# Preventing Clinically Important Deterioration (CID) of COPD With Single-inhaler Triple Therapy Fluticasone Furoate/Umeclidinium/Vilanterol: A Prospective Analysis of the IMPACT Trial

**Poster No. 204 (A2438)**


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## Introduction

- Chronic obstructive pulmonary disease (COPD) is a heterogeneous and frequently progressive disease, and the Global initiative for chronic Obstructive Lung Disease (GOLD) 2019 Report advocates routine monitoring of disease progression via measurements of a patient's symptoms, exacerbations and lung function.[1]
- Clinically important deterioration (CID) is an individualized, multicomponent measure of worsening COPD that includes these aspects of disease worsening in COPD (lung function, health status, and exacerbations).[2]
  - Post hoc and a priori analyses have consistently shown that escalation of treatment with dual versus monotherapy, dual bronchodilator versus inhaled corticosteroid (ICS)/long-acting $\beta_2$-agonist (LABA) therapy and triple therapy versus ICS/LABA therapy can reduce short-term worsening identified by these three largely independent individual CID measures.[2–4]
  - Moreover, all three aspects of short-term worsening have been shown to predict increased risk of all-cause mortality over 3 or 4 years in the TORCH and UPLIFT trials.[5,6]
- The generalizability of the CID concept has been evaluated using two different methods of assessing the health status component: St George's Respiratory Questionnaire (SGRQ) total score and COPD Assessment Test (CAT) score, with both measures demonstrating similar results.[4] This may facilitate the use of the CID measure in clinical practice as the CAT instrument is easier to use and interpret than SGRQ.
- The recent InforMing the PAthway of COPD Treatment (IMPACT) trial has shown that single-inhaler triple therapy (SITT) containing fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) results in a lower rate of moderate/severe exacerbations than dual therapy with FF/VI or UMEC/VI.[7] Based on data from IMPACT, we evaluated prospectively the effect of FF/UMEC/VI versus FF/VI and UMEC/VI on reducing the risk of CID.

## Methods

- IMPACT (GSK study CTT116855; NCT02164513) was a Phase III, double-blind, parallel-group, 52-week, multicenter study in patients ≥40 years of age with symptomatic COPD and ≥1 moderate/severe exacerbation in the prior year. Patients were randomized 2:2:1 to SITT with FF/UMEC/VI 100/62.5/25 mcg, or dual therapy with FF/VI 100/25 mcg, or UMEC/VI 62.5/25 mcg, all once daily via the ELLIPTA inhaler.[7]
- The primary study endpoint was the annual rate of on-treatment moderate/severe exacerbations. This prospective secondary analysis evaluated between-treatment comparisons of CID risk (time-to-first CID) with FF/UMEC/VI versus FF/VI and UMEC/VI.
- CID was defined as the occurrence of any of the following on-treatment events: a moderate/severe exacerbation; or a deterioration in lung function (defined as ≥100 mL decrease from baseline in trough forced expiratory volume in 1 second [$FEV_1$]); or a deterioration in health status (defined as either: ≥4.0 unit increase from baseline in SGRQ total score or an increase in CAT score of ≥2.0 units from baseline). Moderate exacerbations were defined as those requiring treatment with antibiotics and/or oral/systemic corticosteroids; severe exacerbations were those resulting in hospitalization or death.
- Time-to-first CID was assessed at Weeks 28 and 52. A pre-specified analysis evaluated between-treatment comparisons of CID risk (time-to-first) using a Cox proportional hazard model for FF/UMEC/VI versus FF/VI and FF/UMEC/VI versus UMEC/VI.
- Future morbidity associated with short-term worsening (CID+ status) versus stability (CID- status) at Week 28 and the durability of Week 28 CID findings was assessed post hoc using the following outcomes of interest: annual exacerbation rates (analyzed using a generalized linear model assuming a negative binomial distribution) and time-to-first exacerbation (Cox proportional hazard model) over Weeks 29–52; and change from baseline in trough $FEV_1$ (repeated measures model), SGRQ total score (analysis of covariance [ANCOVA] model) and CAT score (ANCOVA model) at Week 52.
- Concordance of CID components was assessed using Kappa statistics.

## Results

### Patients

- Baseline demographic and clinical characteristics for the intent-to-treat population (ITT) are presented in **Table 1**.
- The proportions of patients who had a CID by Week 28 and 52 are presented in **Table 2**.

### CID risk (time-to-first analysis): FF/UMEC/VI versus FF/VI

- At Weeks 28 and 52, FF/UMEC/VI significantly reduced the risk (time-to-first) of a composite CID versus FF/VI by 33% and 31%, respectively, using the definition including SGRQ, respectively, and by 28% and 27%, using the definition including CAT (all *P*<0.001; **Figure 1**).
- FF/UMEC/VI significantly reduced the risk of all CID event types compared with FF/VI, with the greatest reduction observed for the lung function component (56% and 52% risk reduction at Week 28 and 52, respectively, both *P*<0.001; **Figure 1**).

**Table 1. Baseline characteristics (ITT population)**

| | FF/UMEC/VI (N=4151) | FF/VI (N=4134) | UMEC/VI (N=2070) |
|---|---|---|---|
| **Age, mean (SD) years** | 65.3 (8.2) | 65.3 (8.3) | 65.2 (8.3) |
| **Gender, % male** | 67 | 66 | 66 |
| **BMI, mean (SD) kg/m²** | 26.6 (6.2) | 26.7 (6.1) | 26.6 (5.9) |
| **Exacerbation history in prior 12 months, n (%)** | | | |
| ≥2 moderate exacerbations | 1967 (47) | 1921 (46) | 989 (48) |
| ≥1 severe exacerbation | 1087 (26) | 1069 (26) | 515 (25) |
| **Lung function (post-bronchodilator)** | | | |
| Screening $FEV_1$, mean (SD) L | 1.275 (0.488) | 1.272 (0.486) | 1.268 (0.481) |
| $FEV_1$ % predicted, mean (SD) | 45.7 (15.0) | 45.5 (14.8) | 45.4 (14.7) |
| **Lung function (pre-bronchodilator)** | | | |
| Screening $FEV_1$, mean (SD) L | 1.170 (0.468) | 1.163 (0.468) | 1.167 (0.464) |
| $FEV_1$ % predicted, mean (SD) | 41.9 (14.6) | 41.6 (14.5) | 41.8 (14.4) |
| **SGRQ total score, mean (SD)** | 50.8 (16.8) | 50.7 (17.0) | 50.2 (16.7) |
| **CAT score, mean (SD)** | 20.1 (6.1) | 20.1 (6.1) | 20.2 (6.2) |

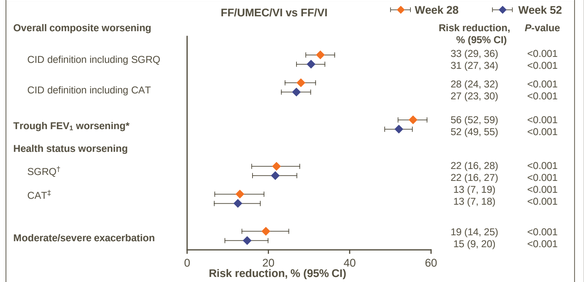
BMI, body mass index; SD, standard deviation

**Table 2. Outcomes post-Week 28 by CID status at Week 28 (definition including SGRQ or CAT)**

| | CID+ | CID- | Difference (CID+ vs CID-) |
|---|---|---|---|
| **Definition including SGRQ** | **N=7008** | **N=3055** | |
| | **Annual rates (95% CI)** | | **% increase in rate (95% CI)** |
| **Rate** | n=5860 | n=2729 | |
| Moderate/severe exacerbations after Week 28 | 0.94 (0.90, 0.98) | 0.54 (0.49, 0.58) | 75 (60, 92); *P*<0.001 |
| Severe exacerbations after Week 28 | 0.14 (0.12, 0.16) | 0.07 (0.06, 0.09) | 96 (56, 147); *P*<0.001 |
| | **Patients with event, n1 (%)** | | **% increase in risk (95% CI)** |
| **Time-to-first** | n=5864* | n=2732* | |
| Moderate/severe exacerbations after Week 28 | 1900 (32) | 548 (20) | 72 (56, 89); *P*<0.001 |
| Severe exacerbations after Week 28 | 391 (7) | 99 (4) | 79 (43, 123); *P*<0.001 |
| | **LS mean CFB (95% CI)** | | **Difference (95% CI)** |
| | n=5359 | n=2557 | |
| Trough $FEV_1$ at Week 52, mL | 9 (2, 15) | 152 (143, 162) | −143 (−155, −132); *P*<0.001 |
| | n=5298 | n=2516 | |
| SGRQ total score at Week 52, unit | −2.4 (−2.7, −2.0) | −9.8 (−10.3, −9.3) | 7.5 (6.8, 8.1); *P*<0.001 |
| | n=5218 | n=2482 | |
| CAT score at Week 52, unit | −1.2 (−1.3, −1.0) | −3.3 (−3.5, −3.0) | 2.1 (1.8, 2.4); *P*<0.001 |
| **Definition including CAT** | **N=7304** | **N=2759** | |
| | **Annual rates (95% CI)** | | **% increase in rate (95% CI)** |
| **Rate** | n=6150 | n=2439 | |
| Moderate/severe exacerbations after Week 28 | 0.92 (0.88, 0.96) | 0.54 (0.49, 0.58) | 72 (56, 89); *P*<0.001 |
| Severe exacerbations after Week 28 | 0.15 (0.13, 0.17) | 0.08 (0.06, 0.10) | 91 (50, 142); *P*<0.001 |
| | **Patients with event, n1 (%)** | | **% increase in risk (95% CI)** |
| **Time-to-first** | n=6153† | n=2443† | |
| Moderate/severe exacerbations after Week 28 | 1959 (32) | 489 (20) | 68 (52, 86); *P*<0.001 |
| Severe exacerbations after Week 28 | 402 (7) | 88 (4) | 78 (41, 125); *P*<0.001 |
| | **LS mean CFB (95% CI)** | | **Difference (95% CI)** |
| | n=5632 | n=2284 | |
| Trough $FEV_1$ at Week 52, mL | 14 (7, 20) | 156 (146, 167) | −143 (−155, −131); *P*<0.001 |
| | n=5565 | n=2249 | |
| SGRQ total score at Week 52, unit | −3.2 (−3.6, −2.9) | −8.6 (−9.2, −8.0) | 5.4 (4.7, 6.0); *P*<0.001 |
| | n=5502 | n=2198 | |
| CAT score at Week 52, unit | −0.9 (−1.1, −0.8) | −4.1 (−4.4, −3.9) | 3.2 (2.9, 3.5); *P*<0.001 |

*7 patients excluded from the analysis due to missing covariates (CID+: n=4; CID-: n=3); †7 patients excluded from the analysis due to missing covariates (CID+: n=3; CID-: n=4).
*CFB*, change from baseline; CI, confidence interval; LS, least squares; N, number of patients with CID status available at Week 28; *n*, number of patients with analyzable data; *n1*, number of patients with event.

**Figure 1. Reduction in CID risk (time-to-first) with FF/UMEC/VI versus FF/VI**

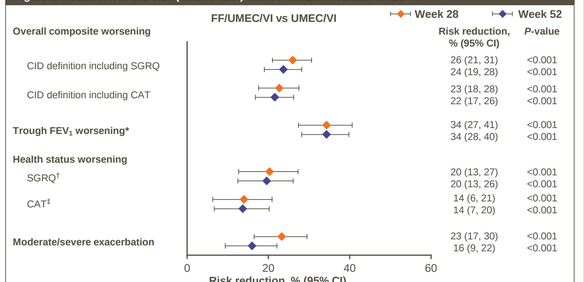



*≥100 mL decrease from baseline in trough $FEV_1$; †≥4.0 unit increase from baseline in SGRQ total score; ‡≥2.0 unit increase from baseline in CAT score.

### CID risk (time-to-first analysis): FF/UMEC/VI versus UMEC/VI

- At Weeks 28 and 52, FF/UMEC/VI significantly reduced the risk (time-to-first) of a composite CID versus UMEC/VI by 26% and 24%, respectively, using the definition including SGRQ, and by 23% and 22%, respectively, using the definition including CAT (all *P*<0.001; **Figure 2**).
- FF/UMEC/VI significantly reduced the risk of all CID event types compared with UMEC/VI, with the greatest reduction observed for the lung function component (34% risk reduction at Weeks 28 and 52, both *P*<0.001; **Figure 2**).

**Figure 2. Reduction in CID risk (time-to-first) with FF/UMEC/VI versus UMEC/VI**




*≥100 mL decrease from baseline in trough $FEV_1$; †≥4.0 unit increase from baseline in SGRQ total score; ‡≥2.0 unit increase from baseline in CAT score.

### Outcomes by CID status at Week 28

- At Week 28, 7008/10,063 (69.6%) patients were CID+ according to the CID definition including SGRQ and 7304/10,063 (72.6%) were CID+ according to the CID definition including CAT.
- Using the CID definition including SGRQ, patients who were CID+ at Week 28 had a 75% increase in annual rate of moderate/severe exacerbations (rate ratio 1.75 [95% CI 1.60, 1.92] *P*<0.001) and a 96% increase in annual rate of severe exacerbations (rate ratio 1.96 [95% CI 1.56, 2.47]; *P*<0.001) over Weeks 29–52 versus CID- patients.
- Sustained clinically relevant improvements in trough $FEV_1$ (difference: 143 mL) and health status (SGRQ difference: −7.5 units; CAT difference: −2.1 units) at Week 52 were seen in the CID-free (CID-) subgroup versus CID+ patients (all *P*<0.001; **Table 2**).
- Similar results were seen using the definition including CAT (**Table 2**): compared with CID- patients, CID+ patients had a 72% and 91% increase in the rate of moderate/severe and severe exacerbations over Weeks 29–52, respectively, and CID-free patients showed clinically relevant benefits in lung function (143 mL) and health status (SGRQ difference: −5.4 units; CAT difference: −3.2 units) at Week 52 versus CID+ patients (all *P*<0.001).
- Consistent with previously published results for the FLAME study,[3] there was no or minimal concordance between CID components at Week 28 (Kappa statistics <0.2; **Table 3**). This suggests that all CID events are largely independent of each other when they occur. The only exception to this finding, albeit not surprising, was the weak level of concordance between CAT and SGRQ CID events (Kappa statistic 0.2–0.3). Kappa statistics up to Week 52 were consistent with these findings.

**Table 3. Kappa statistics (95% CI) for concordance of CID components up to Week 28**

| | FF/UMEC/VI | FF/VI | UMEC/VI | Overall |
|---|---|---|---|---|
| Trough $FEV_1$ vs SGRQ total score | 0.080 (0.048, 0.111) | 0.117 (0.085, 0.148) | 0.072 (0.027, 0.116) | 0.105 (0.085, 0.125) |
| Trough $FEV_1$ vs CAT score | 0.052 (0.023, 0.082) | 0.110 (0.078, 0.141) | 0.048 (0.004, 0.092) | 0.081 (0.062, 0.101) |
| Trough $FEV_1$ vs moderate/severe exacerbation | 0.063 (0.033, 0.094) | 0.080 (0.048, 0.111) | 0.101 (0.057, 0.145) | 0.085 (0.065, 0.105) |
| SGRQ total score vs CAT score | 0.259 (0.229, 0.290) | 0.273 (0.243, 0.304) | 0.233 (0.189, 0.277) | 0.262 (0.242, 0.281) |
| SGRQ total score vs moderate/severe exacerbation | 0.102 (0.070, 0.133) | 0.098 (0.066, 0.130) | 0.066 (0.021, 0.110) | 0.096 (0.076, 0.116) |
| CAT score vs moderate/severe exacerbation | 0.085 (0.054, 0.117) | 0.070 (0.038, 0.102) | 0.077 (0.032, 0.122) | 0.079 (0.059, 0.099) |

### Safety

- Safety data have been previously published.[7] The safety profile of FF/UMEC/VI was similar to that of FF/VI and UMEC/VI, with no new safety signals identified.[7]

## Conclusions

- This prospective analysis highlighted that once-daily FF/UMEC/VI reduced the risk of composite CID and of all CID event types versus FF/VI and UMEC/VI at Week 28 and 52, with the impact of adding ICS or additional bronchodilation evident in protecting against deterioration in lung function, quality of life and exacerbations.
- Short-term disease worsening, assessed using CID status at Week 28, was associated with increased rates of both moderate/severe and severe exacerbations, and freedom from CID at this time point was associated with sustained clinically relevant improvements in lung function and health status at follow-up.
- These results indicate that optimizing bronchodilation and adding ICS in patients with symptomatic COPD and a history of exacerbations is associated with clear benefits on the prevention of future disease worsening in COPD.

## References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## Disclosures


- Editorial support (in the form of writing assistance, including development of the initial draft based on author direction, assembling tables and figures, collating authors' comments, grammatical editing, and referencing) was provided by Chrystelle Rasamison, of Fishawack Indicia Ltd, UK, and was funded by GlaxoSmithKline (GSK).
- This study was funded by GSK (CTT116855; NCT02164513). ELLIPTA is owned by or licensed to the GSK Group of Companies.
- CEJ, SK, DALi, and IPN are GSK employees and hold GSK stocks/shares. SJP was a GSK employee at the time of the study and holds GSK stocks/shares. MKH has received personal fees from AstraZeneca, Boehringer Ingelheim, and GSK, research support from Novartis and Sunovion. GJC has received personal fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, CSA Medical, Eolo, GSK, HGE Technologies, Novartis, Nuvaira, Olympus, Pulmonx, and Verona. MTD has received personal fees from AstraZeneca and GSK and contracted clinical trial support from AstraZeneca, Boehringer Ingelheim, and GSK. DMGH has received personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, and Pfizer. PL has received personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, and GSK. DALo has received personal fees from GSK. FJM has taken part in advisory boards for AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Sunovion, and Teva, steering committees for AstraZeneca and GSK, DSMB for Genentech/Roche and GSK, and has been an advisor for ProTerrix Bio. RAW has been a consultant for AstraZeneca, Boehringer Ingelheim, Contrafect, GSK, Novartis, and Merck, has received research grants from AstraZeneca, Boehringer Ingelheim, and GSK and has taken part in advisory boards for MylanThevarance, Propeller Health, Sunovion, and Verona. DS declares personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Genentech, Glenmark, GSK, Menarini, Mundipharma, Novartis, Peptinnovate, Pfizer, Pulmatrix, Theravance, and Verona.