | C$2606 | (C$2005, C$3290) | C$17,220 | (C$13,506, C$23,471) | −9 |
| **Scenario analyses** |  |  |  |  |  |  |  |  |  |  |
| 5-year time horizon |  | 0.0287 | (0.01, 0.05) | 0.0676 | (0.05, 0.09) | C$1609 | (C$1347, C$1905) | C$23,800 | (C$17,301, C$34,697) | 25 |
| 10-year time horizon |  | 0.0872 | (0.04, 0.14) | 0.1129 | (0.08, 0.15) | C$2208 | (C$1736, C$2729) | C$19,551 | (C$14,813, C$27,419) | 3 |
| Discount rate 0% |  | 0.1395 | (0.07, 0.21) | 0.1499 | (0.10, 0.20) | C$2790 | (C$2139, C$3527) | C$18,611 | (C$14,463, C$25,204) | −2 |
| Discount rate 3% |  | 0.1393 | (0.07, 0.21) | 0.1272 | (0.09, 0.17) | C$2445 | (C$1894, C$3069) | C$19,231 | (C$14,992, C$26,173) | 1 |
| Background exacerbation rate at 50% | 1st cycle reference treatment: 0.348 for MExac; 0.004 for SExac | 0.1125 | (0.05, 0.17) | 0.1243 | (0.08, 0.17) | C$2601 | (C$2163, C$3123) | C$20,919 | (C$16,709, C$27,976) | 10 |
| Background exacerbation rate at 200% | 1st cycle reference treatment: 2.632 for MExac; 1.735 for SExac | 0.2005 | (0.05, 0.34) | 0.1648 | (0.10, 0.25) | −C$862 | (−C$12,870, C$6,712) | Dominant | (−C$96,758, C$54,534) | – |
| Treatment discontinuation for subsequent years 0% |  | 0.4105 | (0.21, 0.63) | 0.3374 | (0.22, 0.46) | C$6284 | (C$4492, C$8460) | C$18,626 | (C$14,352, C$25,190) | −2 |
| Set treatment effect for subsequent therapies same as SITT |  | 0.0996 | (0.05, 0.15) | 0.1026 | (0.07, 0.14) | C$2362 | (C$1913, C$2877) | C$23,025 | (C$18,241, C$31,265) | 21 |
| For subsequent therapies – assume  100% market share of product with highest cost in each treatment class | 5.31 | 0.1386 | (0.07, 0.21) | 0.1373 | (0.09, 0.18) | C$2332 | (C$1723, C$3019) | C$16,988 | (C$12,867, C$23,201) | −11 |
| For subsequent therapies – assume  100% market share of product with  lowest cost in each treatment class | 3.13 | 0.1389 | (0.07, 0.21) | 0.1373 | (0.09, 0.18) | C$2899 | (C$2298, C$3577) | C$21,123 | (C$16,541, C$29,069) | 11 |
| For subsequent therapies – generic  pricing for FP/SAL DPI (75% of current  cost in weight calculation) | 4.22 | 0.1396 | (0.07, 0.21) | 0.1381 | (0.09, 0.18) | C$2624 | (C$2019, C$3284) | C$18,998 | (C$14,822, C$26,058) | 0 |
| For subsequent therapies – generic  pricing for FP/SAL DPI (35% of current  cost in weighted calculation) | 4.10 | 0.1393 | (0.07, 0.21) | 0.1375 | (0.09, 0.18) | C$2654 | (C$2058, C$3357) | C$19,308 | (C$15,087, C$26,407) | 2 |
| Use utilization-weighted cost of all ICS/LABAs replaced for cost of FF/VI | 3.5116 | 0.1392 | (0.07, 0.21) | 0.1374 | (0.09, 0.18) | C$1820 | (C$1223, C$2509) | C$13,243 | (C$9690, C$18,336) | −30 |
| Use utilization-weighted cost of  ICS/LABAs indicated for COPD replaced  for cost of FF/VI | 3.2760 | 0.1391 | (0.07, 0.21) | 0.1376 | (0.09, 0.18) | C$2059 | (C$1451, C$2715) | C$14,969 | (C$11,324, C$20,589) | −21 |

**Abbreviations:** 6MWT, 6-min walk test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; C$, Canadian dollars; DPI, dry-powder inhaler; FF, fluticasone furoate; FP, fluticasone propionate; ICER, incremental cost-effective ratio; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LY, life year; MExac, moderate exacerbation; mMRC, modified Medical Research Council; PA, probability analyses; QALY, quality-adjusted life year; SA, sensitivity analysis; SAL, salmeterol; SExac, severe exacerbation; SITT, single-inhaler triple therapy; UMEC, umeclidinium; VI: vilanterol.

**Table S5. Sensitivity and scenario analyses: incremental outcomes for FF/UMEC/VI versus UMEC/VI**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Input value** | **LYs** | | **QALYs** | | **Costs** | | **ICER/QALY gained** | | **Change from base case, %** |
|  | **SA value** | **PA mean**  **(95% CI)** | | **PA mean**  **(95% CI)** | | **PA mean**  **(95% CI)** | | **PA mean**  **(95% CI)** | |  |
| Base-case lifetime |  | *0.1177* | *(0.05, 0.19)* | *0.1282* | *(0.08, 0.18)* | *C$1766* | *(C$1167, C$2336)* | *C$13,776* | *(C$9787, C$19,448)* | *–* |
| **Sensitivity analyses** |  |  |  |  |  |  |  |  |  |  |
| Baseline fibrinogen lower CI | 472.83 | 0.1183 | (0.05, 0.19) | 0.1283 | (0.08, 0.18) | C$1771 | (C$1143, C$2339) | C$13,807 | (C$9980, C$19,246) | 0 |
| Baseline fibrinogen upper CI | 482.10 | 0.1186 | (0.05, 0.19) | 0.1284 | (0.08, 0.18) | C$1770 | (C$1164, C$2347) | C$13,788 | (C$10,089, C$19,440) | 0 |
| Baseline 6MWT lower CI | 360.42 | 0.1182 | (0.05, 0.19) | 0.1283 | (0.08, 0.18) | C$,774 | (C$1166, C$2336) | C$13,826 | (C$10,080, C$19,391) | 0 |
| Baseline 6MWT upper CI | 371.17 | 0.1188 | (0.05, 0.19) | 0.1287 | (0.08, 0.18) | C$1775 | (C$1181, C$2347) | C$13,790 | (C$10,147, C$19,249) | 0 |
| Baseline mMRC dyspnea score ≥2 −25% | 0.278 | 0.1176 | (0.05, 0.19) | 0.1280 | (0.08, 0.18) | C$1757 | (C$1109, C$2354) | C$13,725 | (C$9735, C$19,283) | 0 |
| Baseline mMRC dyspnea score ≥2 +25% | 0.463 | 0.1176 | (0.05, 0.19) | 0.1276 | (0.08, 0.18) | C$1775 | (C$1193, C$2328) | C$13,910 | (C$10,148, C$19,524) | 1 |
| All hospital costs −25% |  | 0.1176 | (0.05, 0.19) | 0.1278 | (0.08, 0.18) | C$1781 | (C$1295, C$2231) | C$13,933 | (C$10,652, C$19,848) | 1 |
| All hospital costs +25% |  | 0.1186 | (0.05, 0.19) | 0.1286 | (0.08, 0.18) | C$1762 | (C$1008, C$2454) | C$13,696 | (C$9191, C$19,681) | *−*1 |
| All physician visits −25% |  | 0.1182 | (0.05, 0.19) | 0.1280 | (0.08, 0.18) | C$1772 | (C$1165, C$2319) | C$13,846 | (C$10,152, C$19,550) | 1 |
| All physician visits +25% |  | 0.1175 | (0.05, 0.19) | 0.1277 | (0.08, 0.18) | C$1765 | (C$1137, C$2333) | C$13,816 | (C$10,090, C$19,325) | 0 |
| Predicted utility value in each cycle increased by 10% | 0.744 (1st cycle) | 0.1177 | (0.05, 0.19) | 0.1414 | (0.09, 0.20) | C$1768 | (C$1178, C$2340) | C$12,508 | (C$9191, C$17,489) | *−*9 |
| **Scenario analyses** |  |  |  |  |  |  |  |  |  |  |
| 5 -year time horizon |  | 0.0235 | (0.01, 0.04) | 0.0653 | (0.04, 0.09) | C$1137 | (C$856, C$1378) | C$17,420 | (C$11,577, C$27,475) | 26 |
| 10-year time horizon |  | 0.0740 | (0.03, 0.13) | 0.1065 | (0.07, 0.15) | C$1486 | (C$1016, C$1923) | C$13,946 | (C$9695, C$20,827) | 1 |
| Discount rate 0% |  | 0.1176 | (0.05, 0.19) | 0.1387 | (0.09, 0.19) | C$1890 | (C$1200, C$2535) | C$13,622 | (C$9830, C$19,024) | *−*1 |
| Discount rate 3% |  | 0.1183 | (0.05, 0.19) | 0.1189 | (0.08, 0.16) | C$1667 | (C$1118, C$2175) | C$14,025 | (C$10,193, C$19,725) | 2 |
| Background exacerbation rate at 50% | 1st cycle reference treatment: 0.348 for MExac; 0.004 for SExac | 0.069 | (0.03, 0.11) | 0.1020 | (0.07, 0.14) | C$2226 | (C$1936, C$2558) | C$21,818 | (C$16,661, C$32,712) | 58 |
| Background exacerbation rate at 200% | 1st cycle reference treatment: 2.632 for MExac; 1.735 for SExac | 0.2601 | (−0.16, 0.52) | 0.2079 | (0.06, 0.33) | −C$15,752 | (−C$45,232,  −C$1699) | Dominant | (−C$619,606, −C$4863) | NA |
| Treatment discontinuation for subsequent years 0% |  | 0.3575 | (0.13, 0.60) | 0.3168 | (0.19, 0.46) | C$4291 | (C$2430, C$6043) | C$13,546 | (C$9375, C$18,933) | *−*2 |
| Set treatment effect for subsequent therapies same as SITT |  | 0.0735 | (0.03, 0.12) | 0.0856 | (0.05, 0.12) | C$1702 | (C$1321, C$2091) | C$19,880 | (C$15,352, C$28,833) | 44 |
| For subsequent therapies – assume  100% market share of product with  highest cost in each treatment class | 5.31 | 0.1187 | (0.05, 0.19) | 0.1290 | (0.08, 0.18) | C$1432 | (C$809, C$2019) | C$11,107 | (C$7216, C$15,914) | *−*19 |
| For subsequent therapies – assume  100% market share of product with  lowest cost in each treatment class | 3.13 | 0.1170 | (0.05, 0.19) | 0.1276 | (0.08, 0.18) | C$2143 | (C$1554, C$2704) | C$16,798 | (C$12,823, C$23,904) | 22 |
| For subsequent therapies – generic  pricing for FP/SAL DPI (75% of current  cost in weight calculation) | 4.22 | 0.1187 | (0.05, 0.19) | 0.1289 | (0.08, 0.18) | C$1802 | (C$1183, C$2373) | C$13,976 | (C$10,238, C$19,480) | 1 |
| For subsequent therapies – generic  pricing for FP/SAL DPI (35% of current  cost in weighted calculation) | 4.10 | 0.1183 | (0.05, 0.19) | 0.1282 | (0.08, 0.18) | C$1833 | (C$1221, C$2397) | C$14,291 | (C$10,538, C$20,013) | 4 |
| Use utilization-weighted cost of all LABA/LAMAs for UMEC/VI | 2.4717 | 0.1183 | (0.05, 0.19) | 0.1283 | (0.08, 0.18) | C$1987 | (C$1384, C$2566) | C$15,479 | (C$11,474, C$21,929) | 12 |

**Abbreviations:** 6MWT, 6-min walk test; CI, confidence interval; C$, Canadian dollars; DPI, dry-powder inhaler; FF, fluticasone furoate; FP, fluticasone propionate; ICER, incremental cost-effective ratio; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; LY, life year; MExac, moderate exacerbation; mMRC, modified Medical Research Council; NA, not applicable; PA, probability analyses; QALY, quality-adjusted life year; SA, sensitivity analysis; SAL, salmeterol; SExac, severe exacerbation; SITT, single-inhaler triple therapy; UMEC, umeclidinium; VI, vilanterol.