Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Single Inhaler Triple Therapy (FF/UMEC/VI) Versus FF/VI and UMEC/VI in Patients with COPD: Subgroup Analysis of the China Cohort in the IMPACT Trial

Jinping Zheng (jpzhenggy@163.com)
State Key Laboratory of Respiratory Disease https://orcid.org/0000-0002-7511-661X
Nanshan Zhong
State Key Laboratory of Respiratory Disease
Changzheng Wang
Xinqiao Hospital
Li Ping Wei
Third Affiliated Hospital of Guangzhou Medical University
Xiang Dong Zhou
Xinan Hospital
Li Zhao
Shengjing Hospital of China Medical University
Ya Dong Yuan
Second Hospital of China Medical University
Bei He
Peking University Third Hospital
Bin Wu
Affiliated Hospital of Guangdong Medical College
Xin Du
GSK
David A. Lipson
GSK

Research article

Keywords: COPD, dual therapy, triple therapy, fluticasone furoate, umeclidinium, vilanterol, single-inhaler

Posted Date: December 5th, 2019

DOI: https://doi.org/10.21203/rs.2.18023/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Version of Record: A version of this preprint was published at Current Medical Research and Opinion on December 7th, 2020. See the published version at https://doi.org/10.1080/03007995.2020.1844646.

Abstract

Background In the Phase III InforMing the PAthway of COPD Treatment (IMPACT) trial, fluticasone furoate [FF]/umeclidinium [UMEC]/vilanterol [VI] single-inhaler triple therapy resulted in lower rates of moderate/severe exacerbations than dual therapy with FF/VI or UMEC/VI in patients with symptomatic chronic obstructive pulmonary disease (COPD) and a history of exacerbations. Here we present the result in the subpopulation of patients enrolled in China. Methods The IMPACT trial was a 52-week, randomized, double-blind, parallel-group, multicenter trial. Patients (≥40 years of age) with COPD and ≥1 moderate/severe exacerbations in the prior year were randomized 2:2:1 to once-daily FF/UMEC/VI 100/62.5/25 µg, FF/VI 100/25 µg, or UMEC/VI 62.5/25 µg administered via the Ellipta inhaler. Endpoints, assessed in the overall intent-to-treat (ITT) population and in patients from China, included annual rates of exacerbations, time-to-first on-treatment moderate/severe exacerbation, and change from baseline in trough forced expiratory volume in 1 second (FEV1) at Week 52. Results Of the 10,355 patients randomized, 535 (5.2%) were from China. In the China cohort, the rate of on-treatment moderate/severe exacerbations was 0.81 per year with FF/UMEC/VI versus 0.96 with FF/VI (rate ratio [RR]: 0.84; 95% confidence interval [CI]: 0.64, 1.11; p=0.227) and 0.80 with UMEC/VI (RR: 1.02; 95% CI: 0.72, 1.44; p=0.929). Hazard ratio for time-to-first moderate/severe exacerbation was 0.84 (95% CI: 0.63, 1.11; p=0.218) for FF/UMEC/VI versus FF/VI, and 0.89 (95% CI: 0.62, 1.27; p=0.516) for FF/UMEC/VI versus UMEC/VI. Improvements in mean change from baseline in trough FEV1 were observed for FF/UMEC/VI versus FF/VI (treatment difference 137 mL; 95% CI: 86, 188; p<0.001) and FF/UMEC/VI versus UMEC/VI (treatment difference 63 mL; 95% CI: 0, 125; p=0.0.050) in China. Health status was also improved with FF/UMEC/VI versus both dual therapies. Broadly, these results were in the same direction as those seen in the overall ITT population. No new safety signals were identified. Conclusions In the China cohort of the IMPACT trial, single-inhaler triple therapy with FF/UMEC/VI versus dual therapy with FF/VI or UMEC/VI reduced the rate and risk of exacerbations, and improved lung function and quality of life similar to the overall ITT population. Trial registration: NCT02164513 (GSK study number CTT116855).

Background

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disease characterized by persistent respiratory symptoms, including dyspnea, cough and/or sputum production, as well as airflow limitation, which results in a decrease in lung function [1]. The global burden of COPD is high, with the World Health Organization listing the disease as the third leading cause of death worldwide in 2016 [2]. Furthermore, this substantial burden is predicted to continue with COPD projected to remain a leading cause of death by 2030 [3].

The burden of COPD in China is greater than that seen in developed countries, with the condition rapidly becoming a leading cause of morbidity and mortality among Chinese people [4, 5]. The prevalence of COPD in China has recently been estimated to be between 8.6% and 13.6%, with a higher prevalence in men than in women [4, 6]. In a recent cross-sectional survey of a nationally representative sample of patients with COPD from China, the majority (56.4%) had mild disease (Global initiative for chronic

Obstructive Lung Disease [GOLD] stage I), 36.3% moderate disease (GOLD stage II), 6.5% severe disease (GOLD stage III), and 0.9% very severe disease (GOLD stage IV).[6] Chinese physicians are encouraged to follow COPD therapy strategies recommended in the GOLD report, i.e. treatment escalation based on symptoms and exacerbation risk [7]. However, many physicians fail to implement these guidelines adequately and, as a result, appropriate use of COPD medication is inconsistent [5, 7].

The GOLD management strategy for COPD recommends triple therapy with an inhaled corticosteroid (ICS), a long-acting muscarinic antagonist (LAMA), and a long-acting β_2-agonist (LABA) in patients with persistent breathlessness or exercise limitation on dual ICS/LABA therapy, or in patients with recurrent exacerbations despite treatment with dual ICS/LABA or LAMA/LABA [1]. The InforMing the PAthway of COPD Treatment (IMPACT) trial, conducted in 37 countries worldwide, compared once-daily single inhaler triple therapy (fluticasone furoate [FF]/umeclidinium [UMEC]/vilanterol [VI]) with two dual therapies (UMEC/VI [LAMA/LABA] and FF/VI [ICS/LABA]) in patients with symptomatic COPD with at least one moderate/severe exacerbation in the previous year. FF/UMEC/VI significantly reduced the rate of moderate/severe COPD exacerbations and improved lung function and health status compared with either dual therapy [8].

The pharmacokinetic profile of inhaled COPD therapies can be impacted by a number of factors including lung receptor occupancy and the amount of drug absorbed into the systemic circulation, which could elicit additional pharmacological effects and contribute to the safety and tolerability profile of the drug [9].Differences in the pharmacokinetic profile of inhaled FF have been observed between Chinese and Caucasian populations [10], therefore it is of interest to evaluate the efficacy and safety of FF/UMEC/VI triple therapy in patients with COPD in China. The IMPACT trial was conducted in 37 countries and analyses by geographic region were conducted to investigate potential differences from the intent-to-treat (ITT) population.

Here we present results of a subgroup analysis based on patients from China enrolled in the IMPACT trial. The primary objective was to evaluate the efficacy of FF/UMEC/VI to reduce the annual rate of moderate/severe exacerbations compared with FF/VI or UMEC/VI dual therapy in the China cohort. Secondary objectives included evaluation of the long-term safety and other efficacy assessments of FF/UMEC/VI compared with dual therapies in this population.

Methods

Study design

The IMPACT trial (GSK study CTT116855, NCT02164513) is a Phase III, randomized, double-blind, parallel-group, multicenter trial conducted in 37 countries between June 2014 and July 2017. Here we report a subgroup analysis in patients from China. The trial design has been described in detail previously [8, 11]. Briefly, the total trial duration was approximately 55 weeks, consisting of a 2-week run-in period, a 52-week treatment period, and a 1-week safety follow-up period. All patients in the

ITT population provided written informed consent. The trial was conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki and received approval from local institutional review boards or independent ethics committees.

Study population

Eligibility criteria for enrollment in the trial have been reported previously.[8] Eligible patients were ≥40 years of age with a diagnosis of COPD as defined by the American Thoracic Society/European Respiratory Society (ATS/ERS) [12], current or former smokers with a smoking history of ³10 pack-years, had a COPD Assessment Test (CAT) score ≥10 at screening, and had either a post-bronchodilator forced expiratory volume in 1 second (FEV_1) <50% of the predicted normal value and a history of ≥1 moderate or severe exacerbation in the previous year, or a post-bronchodilator FEV_1 of 50% to 80% of the predicted normal value and ≥2 moderate exacerbations or ≥1 severe exacerbation in the previous year. Patients had to have been receiving daily maintenance treatment for COPD for ≥3 months prior to screening.

Exclusion criteria have also been reported previously [8]. Of note, patients with pneumonia or a severe COPD exacerbation that had not resolved ≤14 days prior to screening and ≤30 days following the last dose of corticosteroids (if applicable) were excluded, as were those with respiratory tract infection (RTI) that had not resolved within 7 days of screening, abnormal chest X-ray or resting oxygen requirement of >3 L/min at screening. Patients with a current diagnosis of asthma were also excluded.

The population comprised all randomized patients, excluding those who were randomized in error. The China cohort was derived from the ITT population and only included patients enrolled in China.

Study treatments

Patients were randomized (2:2:1) to receive either once-daily triple therapy FF/UMEC/VI 100/62.5/25 µg, or dual therapy FF/VI 100/25 µg, or UMEC/VI 62.5/25 µg administered via the Ellipta inhaler. Patients continued to use their existing COPD medications during the run-in period and were provided with salbutamol on an as-needed basis (rescue medication) throughout the trial.

Study endpoints

The trial endpoints have been described previously [8, 11]. This subgroup analysis evaluated the following endpoints in the China cohort: annual rate of on-treatment moderate/severe exacerbations (primary endpoint), and secondary efficacy endpoints of time-to-first on-treatment moderate/severe exacerbation, on-treatment severe exacerbations, and change from baseline in trough FEV_1 and change from baseline in St George's Respiratory Questionnaire (SGRQ) at Week 52. Other efficacy endpoints included the proportion of SGRQ responders (patients with ≥4-point decrease in SGRQ total score from baseline), change from baseline in CAT score, the proportion of CAT score responders (patients with ≥2-point decrease in CAT score from baseline), and rates of other exacerbations (mild/moderate/severe, moderate only, and requiring treatment with systemic/oral corticosteroids or antibiotics).

Mild exacerbations were defined as exacerbations that were self-managed by the patient and did not require treatment with oral/systemic corticosteroids or antibiotics, moderate exacerbations were defined as requiring treatment with oral/systemic corticosteroids and/or antibiotics, and severe exacerbations were defined as requiring hospitalization or resulting in death.

Safety endpoints included the incidence of adverse events (AEs), serious AEs (SAEs), and AEs of special interest (AESI). AESIs are AEs which have specified areas of interest for FF, UMEC, or VI, or for patients with COPD and allow for a comprehensive review of safety data that is not limited to a specific Preferred Term. Adjudication of SAEs was performed by an independent adjudication committee, who categorized the primary event in the SAE report.

Statistical analyses

Details of sample size calculations have been described previously.[8] The trial was not powered for subgroup analysis by country. All summaries, analyses or comparisons performed for the China cohort are for descriptive purposes only. No multiplicity adjustment was applied for analyses of these data.

In the overall ITT population, the number of moderate or severe COPD exacerbations was analyzed using a generalized linear model assuming a negative binomial distribution with covariates of treatment group, sex, exacerbation history ($\leq$1, $\geq$2 moderate/severe), smoking status (screening), geographical region, and post-bronchodilator % predicted FEV_1 (screening) [8]. In the China cohort, the region covariate was defined as China/Not China and an additional covariate of treatment group by region (China/Not China) interaction was also included in the analysis. Time-to-first on-treatment moderate or severe COPD exacerbation was analyzed using Cox proportional hazards model. Least squares (LS) mean change from baseline in trough FEV_1 was analyzed using a mixed-model repeated measures (MMRM) analysis. For the overall ITT population, covariates for FEV_1 included group, smoking status (screening), geographical region, visit, baseline, baseline-by-visit, and treatment group-by-visit interactions [8]. For the China cohort, the analyses included the same covariates, except for geographical region which was replaced with China/Not China, and the addition of treatment group by region, visit by region and treatment group by visit by region interactions. For the overall ITT population, the proportion of SGRQ and CAT responders was analyzed using a generalized linear mixed model with a logit link function with the following covariates: treatment group, smoking status (screening), geographic region, visit, baseline value, and baseline-by-visit and treatment-by-visit interactions [8]. For the China cohort, the analyses included the same covariates in the model as the overall ITT population, except for geographic region which was replaced with China/Not China. The proportion of patients reporting AEs and SAEs was summarized for each treatment group. In the overall ITT population, multiplicity across selected treatment comparisons and key secondary endpoints was controlled using a hierarchical, closed testing procedure. Since all treatment comparisons in the testing hierarchy demonstrated adjusted p-values of <0.001, both adjusted and unadjusted p-values were considered the same, and therefore only unadjusted p-values are presented here.

Results

Study population

Results in the overall ITT population have been previously published [8]. A total of 10,355 patients were randomized to treatment in the overall ITT population [8]. Of these, 535 were randomized in China (213 to FF/UMEC/VI, 216 to FF/VI, and 106 to UMEC/VI). Patient disposition for each study cohort is shown in **Supplementary Figure 1**. The percentages of pre-screen or screen failures and reasons for failures were similar across cohorts. The majority of patients completed study treatment and completed the study; of those treated in the China cohort, 463 (87%) completed study treatment and 479 (90%) completed the study (patients who prematurely discontinued study treatment were encouraged to stay in the study to minimize data loss).

Demographics and baseline characteristics were similar across treatment groups. As anticipated, some demographic characteristics in the China cohort differed from the overall ITT population (**Table 1**). These included body mass index (BMI), % predicted post-bronchodilator FEV_1, CAT score and the proportion of current smokers, which were notably lower in patients from China compared with the overall ITT population. In the China cohort, the majority of patients were male (95%–96% compared with 66%–67% in the ITT), with mean age ranging from 65.5 to 66.1 years across the treatment groups (compared with 65.2 to 65.3 in the ITT) and mean BMI ranging from 22.1 to 22.6 kg/m^2 (compared with 26.6 to 26.7 kg/m^2 in the ITT).

Primary efficacy analysis

In the China cohort, the rate of on-treatment moderate/severe exacerbations among patients randomized to FF/UMEC/VI was 0.81 per year, compared with 0.96 per year among those randomized to FF/VI (rate ratio [RR]: 0.84; 95% confidence interval [CI]: 0.64, 1.11; p=0.227) and 0.80 per year among those randomized to UMEC/VI (RR: 1.02; 95% CI: 0.72, 1.44; p=0.929) (**Table 2**). These results were similar to those in the overall ITT population, with a point estimate in favor of FF/UMEC/VI versus FF/VI for the reduction in rate of moderate/severe exacerbations. However, unlike in the ITT population, there was no difference between FF/UMEC/VI and UMEC/VI for this endpoint (**Table 2**).

Secondary efficacy analyses

In the analysis of the time-to-first moderate/severe exacerbation in the China cohort, hazard ratios for FF/UMEC/VI versus FF/VI and UMEC/VI were 0.84 (95% CI: 0.63, 1.11; p=0.218) and 0.89 (95% CI: 0.62, 1.27; p=0.516), respectively (**Figure 1** and **Table 2**).

The proportion of patients experiencing severe exacerbations while on treatment in China was similar across FF/UMEC/VI, FF/VI, and UMEC/VI treatment groups (18%, 17%, and 17%, respectively), and slightly higher to the incidence in the overall ITT population (11%, 11%, and 13%, respectively; **Supplementary Table 1**).

In the China cohort, FF/UMEC/VI improved trough FEV_1 at Week 52 versus FF/VI (treatment difference 137 mL; 95% CI: 86, 188; p<0.001) and versus UMEC/VI (treatment difference 63 mL; 95% CI: 0, 125; p=0.050) (**Figure 2**). These improvements were similar to those in the overall population, although the point estimates for the between-treatment difference were in each case slightly higher in China than in the ITT (**Figure 2**).

Other efficacy endpoints

In the China cohort, the proportion of SGRQ total score responders at Week 52 was higher with FF/UMEC/VI (49%) compared with FF/VI (41%; odds ratio [OR]: 1.40; 95% CI: 0.95, 2.05; p=0.090) and UMEC/VI (41%; OR: 1.34; 95% CI: 0.83, 2.15; p=0.233) (**Figure 3**). These differences were in line with those observed in the overall ITT population. At Week 52, the LS mean change from baseline data were consistent with the responder data (**Supplementary Figure 2**).

In the China cohort, the proportion of CAT score responders at Week 52 was higher in the FF/UMEC/VI group (41%) than in the FF/VI group (34%; OR: 1.31; 95% CI: 0.88, 1.96; p=0.180), and similar between FF/UMEC/VI and UMEC/VI (42%; OR: 0.90; 95% CI: 0.56, 1.46; p=0.665) (**Figure 4**). At Week 52, the LS mean change from baseline data were similar to the results in the overall ITT population (**Supplementary Figure 3**).

In the China cohort, the rates of mild/moderate/severe COPD exacerbations and COPD exacerbations requiring systemic/oral corticosteroids were lowest in the FF/UMEC/VI group, compared with the FF/VI and UMEC/VI groups (**Supplementary Table 2**).

Safety endpoints

The incidence of AEs within the China cohort was similar across the three treatment groups, ranging from 75% to 79% (**Table 3**). The most common AESI in the China cohort were cardiovascular effects (15%) and pneumonia (4%–13%). These were also among the most frequent AESI in the overall ITT population (10%–11% and 5%–8%, respectively) (**Table 3**). There was a higher incidence of pneumonia AESIs in the FF/UMEC/VI and FF/VI groups in the China cohort (13%) compared with the ITT population (8% and 7%), while incidence of pneumonia AESIs in the UMEC/VI group was similar in China and the ITT (4% and 5%, respectively). There were no differences across the cohorts for the incidence of adjudicated pneumonia SAEs (**Table 3**). The incidence of COPD exacerbation with evidence of pneumonia adjudicated SAEs in the FF/UMEC/VI, FF/VI, and UMEC/VI groups was 6%, 5%, and 5% in China and 3%, 3%, and 3% in the ITT, respectively. The incidence of pneumonia/RTI without COPD exacerbation adjudicated SAEs in the FF/UMEC/VI, FF/VI, and UMEC/VI groups was 2%, <1%, and 0% in China and 2%, 2%, and 1% in the ITT, respectively (**Table 3**).

SAEs occurred in 25%–29% of patients in the China cohort, compared with 21%–23% in the overall ITT population (**Table 3**). In total, there were seven fatal SAEs in the China cohort (two [<1%] in the

FF/UMEC/VI group, three [1%] in the FF/VI group, and two [2%] in the UMEC/VI group); these proportions were similar to those seen in the overall ITT population (2% across treatment groups) (**Table 3**).

Discussion

In the China cohort of the IMPACT trial once-daily single-inhaler triple therapy with FF/UMEC/VI reduced the rate of moderate/severe exacerbation versus FF/VI and reduced the risk of these events versus both FF/VI and UMEC/VI in patients with symptomatic COPD and a history of exacerbations. Furthermore, FF/UMEC/VI improved lung function (as assessed by trough FEV_1) and health-related quality of life (as assessed by SGRQ score) versus both dual therapy comparators, and reduced disease impact (as assessed by CAT score) versus FF/VI in this cohort. Given the small size of the China cohort and the fact that the trial was not powered for between-treatment comparisons in this cohort, the results of the current analysis should be interpreted based on the similarity of the results relative to the overall ITT population.

As anticipated in a population of patients with a history of exacerbations [13], a high proportion of patients experienced moderate/severe exacerbations during the trial. In the China cohort, consistent with the pattern in the overall ITT population, FF/UMEC/VI reduced the annual rate of on-treatment moderate/severe exacerbations compared with FF/VI, albeit without statistical significance. This improvement was of a similar direction and magnitude to the results in the overall ITT population. In contrast, there was no clear difference in the annual rate of moderate/severe exacerbations between FF/UMEC/VI and UMEC/VI among patients from China. This may be due to chance variation in the relatively small patient sample receiving UMEC/VI, as patients were randomized to FF/UMEC/VI, FF/VI, and UMEC/VI in a 2:2:1 ratio. Importantly, the treatment effects of both FF/UMEC/VI versus FF/VI and FF/UMEC/VI versus UMEC/VI on the time-to-first on-treatment moderate/severe exacerbation in the China cohort were similar to the results seen in the overall ITT population. Of note, rates of mild/moderate/severe COPD exacerbations and COPD exacerbations requiring systemic/oral corticosteroids were lowest in the FF/UMEC/VI group in the China cohort, as compared with FF/VI and UMEC/VI treatment groups. These results illustrate that ICS may have less impact on infective exacerbations treated with antibiotics but could play an important role in the prevention of inflammatory exacerbations that respond to oral corticosteroid use, which is consistent with a previous report [14]. Complex patterns of exacerbation data and prevention can occur between the three treatment regimens and this can be impacted by the way exacerbations are treated, including the preference for antibiotic or oral corticosteroid use in various countries. The proportion of patients experiencing severe exacerbations was higher in China than in the ITT population across all treatment arms. This difference between the two populations may be due to access to healthcare, as in China many people attend hospital as their primary means of healthcare access [15].

A number of studies have demonstrated the importance of wider measures of clinical efficacy on the patient experience of COPD [16-18]. As such, other clinically relevant non-exacerbation measures were also analyzed in this China cohort, and demonstrated results that were generally consistent with those seen in the overall ITT population. Firstly, statistically significant differences between FF/UMEC/VI and

both FF/VI and UMEC/VI were shown for the mean change from baseline in trough FEV_1 at Week 52 in the China cohort. Furthermore, the proportion of SGRQ responders at Week 52 was highest in the FF/UMEC/VI group compared with either dual therapy in China, with between-treatment differences similar to those in the overall ITT population. Finally, at Week 52 in the China cohort, FF/UMEC/VI numerically improved the LS mean change from baseline in CAT score compared with FF/VI and UMEC/VI , although the results did not reach statistical significance. In addition, the proportion of CAT responders at Week 52 in the China cohort was higher in the FF/UMEC/VI group compared with FF/VI, and similar between FF/UMEC/VI and UMEC/VI.

As previously reported, the safety profile of FF/UMEC/VI in the original IMPACT trial was in line with the profile of each of the individual components and that of the dual combinations FF/VI and UMEC/VI [19, 20]. This sub-analysis in the China cohort identified no new safety signals compared with the ITT population, with similar incidences of overall AEs, drug-related AEs, and SAEs across the three treatment groups. As expected, based on the class effect for ICS in patients with COPD [1], the incidence of pneumonia was highest in ICS-containing treatment groups. The incidences of reported pneumonia AESI were 13%, 13%, and 4% in the FF/UMEC/VI, FF/VI, and UMEC/VI groups in the China cohort compared with 8%, 7%, and 5%, respectively, in the ITT population. The higher proportion of males, lower BMI, and worse lung function in the China cohort may have influenced some of these differences, as these are known risk factors for pneumonia. It is worth noting that the IMPACT trial used a broad definition of pneumonia to ensure all pneumonia events were captured; serious adverse reports were adjudicated to determine the primary event. Reassuringly, incidences of these reports, primarily adjudicated to be pneumonia with or without evidence of COPD exacerbation, were consistent across these treatment groups in the two cohorts and of much lower magnitude compared with the reported pneumonia events (COPD exacerbation with evidence of pneumonia – China: FF/UMEC/VI 6%, FF/VI 5%, UMEC/VI 5%; ITT: FF/UMEC/VI 3%, FF/VI 3%, UMEC/VI 3%; pneumonia/RTI without COPD exacerbation – China: FF/UMEC/VI 2%, FF/VI <1%, UMEC/VI 0%; ITT: FF/UMEC/VI 2%, FF/VI 1%, UMEC/VI 1%). The results presented here are similar to those in the KRONOS study, which evaluated patients at low risk of pneumonia or exacerbation, of whom 23% were from China [21, 22]. In the KRONOS study, physician-reported pneumonia rates were higher than adjudicated rates in the overall study population, and the incidence of adjudicated pneumonia in the budesonide/glycopyrrolate/formoterol fumarate treatment arm of the China sub-group was higher than that observed in the overall population [21, 22].

This study provides valuable data on the efficacy and safety of FF/UMEC/VI relative to FF/VI and UMEC/VI in a population of patients from China with symptomatic COPD and a history of exacerbations. However, some limitations should be considered when interpreting the results. Firstly, and importantly, the analysis was carried out in only a small sample of patients, representing only 5% of the appropriately statistically powered overall ITT population. In addition, there were clear and distinct demographic differences between the China and ITT cohorts which may have affected the magnitude in results seen in drug efficacy and safety. Finally, differences in medical practice between China and the overall ITT population, including lower total use of oral/systemic corticosteroids and higher use of antibiotics, may

limit the comparability of the China cohort and overall ITT population. Despite these limitations, our data demonstrate that FF/UMEC/VI is an effective treatment in China for patients with symptomatic COPD and a history of exacerbations. There are no inter-country differences in response to FF/UMEC/VI between patients with COPD in China and the overall ITT population, across multiple efficacy endpoints, providing valuable and relevant information for prescribing physicians in China.

Conclusions

While the IMPACT trial was not powered to demonstrate statistical significance for the primary endpoint of annual rate of on-treatment moderate/severe exacerbations in the China cohort, the treatment comparison for triple therapy with FF/UMEC/VI versus dual therapy with FF/VI for this endpoint was similar to the results in the overall ITT population. Furthermore, treatment with FF/UMEC/VI resulted in clinically meaningful improvements in lung function and health-related quality of life compared with FF/VI and UMEC/VI. No new safety signals were identified in this cohort. These results highlight the favorable benefit/risk profile of FF/UMEC/VI single-inhaler triple therapy in China for patients with symptomatic COPD and a history of exacerbations.

Abbreviations

AE, adverse event; AESI, adverse events of special interest; ATS, American Thoracic Society; BMI, body mass index; CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; ERS, European Respiratory Society; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; GI, gastrointestinal; GOLD, Global initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; ITT, intent-to-treat; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LS, least squares; MedDRA, Medical Dictionary for Regulatory Activities; MMRM, mixed-model repeated measures; OR, odds ratio; RR, rate ratio; RTI, respiratory tract infection; SAE, serious adverse event; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire; SMQ, Standardized MedDRA Query; UMEC, umeclidinium; VI, vilanterol

Declarations

Ethics approval and consent to participate

All patients provided written informed consent. The trial protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational site ethics committee or institutional review board, in accordance with the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice and applicable country-specific requirements, including United States 21 Code of Federal Regulations 312.3(b) for constitution of independent ethics committees.

Consent for publication

Not applicable.

Availability of data and material

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Competing interests

Jinping Zheng is a GSK advisory board member.

Nanshan Zhong, Changzheng Wang, Xiang Dong Zhou, Li Zhao, Ya Dong Yuan, Bei He, Bin We and Li Ping Wei do not have any conflicts of interest to report.

Xin Du and David A. Lipson are GSK employees and hold stock/shares in GSK.

Funding

Editorial support (in the form of writing assistance, assembling figures, collating author comments, grammatical editing and referencing) was provided by Hayley Mukherjee, PhD, at Fishawack Indicia Ltd, UK, and was funded by GSK. This study was funded by GSK (study number CTT116855). The funders of the study had a role in the study design, data analysis, data interpretation, and writing of the report.

Authors' contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors, take responsibility for the integrity of the work as a whole, contributed to the writing and reviewing of the manuscript, and have given final approval for the version to be published. All authors had full access to the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

N Zhong and J Zheng were involved in the acquisition of data and data analysis/interpretation. C Wang, LP Wei, XD Zhou, L Zhao, YD Yuan, B He and B Wu were involved in analysis/interpretation of data. X Du was involved in data analysis/interpretation. DA Lipson was involved in the conception/design of the study, acquisition of data and data analysis/interpretation.

Acknowledgments

Editorial support (in the form of writing assistance, assembling figures, collating author comments, grammatical editing and referencing) was provided by Hayley Mukherjee, PhD, at Fishawack Indicia Ltd, UK, and was funded by GSK. The authors thank the investigators, patients and their families, for participation in the IMPACT trial.

References

1. Global Initiative for Chronic Obstructive Lung Disease: Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease (2019 report). 2019.
2. World Health Organization. The top 10 causes of death. 2018 http://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death Accessed: 30 July 2019
3. Mathers CD, Loncar D: Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3(11):e442.
4. Wang C, Xu J, Yang L, Xu Y, Zhang X, Bai C, Kang J, Ran P, Shen H, Wen F, et al: Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study. Lancet 2018;391(10131):1706-1717.
5. Kurmi OP, Davis KJ, Hubert Lam KB, Guo Y, Vaucher J, Bennett D, Wang J, Bian Z, Du H, Li L, et al: Patterns and management of chronic obstructive pulmonary disease in urban and rural China: a community-based survey of 25 000 adults across 10 regions. BMJ Open Respir Res 2018;5(1):e000267.
6. Fang L, Gao P, Bao H, Tang X, Wang B, Feng Y, Cong S, Juan J, Fan J, Lu K, et al: Chronic obstructive pulmonary disease in China: a nationwide prevalence study. Lancet Respir Med 2018;6(6):421-430.
7. Gao J, Prasad N: Chronic obstructive pulmonary disease in China: the potential role of indacaterol. J Thorac Dis 2013;5(4):549-558.
8. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, Dransfield MT, Halpin DMG, Han MK, Jones CE, et al: Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. N Engl J Med 2018;378(18):1671-1680.
9. Hu C, Jia J, Dong K, Luo L, Wu K, Mehta R, Peng J, Ren Y, Gross A, Yu H: Pharmacokinetics and tolerability of inhaled umeclidinium and vilanterol alone and in combination in healthy Chinese subjects: a randomized, open-label, crossover trial. PLoS One 2015;10(3):e0121264.
10. Allen A, Bal J, Cheesbrough A, Hamilton M, Kempsford R: Pharmacokinetics and pharmacodynamics of intravenous and inhaled fluticasone furoate in healthy Caucasian and East Asian subjects. Br J Clin Pharmacol 2014;77(5):808-820.
11. Pascoe SJ, Lipson DA, Locantore N, Barnacle H, Brealey N, Mohindra R, Dransfield MT, Pavord I, Barnes N: A phase III randomised controlled trial of single-dose triple therapy in COPD: the IMPACT protocol. Eur Respir J 2016;48(2):320-330.
12. Celli BR, MacNee W, Force AET: Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23(6):932-946.
13. Husebo GR, Bakke PS, Aanerud M, Hardie JA, Ueland T, Gronseth R, Persson LJ, Aukrust P, Eagan TM: Predictors of exacerbations in chronic obstructive pulmonary disease--results from the Bergen COPD cohort study. PLoS One 2014;9(10):e109721.
14. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA: The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med 2008;177(1):19-26.

15. The Commonwealth Fund. The Chinese Health Care System https://international.commonwealthfund.org/countries/china/ Accessed: 11 June 2019.
16. Lee SD, Huang MS, Kang J, Lin CH, Park MJ, Oh YM, Kwon N, Jones PW, Sajkov D, Investigators of the Predictive Ability of CATiAEoCS: The COPD assessment test (CAT) assists prediction of COPD exacerbations in high-risk patients. Respir Med 2014;108(4):600-608.
17. Wacker ME, Jorres RA, Karch A, Wilke S, Heinrich J, Karrasch S, Koch A, Schulz H, Watz H, Leidl R, et al: Assessing health-related quality of life in COPD: comparing generic and disease-specific instruments with focus on comorbidities. BMC Pulm Med 2016;16(1):70.
18. Tantucci C, Modina D: Lung function decline in COPD. Int J Chron Obstruct Pulmon Dis 2012;7:95-99.
19. Zheng J, de Guia T, Wang-Jairaj J, Newlands AH, Wang C, Crim C, Zhong N: Efficacy and safety of fluticasone furoate/vilanterol (50/25 mcg; 100/25 mcg; 200/25 mcg) in Asian patients with chronic obstructive pulmonary disease: a randomized placebo-controlled trial. Curr Med Res Opin 2015;31(6):1191-1200.
20. Donohue JF, Maleki-Yazdi MR, Kilbride S, Mehta R, Kalberg C, Church A: Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. Respir Med 2013;107(10):1538-1546.
21. Ferguson GT, Rabe KF, Martinez FJ, Fabbri LM, Wang C, Ichinose M, Bourne E, Ballal S, Darken P, DeAngelis K, et al: Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. Lancet Respir Med 2018;6(10):747-758.
22. Wang C, Yang T, Kang J, Chen R, Zhao L, He H, Assam PN, Su R, Bourne E, Ballal S, et al: Efficacy and Safety of Inhaled Triple Therapy Budesonide/Glycopyrrolate/Formoterol Fumarate Metered Dose Inhaler (BGF MDI) Versus Dual Therapies in Chinese Patients with Moderate-to-Very Severe COPD. Am J Respir Crit Care Med 2019;199:A3333.

Tables

Table 1. Demographics and baseline characteristics

Characteristic	China			Overall ITT		
	FF/UMEC/VI	FF/VI	UMEC/VI	FF/UMEC/VI	FF/VI	UMEC/VI
	N=213	N=216	N=106	N=4151	N=4134	N=2070
Male, n (%)	204 (96)	205 (95)	102 (96)	2766 (67)	2748 (66)	1356 (66)
Age, years, mean (SD)	66.1 (7.4)	65.5 (7.2)	66.0 (7.8)	65.3 (8.2)	65.3 (8.3)	65.2 (8.3)
BMI, kg/m^2, mean (SD)	22.6 (3.8)	22.3 (3.6)	22.1 (3.3)	26.6 (6.2)	26.7 (6.1)	26.6 (5.9)
COPD medication, n (%)[a]						
ICS + LABA + LAMA	60 (28)	53 (25)	35 (33)	1396 (34)	1433 (35)	734 (35)
ICS + LABA	74 (35)	90 (42)	39 (37)	1103 (27)	1067 (26)	523 (25)
LABA + LAMA	2 (<1)	2 (<1)	1 (<1)	330 (8)	308 (7)	163 (8)
LAMA	20 (9)	27 (13)	8 (8)	273 (7)	331 (8)	140 (7)
Post-bronchodilator FEV_1, mL, mean (SD)[b]	1131 (441)	1113 (409)	1127 (437)	1275 (488)	1272 (486)	1268 (481)
Post-bronchodilator FEV_1, % predicted normal, mean (SD)	40.5 (14.7)	39.7 (14.3)	40.3 (14.4)	45.7 (15.0)	45.5 (14.8)	45.4 (14.7)
Exacerbation history, n (%)[c]						
<2 moderate, no severe	61 (29)	77 (36)	39 (37)	1198 (29)	1242 (30)	616 (30)
≥2 moderate, ≥1 severe	152 (71)	139 (64)	67 (63)	2953 (71)	2892 (70)	1454 (70)
CAT score, mean (SD)[c]	18.5 (6.0)	19.4 (5.9)	19.8 (6.0)	20.1 (6.1)	20.1 (6.1)	20.2 (6.2)
Smoking status, n (%)	48 (23)	51 (24)	28 (26)	1436 (35)	1423 (34)	728 (35)
Current smoker	165 (77)	165 (76)	78 (74)	2715 (65)	2711 (66)	1342 (65)
Former smoker[d]						

[a]Includes all COPD medications taken on the day of the Screening Visit, excluding medications that stopped on the day of the Screening Visit.

[b]Overall ITT: N=4145, 4133, and 2069 for FF/UMEC/VI, FF/VI, and UMEC/VI, respectively

[c]Exacerbations in previous year

[c]Overall ITT: N=4142, 4124, and 2061 for FF/UMEC/VI, FF/VI, and UMEC/VI, respectively

[d]Former smokers were defined as patients who had not smoked for >6 months prior to the visit

BMI, body mass index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; ICS, inhaled corticosteroids; ITT, intent-to-

treat; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol.

Table 2. Rates and risk (time-to-first analysis) of on-treatment moderate/severe exacerbation

	China			Overall ITT		
	FF/UMEC/VI N=213	FF/VI N=216	UMEC/VI N=106	FF/UMEC/VI N=4151	FF/VI N=4134	UMEC/VI N=2070
n	213	216	106	4145	4133	2069
Patients with an event, n (%)	89 (42)	101 (47)	47 (44)	1959 (47)	2039 (49)	1036 (50)
Model-estimated annual exacerbation rate (95% CI)	0.81 (0.67, 0.99)	0.96 (0.80, 1.17)	0.80 (0.60, 1.07)	0.91 (0.87, 0.95)	1.07 (1.02, 1.12)	1.21 (1.14, 1.29)
FF/UMEC/VI versus comparator						
Rate ratio (95% CI)		0.84 (0.64, 1.11)	1.02 (0.72, 1.44)		0.85 (0.80, 0.90)	0.75 (0.70, 0.81)
Unadjusted p-value		0.227	0.929		<0.001	<0.001
Hazard ratio (95% CI)		0.84 (0.63, 1.11)	0.89 (0.62, 1.27)		0.85 (0.80, 0.91)	0.84 (0.78, 0.91)
Unadjusted p-value		0.218	0.516		<0.001	<0.001

CI, confidence interval; FF, fluticasone furoate; ITT, intent-to-treat; UMEC, umeclidinium; VI, vilanterol.

Table 3. Summary of on-treatment AESI and adjudicated SAEs

	China			Overall ITT		
	FF/UMEC/VI N=231	FF/VI N=216	UMEC/VI N=106	FF/UMEC/VI N=4151	FF/VI N=4134	UMEC/VI N=2070
On-treatment AEs, n (%)						
Any	165 (77)	171 (79)	80 (75)	2897 (70)	2800 (68)	1429 (69)
Drug-related	24 (11)	21 (10)	16 (15)	478 (12)	492 (12)	214 (10)
On-treatment AESI, n (%)*						
Anticholinergic syndrome (SMQ)	15 (7)	10 (5)	4 (4)	184 (4)	140 (3)	70 (3)
Asthma/bronchospasm (SMQ)	2 (<1)	2 (<1)	2 (2)	27 (<1)	34 (<1)	16 (<1)
CV effects	31 (15)	32 (15)	16 (15)	450 (11)	430 (10)	224 (11)
Ocular effects	3 (1)	3 (1)	2 (2)	55 (1)	45 (1)	26 (1)
Decreased bone mineral density/fractures	3 (1)	4 (2)	2 (2)	98 (2)	85 (2)	37 (2)
Effects on potassium	7 (3)	2 (<1)	1 (<1)	34 (<1)	25 (<1)	8 (<1)
GI obstruction (SMQ)	0	0	1 (<1)	9 (<1)	10 (<1)	2 (<1)
Hyperglycemia/new onset diabetes mellitus (SMQ)	16 (8)	11 (5)	2 (2)	152 (4)	117 (3)	73 (4)
Hypersensitivity	15 (7)	14 (6)	1 (<1)	196 (5)	195 (5)	95 (5)
Local steroid effects	8 (4)	7 (3)	3 (3)	337 (8)	301 (7)	108 (5)
Pneumonia	27 (13)	29 (13)	4 (4)	317 (8)	292 (7)	97 (5)
LRTI excluding pneumonia	12 (6)	9 (4)	4 (4)	200 (5)	199 (5)	108 (5)
Tremor	1 (<1)	0	0	8 (<1)	4 (<1)	6 (<1)
Urinary retention	0	0	0	8 (<1)	12 (<1)	9 (<1)
On-treatment SAEs, n (%)						
Any	61 (29)	57 (26)	26 (25)	895 (22)	850 (21)	470 (23)
Drug-related	8 (4)	8 (4)	5 (5)	64 (2)	57 (1)	27 (1)
Fatal	2 (<1)	3 (1)	2 (2)	68 (2)	76 (2)	49 (2)
Adjudicated respiratory SAES, n (%)	43 (20)	43 (20)	19 (18)	541 (13)	544 (13)	299 (14)
COPD exacerbation with evidence of pneumonia	13 (6)	10 (5)	5 (5)	123 (3)	129 (3)	57 (3)

Pneumonia/RTI without COPD exacerbation	4 (2)	2 (<1)	0	63 (2)	59 (1)	21 (1)

*AESI were AEs which have specified areas of interest for ICS, LAMA, or LABA, or for patients with COPD

AE, adverse event; AESI, AE of special interest; COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; GI, gastrointestinal; ICS, inhaled corticosteroids; ITT, intent-to-treat; LABA, long-acting β_2-agonists; LAMA, long-acting muscarinic antagonists; LRTI, lower respiratory tract infection; MedDRA, Medical Dictionary for Regulatory Activities, RTI, respiratory tract infection; SAE, serious adverse event; SMQ, Standardized MedDRA Query; UMEC, umeclidinium; VI, vilanterol.

Figures

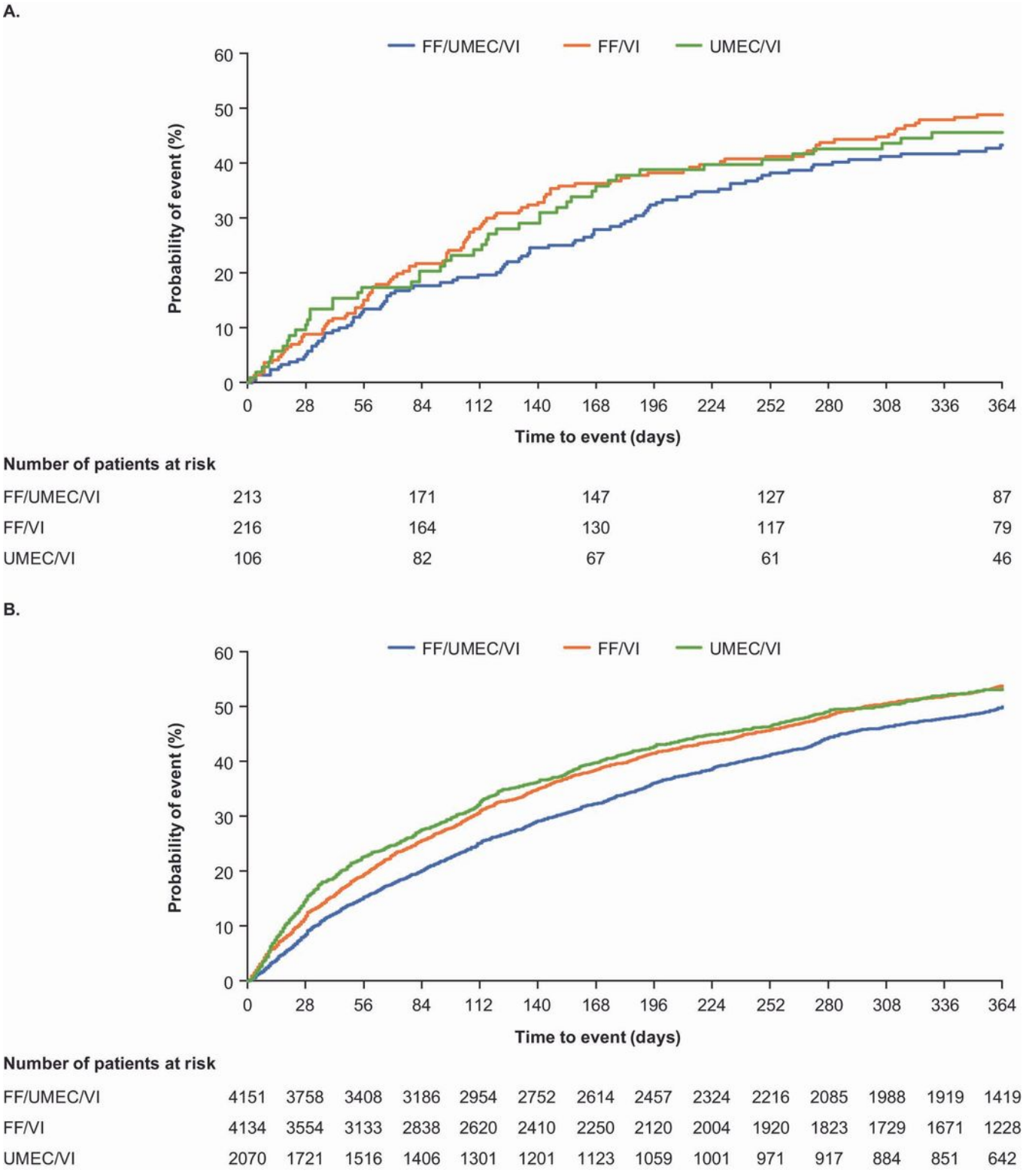

Figure 1

Time-to-first on-treatment moderate/severe exacerbation in (A) China; (B) overall ITT* FF, fluticasone furoate; ITT, intent-to-treat; UMEC, umeclidinium; VI, vilanterol. *From: New England Journal of Medicine. David A. Lipson, Frank Barnhart, Noushin Brealey, Jean Brooks, Gerard J. Criner, Nicola C. Day, Mark T. Dransfield, David M.G. Halpin, MeiLan K. Han, C. Elaine Jones, Sally Kilbride, Peter Lange, David A. Lomas, Fernando J. Martinez, Dave Singh, Maggie Tabberer, Robert A. Wise, and Steven J. Pascoe, for the

IMPACT Investigators. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. Volume 378, pages 1671–1680. Copyright © 2018 Massachusetts Medical Society, Reprinted with permission from Massachusetts Medical Society.

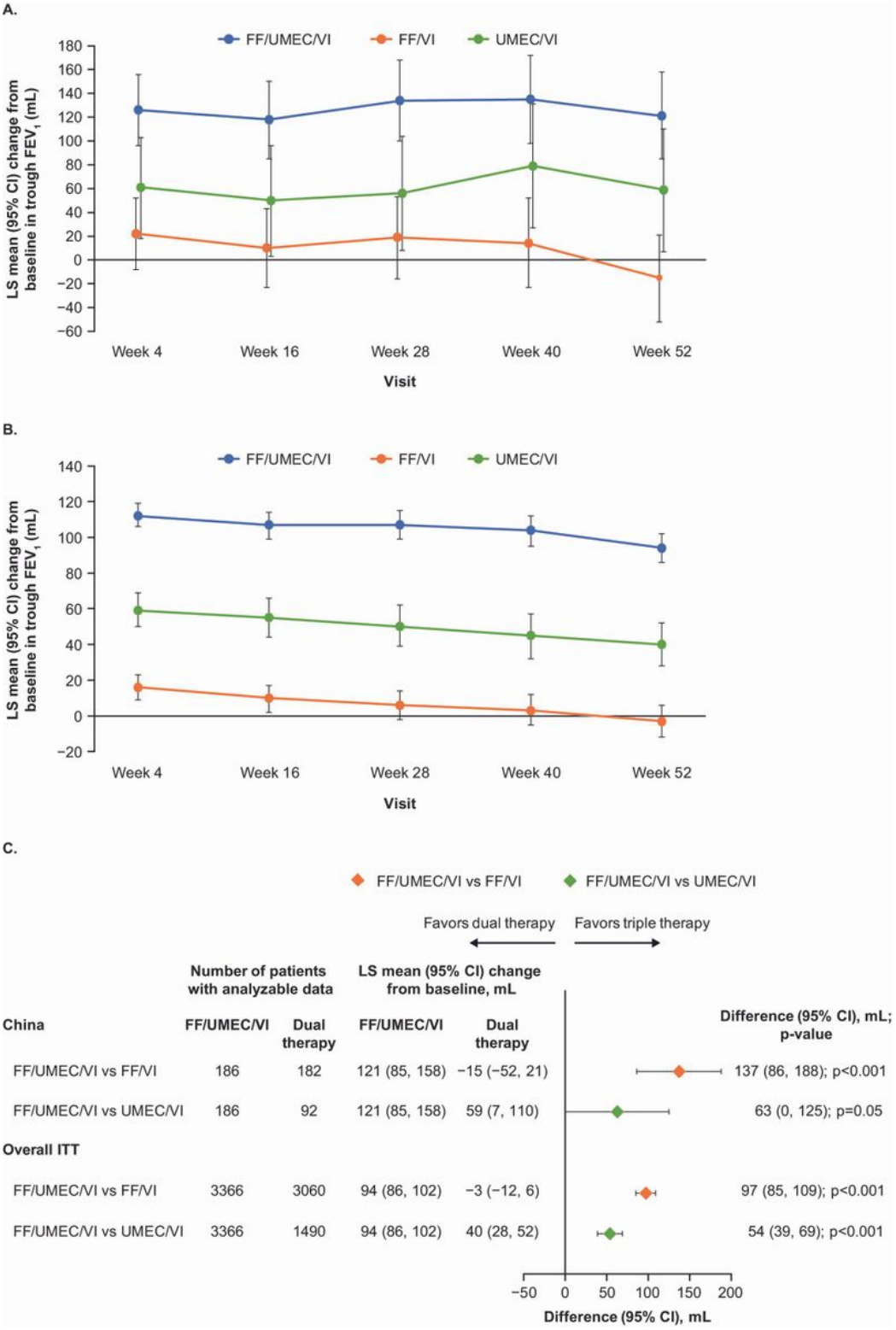

Figure 2

Change from baseline in trough FEV1: (A) China, (B) overall ITT; (C) treatment difference at Week 52 CI, confidence interval; FEV1, forced expiration volume in 1 second; FF, fluticasone furoate; ITT, intent-to-treat;

LS, least squares; UMEC, umeclidinium; VI, vilanterol.

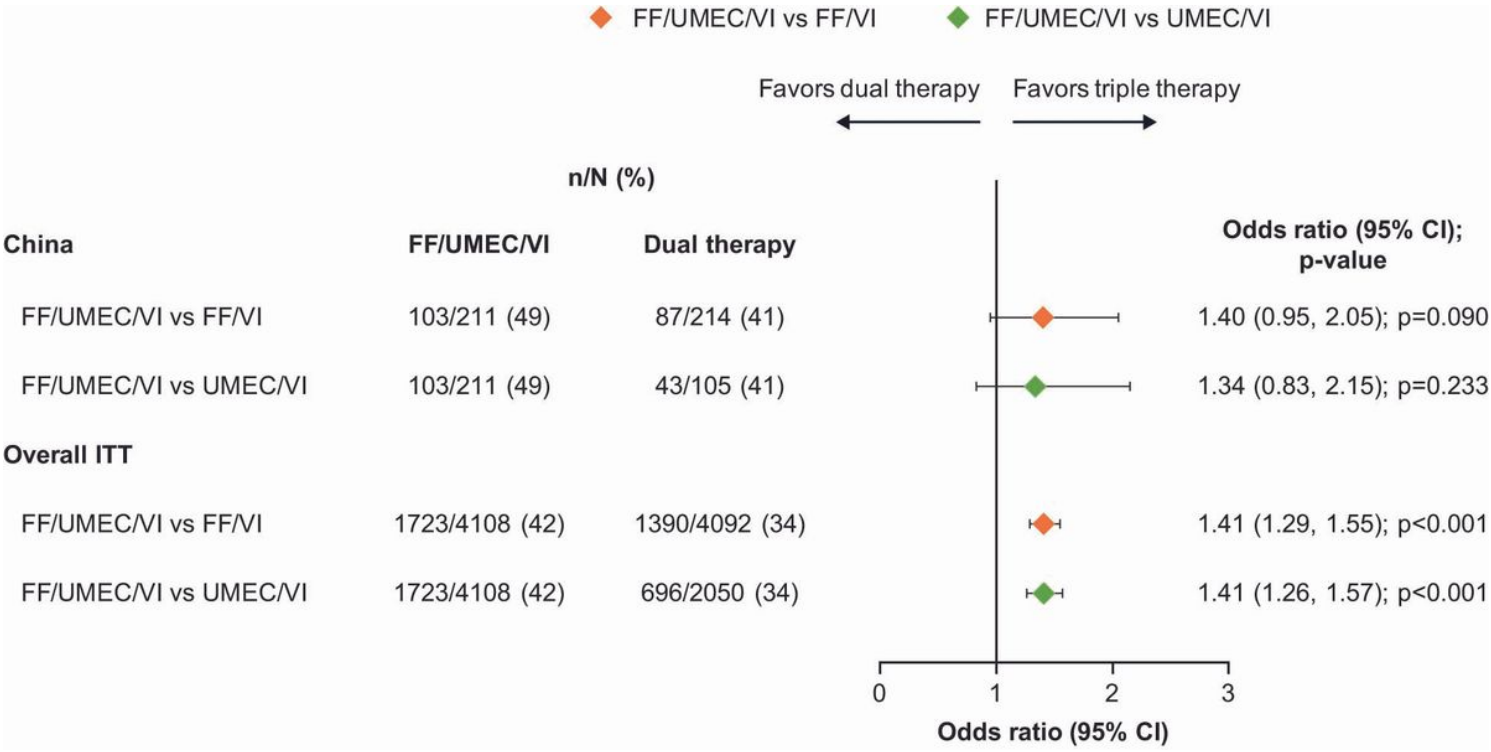

Figure 3

Odds of SGRQ response with FF/UMEC/VI versus dual therapy comparators at Week 52 Response is defined as a decrease from baseline in SGRQ total score of ≥4 units. Non-response is defined a decrease from baseline in SGRQ total score <4 units below baseline, or an increase from baseline in SGRQ total score or a missing SGRQ total score with no subsequent on-treatment scores. Patients did not have a responder status derived if baseline SGRQ total score was missing, or if the SGRQ total score at a particular visit was missing but subsequent on-treatment SGRQ total scores were present. n, number of responders; N, total number of analyzable patients; CI, confidence interval; FF, fluticasone furoate; ITT, intent-to-treat; SGRQ, St George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.

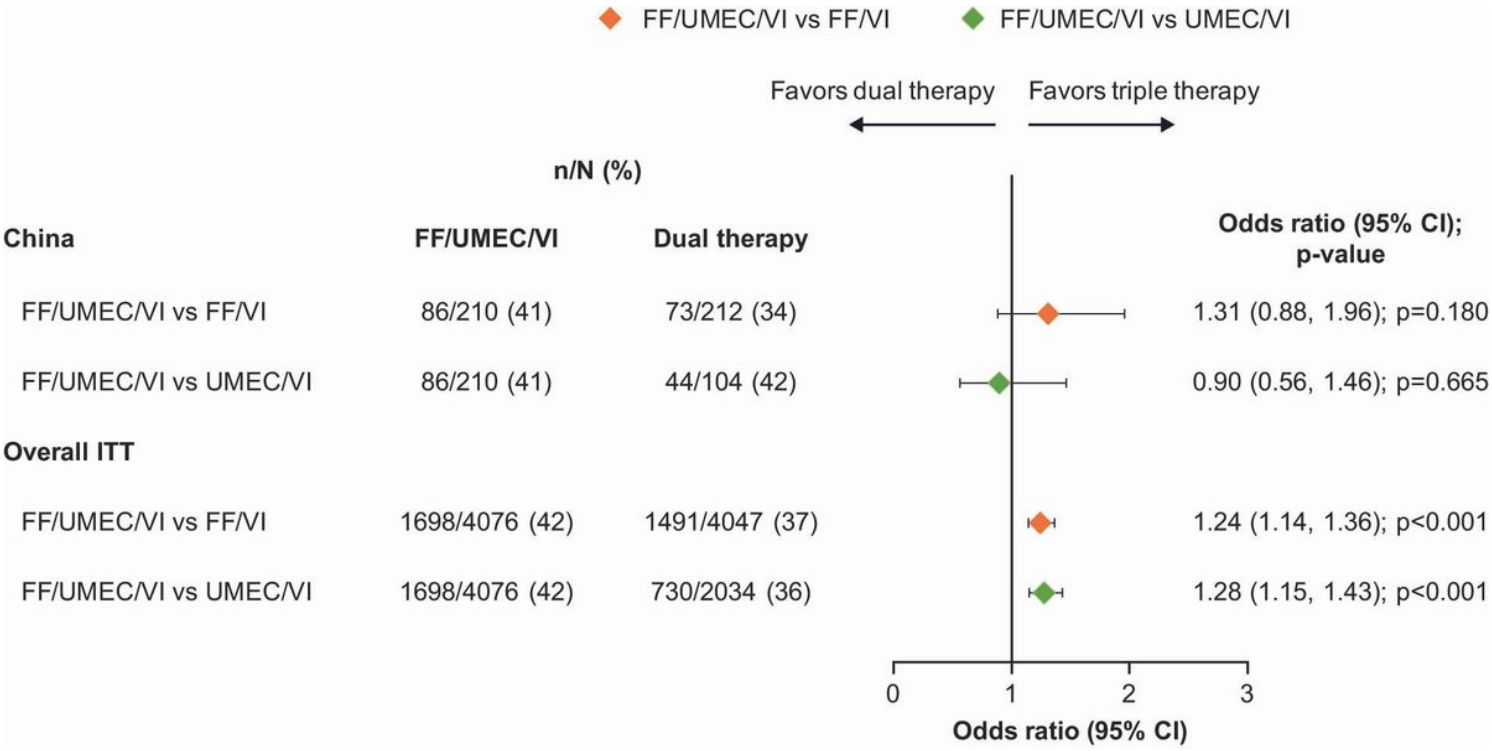

Figure 4

Odds of CAT response with FF/UMEC/VI versus dual therapy comparators at Week 52 Response is defined as a decrease from baseline in CAT score of ≥2 units. Non-response is defined as a decrease from baseline in CAT score <2 units, or an increase from baseline in CAT score, or a missing CAT score with no subsequent non-missing on-treatment scores. Patients did not have a responder status derived if baseline CAT score was missing but subsequent on-treatment CAT scores were present. CAT; COPD Assessment Test; n, number of responders; N, total number of analyzable patients; CI, confidence interval; FF, fluticasone furoate; ITT, intent-to-treat; UMEC, umeclidinium; VI, vilanterol.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- GSK4307SuppFigure2.eps
- SupplementaryFiles.docx
- GSK4307SuppFigure1.eps
- GSK4307SuppFigure3.eps