Supplementary Table 1: Overview of triple therapy clinical trials in patients with COPD.

| Items                      | TRILOGY       | TRINITY      | TRIBUTE     | FULFIL          | IMPACT         | KRONOS        | ETHOS          |
|----------------------------|---------------|--------------|-------------|-----------------|----------------|---------------|----------------|
| **Study duration**         | 12 months     | 12 months    | 12 months   | 24 weeks, with extension to 52 weeks for first 430 patients | 52 weeks       | 24 weeks      | 52 weeks       |
| **Treatment**              | BDP/FOR/GLY  | BDP/FOR/GLY  | BDP/FOR/GLY | FF/UMEC/VI      | FF/UMEC/VI     | BUD/FOR/GLY   | BUD/FOR/GLY    |
| (n=687)                    | (n=1077)      | (n=764)      | (n=911)     | (n=4151)        | (n=4134)       | (n=640)       | (n=627)        |
| BDP/FOR (n=680)            | Tiotropium (n=1074) | IND/GLY (n=768) | BUD/FOR (n=899) | FF/VI (n=2070) | BUD/FOR DPI (n=319) | 320-μg-BUD/FOR/GLY |
| BDP/FOR+tiotropium (n=538) |               |              |             |                 |                | (n=2120)      | (n=2137)       |
|                            |               |              |             |                 |                | BUD/FOR (n=316) |               |
|                            |               |              |             |                 |                | 160-μg-BUD/FOR/GLY |
|                            |               |              |             |                 |                | (n=2121)      | BUD/FOR (n=2131) |

| Eligible criteria          | >40 years;    | >40 years;   | >40 years;    | 40–80 years     | 40–80 years    | Current or former smokers (≥10 pack-years) | FEV₁ 25–65% |
|                            | FEV₁<50%;     | CAT ≥10;     | CAT ≥10;     | Current or former smokers (≥10 pack-years) | <40 years;     | FEV₁ 25–80%   | Current or former smokers (≥10 pack-years) |
|                            | ≥1 moderate or severe exacerbation; | FEV₁<50%; and >1 exacerbation; | FEV₁<50%; and >1 exacerbation; | ≥2 exacerbations | ≥2 exacerbations | CAT total score ≥10 |
|                            | CAT ≥10;      |                | FEV₁ 50–80% and ≥2 exacerbations |          |                |                |
|                            | No triple therapy in previous 2 months; | or ≥1 hospitalization | FEV₁ 50–80% and ≥2 exacerbations |          |                |                |
|                            | TRILOGY also required Baseline Dyspnea Index focal score > 10 | or ≥1 hospitalization | FEV₁<50% and ≥1 exacerbation; |          |                |                |

| Devices                    | Fine particle metered dose inhalers (MDI) | Dry Powder (Ellipta) inhalers | Co-suspension metered dose inhalers (MDI) |
|----------------------------|------------------------------------------|-------------------------------|------------------------------------------|

**Results**

**Exacerbation rate (adjusted annualized)**

Moderate-severe
| RR (95% CI) | 0.77 (0.65–0.92) | 0.80 (0.69–0.92)
| 1.01 (0.85–1.21) | 0.85 (0.72–0.95) | 0.65 (0.49–0.86) | 0.85 (0.80–0.90) | 0.76 (0.69–0.83) |
| P value | =0.005 | 0.0025<sup>c</sup>; 0.89<sup>d</sup> | 0.043<sup>c</sup> | 0.002 | <0.001<sup>c</sup>; <0.001<sup>d</sup> | 0.0001<sup>11</sup>; 0.2792<sup>10</sup> | <0.001<sup>11</sup>; 0.003<sup>c</sup>; 0.312<sup>10</sup> |
| P value | Severe (hospitalization) | Not stated | 0.68 (0.50–0.94) | 0.79 (0.55–1.13) | Not stated | 0.87 (0.76–1.01) | 0.66 (0.56–0.78) | 0.84 (0.69–1.03) |
| P value | 0.0174<sup>c</sup>; 0.45<sup>d</sup> | =0.189 | 0.06<sup>i</sup>; <0.001<sup>i</sup> | <0.001<sup>d</sup>; <0.001; NS | NS | <0.001 | 0.019<sup>d</sup>; <0.0001<sup>et</sup>; <0.0001<sup>et</sup> |
| Pre-dose FEV<sub>1</sub> change from baseline, L | | | | | | | | |
| Week 26 | | | | | | | | |
| MD (95% CI) | 0.081 (0.052–0.109) | BDP/FOR/GLY vs. Tiotropium; BDP/FOR/GLY vs. open triple | 0.02 | 0.17 (0.15–0.19) | Not stated | 0.022 (0.004–0.039) | Not stated |
| P value | <0.001<sup>d</sup> | <0.001; NS | NS | <0.001 | 0.0139<sup>11</sup>; <0.0001<sup>et</sup>; <0.0001<sup>et</sup> |
| Week 52 | | | | | | | | |
| MD (95% CI) | 0.063 (0.032–0.094) | 0.06 (0.04–0.09); 0.003 (~0.03 to 0.03) | 0.019 | 0.18 (0.13–0.23) | 0.10 (0.09–0.11) | 0.05 (0.04–0.07) | 0.016 (~0.006 to 0.038) | Not stated |
| P value | 0.05 (0.04–0.07)<sup>i</sup> | 0.0104 (0.077–0.131)<sup>i</sup> | 0.091 (0.064–0.117)<sup>i</sup> | 0.06 (0.05–0.07) | 0.019<sup>11</sup>; <0.001<sup>et</sup>; <0.0001<sup>et</sup> | 0.001<sup>et</sup>; 0.002<sup>c</sup> | | | |
| P value | SGRQ total score change from baseline at Week 52 |
|---------|-----------------------------------------------|
|         | MD (95% CI)                                   |
| <0.001 | -1.69 (-3.2 to -0.17)                         |
| <0.001; 0.85 | BDP/FOR/GLY superior to Tiotropium |
| NS      | -2.7 (-5.5 to 0.2)                            |
| <0.001 | -1.8 (-2.4 to -1.1)                            |
| <0.001; 0.85 | Tiotropium superior to BDP/FOR/GLY |
| <0.001 | -0.45 (-1.78 to 0.87)                          |
| <0.001; 0.85 | Open triple superior to BDP/FOR/GLY |
| 0.1448\(d\); <0.0001\(e\); <0.001\(f\); <0.0001\(g\); <0.001\(h\); <0.001\(i\); <0.0001\(j\) | |

**P value**

| All-cause mortality |
|---------------------|
| 2.2%, 2.4%          |
| 1.9%, 2.7%, 1.5%    |
| 2.1%, 2.7%          |
| 1.9%                |

**HR (95% CI)**

| Patients with pneumonia, n (%) |
|--------------------------------|
| 23 (3); 18 (3)                 |
| 28 (3); 19 (2); 12 (2)         |
| 28 (4); 27 (4)                 |
| 20 (2.2); 7 (0.8) over 24 weeks |
| 317 (8); 292 (7); 97 (5)       |
| 12 (2); 10 (2); 6 (2); 4 (1)   |
| 98 (4.6); 85 (4.0); 61 (2.9); 107 (5.0) |

**P value**

| Both <0.05 | <0.01 | 0.07 | <0.001; 0.85 | 0.03; 0.50; 0.06 ** | P <0.05 for all |
|------------|-------|------|--------------|--------------------|----------------|

**\(^a\) N values are the number of patients in the intention-to-treat population; \(^b\) Results are presented as the sequence listed in treatment column; \(^c\) Primary endpoint of the study; \(^d\) Coprimary endpoints; \(^*\)BDP/FOR/GLY vs. Tiotropium; \(^\dagger\)BDP/FOR/GLY vs. BDP/FOR+tiotropium; \(^\ddagger\)FF/UMEC/VI vs. FF/VI; \(^\ddagger\)FF/UMEC/VI vs. UMEC/VI.**
BUD/FOR/GLY vs. FOR/GLY; *BUD/FOR/GLY vs. BUD/FOR; **BUD/FOR/GLY vs. BUD/FOR DPI; ††320-μg-BUD/FOR/GLY vs. BOR/GLY; △320-μg-BUD/FOR/GLY vs. BUD/FOR; ‡‡160-μg-BUD/FOR/GLY vs. BOR/GLY; △△160-μg-BUD/FOR/GLY vs. BUD/FOR. AUC: Area under the curve; BDP: Beclomethasone-dipropionate; BUD: Budesonide; CAT: COPD assessment test; CI: Confidence interval; COPD: Chronic Obstructive Pulmonary Disease; DPI: Dry powder inhaler; FEV₁: Forced expiratory volume in one second; FF: Fluticasone-furoate; FOR: Formoterol; GLY: Glycopyrronium; IND: Indacaterol; HR: Hazard ratio; MD: Mean difference; MDI: Metered dose inhalers; RR: Rate ratio; SGRQ: St George’s Respiratory Questionnaire; UMEC: Umeclidinium; VI: Vilanterol.