Name of investigation	Cohort study to estimate incidence of pneumonia in users of Trelegy 100 or multiple inhaler triple therapy among patients with chronic obstructive pulmonary disease using health insurance claims data provided by Medical Data Vision Co., Ltd. in Japan
Protocol No.	212606
Date of preparation of final report	Final report (30 July 2024)
Brand Name	Trelegy 100 Ellipta 14 doses Trelegy 100 Ellipta 30 doses
Active ingredient	Fluticasone furoate/Umeclidinium/Vilanterol
Marketing Authorization Holder (MAH)	GlaxoSmithKline K.K.

1. Protocol summary

Title: Cohort study to estimate incidence of pneumonia in users of Trelegy 100 or multiple inhaler triple therapy among patients with chronic obstructive pulmonary disease using health insurance claims data provided by Medical Data Vision Co., Ltd. in Japan	
Safety specification	Pneumonia Rationale: To collect information on the incidence of the safety specification in clinical practice.
Objectives	Primary Objective: Compare the occurrence of hospitalization due to community-acquired pneumonia (CAP) among patients with COPD who were incident users of Trelegy 100 or multiple inhaler triple therapy (MITT). Hazard ratio (HR) will be calculated to investigate if the risk of CAP in Trelegy 100 group is not higher than a certain level (HR>3) compared to MITT group. Secondary Objectives: a) Estimate the incidence rate of hospitalization due to CAP among COPD patients who were treated with Trelegy 100 or MITT. Overall, or incident triple use patients will be analysed in Trelegy group and MITT group, respectively. b) Describe characteristics of COPD patients who were treated with Trelegy 100 or MITT. Overall, or incident triple use patients will be analysed in Trelegy group and MITT group, respectively. c) Calculate crude and adjusted HRs for hospitalization due to CAP within Trelegy 100 or MITT group for each covariate, with one of the covariate subgroups serving as the reference group. Each model would be adjusted for all the other stated covariates. Overall, or incident triple use patients will be analysed in Trelegy 100 group and MITT group, respectively. In the model, following subgroups will be considered; gender, age, calendar year of Index date, month of Index date, COPD treatments in look-back period, hospitalization due to COPD exacerbation in look-back period, hospitalization due to CAP in look-back period, comorbidities of pre-defined disease such as asthma, myocardial infarction, congestive heart failure, cerebrovascular disease, dementia, peptic ulcer, peripheral vascular disease, connective tissue disease, diabetes, anxiety, depression, body mass index (BMI), smoking history, and execution of lung function test within Trelegy 100 or MITT group. d) Describe change over time in the expansion of triple therapy, use of an ICS-containing medications, and proportion of asthma comorbidity among COPD patients. Over-time refers to 360 days prior to date of launch of Trelegy 100, and 0-359 days, 360-719 days, 720- 1079 days after the launch. Target population for this objective includes COPD patients regardless of treatment. *Overall users refer to those have prescriptions of Trelegy 100 or MITT between May 22, 2019 (launch date of Trelegy 100) and May 5, 2022. The index date will be the first prescription date on or after May 22, 2019. Incident users are subpopulation of overall users who do not have any triple therapies for 360 days before the index date.
Priority investigation items	Not applicable
Efficacy specification	Not applicable
Study method	Post-marketing database survey
Data source	The proposed study will be conducted using the Japanese MDV hospital claims database. MDV is a Japanese company specializing in integrated medical systems that manages a large administrative database constructed from hospitals (mainly tertiary) in Japan. The MDV data cover around 25% of acute care hospitals in Japan (439 hospitals) and include both inpatient and outpatient services. For the cumulative period between April 2008 and February 2021, the database has over 35.7 million patients, making it one of the largest Japanese healthcare datasets. The data is updated monthly, thereby minimizing the time lag for data access and analyses. The database contains disease diagnoses, claims for medical procedures and pharmacy prescriptions (from inpatient and outpatient services in the hospitals covered), and laboratory test results available for approximately 10% of patients. In addition, MDV establishes and operates the hospital claims database in an appropriate manner to ensure data authenticity, legibility and proper archival. Each DPC hospital has assigned a hospital-specific ID for each patient, and patients can be followed both as inpatients and outpatients in the same DPC hospital, but they cannot be followed after transfer. This study will use all available data between November 2017 and Apr 2023 in the MDV hospital claims database to assess the proposed study objectives.
Study population	Inclusion Criteria ・At least one prescription of Trelgy 100 or MITT between May 22, 2019 (date of launch of Trelegy 100) and May 5, 2022. The index date is the first prescription date on or after May 22, 2019. ・Age ≥ 40 years at the time of the index ・At least one inpatient or outpatient diagnosis of COPD (J42, J43, or J44) at the time of the index and at least 2 times during the look back period (-360 to -1 days from the index date) ・Diagnosis with any ICD-10 code during the 180 days prior to the look back period (-540 to -360 days from the index date) Exclusion Criteria Patients who meet the definition of hospitalization due to CAP within 30 days before the index date to the day before the index date will be excluded Incident users are subpopulation of overall users who do not have any triple therapies during the look back period (-

	360 to -1 days from the index date). The primary objective analysis will include patients who are incident users of Trelegy 100 or MITT, and the secondary objective analysis will include overall users.
Outcome	Hospitalization due to CAP which occurs 1 day or more after the index date. Admission date will be treated as the first day of hospitalization due to CAP. ・Diagnosis of pneumonia (ICD10 Code J10.0, J11.0, or J12 - J18) with DPC disease segment #21 (disease which triggered the hospitalization) ・Prescription of antibiotics (Anatomical Therapeutic Chemical (ATC) code: J01) on the day or next day of admission ・Diagnostic imaging (X-ray or computerized tomography (CT) scan) conducted between 2 days before and 7 days after the hospitalization
Data period	November 2017 to April 2023
Study design	Cohort design
Expected sample size	Trelegy 100 : ≥ 1,935, MITT : ≥ 1,311
Observation period	Until the following date, whichever comes first. 1) Hospitalization due to CAP, 2) Death, 3) Discontinuation of treatment, 4) 360 days after the Index Date (1440 days for sensitivity analysis)
Data Analysis	Primary analysis : HR for hospitalization due to CAP among incident Trelegy 100 users compared to incident MITT users Secondary analysis: a) Incidence rates of "hospitalization due to CAP" in Trelegy 100 or MITT groups b) Characteristics of patients in Trelegy 100 or MITT groups Age, gender, medical history/comorbidities, history of COPD treatments/exacerbation/pneumonia For secondary objectives, both Trelegy 100 and MITT groups will be analysed in overall or incident users. *Overall users refer to those have prescriptions of Trelegy 100 or MITT between May 22, 2019 (launch date of Trelegy 100) and May 5, 2022. The index date will be the first prescription date on or after May 22, 2019. Incident users are subpopulation of overall users who do not have any triple therapies for 360 days before the index date. c) Crude and adjusted HRs for "hospitalization due to CAP" by gender, age, calendar year of Index date, month of Index date, COPD treatments in look-back period, hospitalization due to COPD exacerbation in look-back period, hospitalization due to CAP in look-back period, comorbidities of pre-defined disease such as asthma, myocardial infarction, congestive heart failure, cerebrovascular disease, dementia, peptic ulcer, peripheral vascular disease, connective tissue disease, diabetes, anxiety, depression, BMI, smoking history, and execution of lung function test within Trelegy 100 or MITT group in overall or incident users. d) Proportion of triple therapy among COPD patients before the launch date of Trelegy 100 (May 22, 2019) and annually after the launch date (360 days prior to date of launch of Trelegy 100, and 0-359 days, 360-719 days, 720- 1079 days after the launch). Proportion of any ICS-containing therapies and comorbid asthma will be calculated as well. Target population for this objective includes COPD patients regardless of treatment. Sensitivity analysis: For the purpose of confirming the robustness of the analysis of the primary and secondary objectives, the sensitivity analysis will be performed when the following conditions are changed. a) One of inclusion criteria is changed from "patients with ICD-10 codes for COPD (J42, J43 or J44)" to "patients with ICD-10 codes for COPD (J42, J43 or J44) and with prescription of any inhaled medicine with the indication of COPD", at the index date and on at least 2 visits (outpatient visit or hospital admission) in the look-back period b) Overlap of 3 components for MITT group is changed from at least 1 day to at least 14 days (including the index date) c) Follow-up period is changed from maximum 360 days to maximum 1,440 days (after the index date) Supplemental analyses: Based on the discussion at the epidemiology consultation (P24, December 23, 2020), supplemental analyses for the primary and secondary objectives a) will be performed as follows. a) Regarding the definition of hospitalization due to CAP, if antibiotics are limited to injectable medications b) If outcome is limited to CAP hospitalization in non-COVID -19 infected patients
Efficacy evaluation criteria	Not applicable
Remarks	Protocol Modifications: August 24, 2021: Newly created October 27, 2022: Minor change

2. Study results

2.1. Study Population

The disposition of patients in this study was as shown in F1.01. A total of 8790 patients in the Trelegy 100 group and 10881 patients in the MITT group were prescribed Trelegy 100 or MITT between May 22, 2019 (date of launch of Trelegy 100) and May 5, 2022 and met the inclusion/exclusion criteria. Of overall users, 3939 in the Trelegy 100 group and 4017 in the MITT group were incident users who did not receive any triple therapy during the look back period (-360 to -1 days from the index date).

The patient disposition in the sensitivity analyses a) "If COPD is defined on the condition that the patient has a record of prescription of an inhaled COPD medicine in addition to the diagnosis." and b) "If the definition of MITT is based on at least 14 days of overlapping prescription periods for 3 components" are shown in F1.02 and F1.03, respectively. The total number of patients included in the sensitivity analysis a) was 7545 in the Trelegy 100 group and 9491 in the MITT group. Among them, the number of incident users was 2685 in the Trelegy 100 group and 2586 in the MITT group. The total number of patients in the sensitivity analysis b) was 8790 in the Trelegy 100 group and 10358 in the MITT group. The number of incident users was 3939 in the Trelegy 100 group and 3553 in the MITT group. The patient disposition in the sensitivity analysis c) “when the maximum observation period is 1440 days from the index date” is the same as that in F 1.01.

2.2. Patient characteristics

The patient characteristics of overall users and incident users of Trelegy 100 or MITT are shown in T1.01. In the Trelegy 100 and MITT groups of overall users, 79.3% and 69.7% were male, respectively, and the mean age was 74.2±9.2 years and 73.1±10.5 years, respectively. The percentages of patients with non-missing BMI were 54.2% and 54.3%, respectively, and the mean values were 22.4±4.1 and 22.5±4.5. The percentage of patients with asthma (defined by ICD-10 codes and prescription of asthma medication) was 56.7% in the Trelegy 100 group and 85.7% in the MITT group. The proportions of patients who had a record of ICS prescription in the year before the Index Date were 67.1% and 80.0%, respectively. In the incident users of Trelegy 100 and MITT groups, the proportion of males was 81.3% and 69.4%, respectively, and the mean age was 74.9±8.7 years and 73.3±10.6 years, respectively. The percentages of patients with non-missing BMI were 55.2% and 58.0%, respectively, and the mean values were 22.3±4.0 and 22.4±4.4. The percentage of patients with asthma (defined by ICD-10 codes and prescription of asthma medication) was 31.1% in the Trelegy 100 group and 76.4% in the MITT group. The proportions of patients who had a record of ICS prescription in the year before the Index Date were 27.6% and 47.5%, respectively. The mean observation period was 222.5±125.8 days in the Trelegy 100 group and 159.7±120.3 days in the MITT group for overall users. The corresponding values in incident users were 208.0±126.2 days and 126.9±108.8 days, respectively. Patient characteristics in sensitivity analyses a) and b) were also generally similar (T1.02, T1.03). The patient characteristics in the sensitivity analysis c) are the same as those in T 1.01.

2.3. Safety

2.3.1. HR of CAP hospitalization among incident users

The crude and covariate-adjusted HRs (hereinafter, adjusted HR) of hospitalization due to CAP in patients newly prescribed Trelegy 100 versus MITT newly prescribed patients are shown in T2.01 and T2.011 to T2.013. Of the covariates, BMI data were frequently missing: missing data were found in 44.8% of patients in the Trelegy 100 group and 42.0% of patients in the MITT group who were incident users (T 1.01). BMI is a major risk factor for ICS-related pneumonia and many missing data may not appropriately adjust the analysis. However, it was unclear whether missing BMI was "Missing Completely At Random", "Missing At Random,", or "Not Missing At Random." The following four adjustments were made to address each missing pattern:

- PS adjustment including BMI without BMI missing imputation (complete case analysis)
- PS adjustment without BMI
- PS adjustment with multiple imputation for BMI
- PS adjustment with missing-indicator method for BMI

In the complete case analysis, the crude HR was 0.99 (95% CI: 0.74-1.32) and the adjusted HR was 1.15 (95% CI: 0.80-1.65) for CAP hospitalization among patients newly prescribed with Trelegy 100 compared with patients newly prescribed with MITT (T 2.01). The crude HR was 0.92 (95% CI: 0.72-1.17) and the adjusted HR was 1.05 (95% CI: 0.76-1.44), 1.07 (95% CI: 0.78-1.47) and 1.07 (95% CI: 0.78-1.48), respectively, when BMI was not adjusted, when it was adjusted by imputing missing BMI using multiple imputation, or when it was adjusted by imputing missing BMI using the missing-indicator method (T 2.011 to T 2.013). Patient characteristics before and after adjustment were as shown in T 1.11 and T 1.111 to T 1.113. Neither of the adjustment methods showed any bias in patient characteristics in both groups after adjustment.

The results of sensitivity analysis are shown in T 2.02 to T 2.04. In the complete case analysis of sensitivity analysis a) "If COPD is defined on the condition that the patient has a record of prescription of an inhaled COPD medicine in addition to the diagnosis", sensitivity analysis b) "If the definition of MITT is based on at least 14 days of overlapping prescription periods for 3 components" and sensitivity analysis c) "when the maximum observation period was 1440 days after the Index Date", the crude HR was 1.20 (95% CI: 0.83-1.72), 0.94 (95% CI: 0.70-1.26), and 1.01 (95% CI: 0.77-1.34), and the adjusted HR was 1.46 (95% CI: 0.91-2.36), 1.08 (95% CI: 0.75-1.55), and 1.16 (95% CI: 0.83-1.64), respectively. The results of different adjustment methods for BMI in each sensitivity analysis were as shown in T 2.021 to T2.023, T2.031 to T2.033, and T2.041 to T 2.043, respectively. In sensitivity analysis a), the crude HR was 0.98 (95% CI: 0.72-1.32) and the adjusted HR was 1.13 (95% CI: 0.73-1.74), 1.14 (95% CI: 0.74-1.76), and 1.19 (95% CI: 0.77-1.84), respectively, when BMI was not adjusted, when it was adjusted by imputing missing BMI using multiple imputation, or when it was adjusted by imputing missing BMI using the missing-indicator method (T 2.021 to T 2.023). In sensitivity analysis b), the crude HR was 0.88 (95% CI: 0.69-1.12) and the adjusted HR was 0.97 (95% CI: 0.70-1.34), 0.99 (95% CI: 0.72-1.37), and 1.00 (95% CI: 0.72-1.38), respectively, when BMI was not adjusted, when it was adjusted by imputing missing BMI using multiple imputation, or when it was adjusted by imputing missing BMI using the missing-indicator method (T 2.031 to T 2.033). In sensitivity analysis c), the crude HR was 0.92 (95% CI: 0.73-1.16) and the adjusted HR was 1.05 (95% CI: 0.78-1.41), 1.07 (95% CI: 0.79-1.44), and 1.07 (95% CI: 0.79-1.45), respectively, when BMI was not adjusted, when it was adjusted by imputing missing BMI using multiple imputation, or when it was adjusted by imputing missing BMI using the missing-indicator method (T 2.041 to T 2.043). There were no major differences in the results with any adjustment method. Patient characteristics before and after adjustment in sensitivity analyses a) and b) were as shown in T 1.12, T1.121 to T1.123, T 1.13 and T 1.131 to T 1.133. There was no bias in the characteristics of both groups after adjustment. The patient characteristics before and after adjustment in the sensitivity analysis c) are the same as those in T 1.11 and T 1.111 to T 1.113.

Based on the discussion at the epidemiology consultation (P24, December 23, 2020), the results of supplemental analysis for the primary objective are shown in T 2.05 and T 2.06. In the complete case analysis in the supplemental analyses a) "Regarding the definition of hospitalization due to CAP, if antibiotics are limited to injectable medications" and b) "If outcome is limited to CAP hospitalization in non-COVID -19 infected patients", the crude HR was 0.97 (95% CI: 0.73-1.30) and 0.98 (95% CI: 0.73-1.31), and the adjusted HR was 1.14 (95% CI: 0.79-1.63) and 1.14 (95% CI: 0.80-1.65), respectively. The results of different adjustment methods for BMI in each supplementary analysis were as shown in T 2.051 to T2.053, T2.061 to T 2.063, respectively. In supplementary analyses a), the crude HR was 0.91 (95% CI: 0.71-1.17) and the adjusted HR was 1.03 (95% CI: 0.75-1.42), 1.05 (95% CI: 0.76-1.45), and 1.06 (95% CI: 0.76-1.47), respectively, when BMI was not adjusted, when it was adjusted by imputing missing BMI using multiple imputation, or when it was adjusted by imputing missing BMI using the missing-indicator method (T2.051 to T2.053). In the supplementary analysis b), the crude HR was 0.91 (95% CI: 0.71-1.17) and the adjusted HR was 1.05 (95% CI: 0.76-1.44), 1.07 (95% CI: 0.77-1.47) and 1.07 (95% CI: 0.77-1.48), respectively, when BMI was not adjusted, when it was adjusted by imputing missing BMI using multiple imputation, or

when it was adjusted by imputing missing BMI using the missing-indicator method (T2.061 to T2.063). There were no major differences in the results with any adjustment method. The patient characteristics before and after adjustment are the same as those in T 1.11 and T 1.111 to T 1.113.

In summary, the risk of hospitalization due to CAP in the Trelegy 100 group was below the pre-specified level (HR>3) and there were no safety concerns with hospitalization due to CAP. Therefore, no additional precautionary statement in the package insert is necessary at present.

2.3.2. Incidence rates of hospitalization due to CAP

The crude and adjusted incidence rates of hospitalization due to CAP in the Trelegy 100 or MITT groups are shown in T 2.11. The crude incidence rate based on the complete case analysis was 86.18 (95%CI: 75.74 – 98.07) [/1000 Person-years] in the Trelegy 100 group and 110.28 (95%CI: 97.66 – 124.53) [/1000 Person-years] in the MITT group among overall users. The adjusted incidence rates were 227.24 (95%CI: 155.48 – 332.13) [/1000 person-years] and 296.86 (95%CI: 200.38 – 439.78) [/1000 person-years], respectively. In the incident users in Trelegy 100 and MITT groups, the crude incidence rates based on the complete case analysis were 89.44 (95%CI: 73.71 – 108.52) [/1000 Person-years] and 105.30 (95%CI: 84.21 – 131.68) [/1000 Person-years], respectively, and the adjusted incidence rates were 182.74 (95%CI: 97.16 – 343.67) [/1000 Person-years] and 252.68 (95%CI: 128.85 – 495.49) [/1000 Person-years], respectively. The results of different adjustment methods for BMI were as shown in T 2.111 to T 2.113. There were no major differences in the results with any adjustment method.

The results of sensitivity analysis are shown in T 2.12 to T 2.14. In the complete case analysis of sensitivity analysis a) "If COPD is defined on the condition that the patient has a record of prescription of an inhaled COPD drug in addition to the diagnosis," sensitivity analysis b) "If the definition of MITT is based on at least 14 days of overlapping prescription periods for 3 components," and sensitivity analysis c) "when the maximum observation period was 1440 days after the Index Date," the crude incidence rates in the Trelegy 100 group of overall users were 87.31 (95% CI: 76.19-100.07), 86.18 (95% CI: 75.74-98.07), and 74.95 (95% CI: 66.86-84.02), respectively, and those in the MITT group were 105.43 (95% CI: 92.58-120.05), 110.99 (95% CI: 98.30-125.32), and 93.42 (95% CI: 83.11-105.00), respectively. The adjusted incidence rates for overall users in the Trelegy 100 group were 225.26 (95% CI: 149.67-339.04), 228.69 (95% CI: 156.52-334.15), and 215.51 (95% CI: 152.21-305.13), respectively, and the adjusted incidence rates in the MITT group were 264.08 (95% CI: 173.65-401.61), 303.19 (95% CI: 204.46-449.59), and 277.96 (95% CI: 194.44-397.34), respectively. For incident users, the crude incidence rates in the Trelegy 100 group were 96.13 (95% CI: 77.24-119.65), 89.44 (95% CI: 73.71-108.52), and 76.00 (95% CI: 63.59-90.84), respectively, and the crude incidence rates in the MITT group were 88.58 (95% CI: 66.17-118.57), 108.64 (95% CI: 86.85-135.89), and 91.45 (95% CI: 73.50-113.78), respectively. For incident users, the adjusted incidence rates were 149.16 (95% CI: 71.11-312.90), 182.33 (95% CI: 96.56-344.28), and 170.74 (95% CI: 93.31-312.44), respectively, for the Trelegy 100 group and 132.20 (95% CI: 59.89-291.80), 265.63 (95% CI: 134.58-524.29), and 230.44 (95% CI: 119.58-444.08), respectively, for the MITT group. The results of different adjustment methods for BMI in each sensitivity analysis were as shown in T 2.121 to T2.123, T2.131 to T2.133, and T2.141 to T 2.143, respectively. There were no major differences in the results with any adjustment method.

The results of supplemental analysis performed based on the discussion at the epidemiology consultation (P24 dated December 23, 2020) are shown in T 2.15 and T 2.16. The results of the complete case analysis in the supplemental analyses a) "Regarding the definition of hospitalization due to CAP, if antibiotics are limited to injectable medications" and b) "If outcome is limited to CAP hospitalization in non-COVID -19 infected patients" showed that the crude incidence rates of overall users in the Trelegy 100 group were 85.44 (95% CI: 75.05-97.28) and 85.81 (95% CI: 75.39-97.67), respectively, and those in the MITT group were 109.83 (95% CI: 97.24-124.06) and 110.27 (95% CI: 97.65-124.52), respectively. For overall users, the adjusted incidence rates were 219.70 (95% CI: 149.83-322.14) and 226.90 (95% CI: 155.15-331.82), respectively, for the Trelegy 100 group and 287.50 (95% CI: 193.66-426.82) and 297.23 (95% CI: 200.51-440.60), respectively, for the MITT group. For incident users, the crude incidence rates in the Trelegy 100 group were 88.57 (95% CI: 72.94-107.56) and 88.56 (95% CI: 72.92-107.56), respectively, and the crude incidence rates in the MITT group were both 105.28 (95% CI: 84.19-131.65). For incident users, the adjusted incidence rates were 174.20 (95% CI: 92.58-327.78) and 180.52 (95% CI: 95.49-341.28) for the Trelegy 100 group and 243.78 (95% CI: 124.15-478.70) and 253.68 (95% CI: 128.85-499.44) for the MITT group, respectively. The results of different methods of adjustment for BMI in each supplementary analysis were as shown in T 2.151 to T2.153, T2.161 to T 2.163, respectively. There were no major differences in the results with any adjustment method.

Thus, the incidence of hospitalization due to CAP in the Trelegy100 group confirmed in this study was comparable to that in the MITT group, and there was no new concern about the incidence of pneumonia associated with Trelegy 100.

2.3.3. HR of hospitalization due to CAP among covariate subgroups

The crude and adjusted HRs of hospitalization due to CAP with one of the covariate subgroups as reference are presented in T 2.31 and T 2.41 for each covariate. The respective forest plots are shown in F 2.11 to F 2.14 and F 2.21 to F 2.24. In the Trelegy 100 group of overall users, the covariates whose adjusted HR for hospitalization due to CAP met the certain criteria (> 2 or < 0.5, and the asymptotic 95% confidence interval does not exceed 1) were “history of hospitalization due to COPD exacerbation ” Yes/No: 2.84 (95% CI: 1.98, 4.07),“ history of hospitalization due to CAP ” Yes/No: 3.30(95% CI: 2.30, 4.73), and “history or complication of connective tissue disease ” Yes/No: 2.21(95% CI: 1.50, 3.26). For each covariate that met the specified criteria in the Trelegy 100 group, the results in the MITT group were as follows: "history of hospitalization due to COPD exacerbation" Yes/No: 2.74(95% CI: 1.97, 3.81), "history of hospitalization due to CAP" Yes/No: 3.47(95% CI: 2.50, 4.84), and "history or complication of connective tissue disease" Yes/No: 1.26(95% CI: 0.84, 1.90). Although the specific criteria for "prior or concurrent connective tissue disease" were not met in the MITT group, the 95% CIs overlapped between the two groups and no significant difference was considered. Based on the above, there was no notable trend in the risk of CAP hospitalization following administration of Trelegy 100, and it was considered unnecessary to take new measures to ensure proper use at the present point in time.

2.3.4. Time to occurrence of hospitalization due to CAP

The cumulative crude incidence of first occurrence of hospitalization due to CAP in the Trelegy 100 and MITT groups are presented in F 2.01 (overall users) and F 2.03 (incident users). Also, the results of sensitivity analysis c) "when the maximum observation period was 1440 days after the Index Date" are shown in F2.02 (overall users) and F2.04 (incident users). The cumulative crude incidence at 360 days was 0.053 in the Trelegy 100 group and 0.056 in the MITT group for overall users, and 0.056 in the Trelegy 100 group and 0.051 in the MITT group for incident users. A sensitivity analysis showed that the cumulative crude incidence at 1440 days was 0.127 in the Trelegy 100 group and 0.124 in the MITT group for overall users, and 0.121 in the Trelegy 100 group and 0.124 in the MITT group for incident users.

The cumulative adjusted incidence of hospitalization due to CAP among incident users is shown in F 2.05. The cumulative adjusted incidence at 360 days based on the complete case analysis was 0.080 in the Trelegy 100 group and 0.062 in the MITT group. The results of different adjustment methods for BMI were as shown in F 2.051 to F 2.053. The cumulative adjusted incidence at 360 days were 0.058, 0.058, and 0.060, respectively, for the Trelegy 100 group and 0.055, 0.054, and 0.054, respectively, for the MITT group, if BMI was not adjusted, adjusted for missing values using multiple imputation, or adjusted for missing values using the missing-indicator method. There were no major differences in the results with any adjustment method. The results of sensitivity analysis are shown in F 2.06. The cumulative adjusted incidence at 1440 days based on the complete case analysis was 0.162 in the Trelegy 100 group and 0.100 in the MITT group. The results of the different methods of adjustment for BMI were as shown in F 2.061 to F 2.063. The cumulative adjusted incidence at 360 days were 0.118, 0.120, and 0.122, respectively, for the Trelegy 100 group and 0.119, 0.118, and 0.119, respectively, for the MITT group, if BMI was not adjusted, adjusted for missing values using multiple imputation, or adjusted for missing values using the missing-indicator method. There were no major differences in the results with any adjustment method.

In summary, there were no major differences in the time to onset of hospitalization due to CAP between both groups and no safety concerns about hospitalization due to CAP in patients receiving Trelegy 100.

2.3.5. Changes over time in the proportion of triple therapy, the proportion of ICS-containing therapies, and the proportion of patients with comorbid asthma

The proportions of COPD patients prescribed triple therapy, treated with ICS, and complicated with asthma were calculated for each period around the launch date of Trelegy 100 (May 22, 2019); the results are shown in T 1.21. During the period from -360 to -1 days before the launch of Trelegy 100 and from 0 to 359, 360~719, and 720~1079 days after the launch, the proportion of prescriptions for the triple therapy in COPD patients was 4.9% (-360 to -1 days), 4.8% (0 to 359 days), 3.9% (360 to 719 days), and 3.3% (720 to 1079 days), respectively. The percentage of ICS-containing therapies was 8.3% (-360 to -1 days), 7.0% (0 to 359 days), 4.7% (360 to 719 days), and 3.6% (720 to 1079 days). The proportion of patients with comorbid asthma was 28.1% (-360 to -1 days), 27.3% (0 to 359 days), 25.8% (360 to 719 days), and 24.7% (720 to 1079 days). Of patients prescribed the triple therapy, 100% (-360 to -1 days), 77.3% (0 to 359 days), 50.2% (360 to 719 days), and 31.1% (720 to 1079 days) were prescribed the MITT regimen. The proportion of SITT prescriptions was 0% (-360 to -1 days), 35.5% (0 to 359 days), 58.2% (360 to 719 days), and 74.8% (720 to 1079 days), and the proportion of Trelegy 100 prescriptions was 0% (-360 to -1 days), 32.8% (0 to 359 days), 43.7% (360 to 719 days), and 38.0% (720 to 1079 days).

2.4. Efficacy

Not applicable

2.5. Patients with Specific Backgrounds

2.5.1. Safety

2.5.1.1. Pediatrics (< 15 years)

Not applicable (not included in the target population of this study)

2.5.1.2. Elderly (≥ 65 years)

The adjusted HR for hospitalization due to CAP across age subgroups is shown in T 2.41. For overall users in Trelegy 100 or MITT groups, the adjusted HRs of "65 to < 75 years " versus " 40 to < 65 years " were 0.77 (95% CI: 0.42-1.40) and 1.43 (95% CI: 0.85-2.39), respectively, the adjusted HRs of "75 to < 85 years " versus " 40 to < 65 years " were 1.29 (95% CI: 0.73-2.28) and 1.50 (95% CI: 0.91-2.48), respectively, and the adjusted HRs of " ≥ 85 years " versus " 40 to < 65 years " were 1.91 (95% CI: 1.03-3.53) and 1.87 (95% CI: 1.08-3.25), respectively. There was a tendency toward increase in the risk of hospitalization due to CAP with increasing age, but there was a similar tendency also in the MITT group, and it was not considered to be unique to Trelegy 100, and it was considered unnecessary to take new measures to ensure proper use at the present point in time.

2.5.1.3. Pregnancy

Not applicable (not a covariate for CAP hospitalization)

2.5.1.4. Patients with renal impairment

Not applicable (not a covariate for CAP hospitalization)

2.5.1.5. Patients with hepatic impairment

Not applicable (not a covariate for CAP hospitalization)

2.5.2. Efficacy

Not applicable

3. Summary of post-marketing database studies

3.1. Safety Summary

In the complete case analysis, the crude HR for hospitalization due to CAP was 0.99 (95% CI: 0.74-1.32) and the adjusted HR was 1.15 (95% CI: 0.80-1.65) for incident users of Trelegy 100 compared with incident users of MITT. The crude HR was 0.92 (95% CI: 0.72-1.17) and the adjusted HR was 1.05 (95% CI: 0.76-1.44), 1.07 (95% CI: 0.78-1.47), and 1.07 (95% CI: 0.78-1.48), respectively, when BMI was not adjusted, when it was adjusted by imputing missing BMI using multiple imputation, or when it was adjusted by imputing missing BMI using the missing-indicator method. The results of the complete case analysis in the supplemental analyses a) "Regarding the definition of hospitalization due to CAP, if antibiotics are limited to injectable medications" and b) "If outcome is limited to CAP hospitalization in non-COVID -19 infected patients" performed based on the discussion at the epidemiology consultation (P24 dated December 23, 2020) showed that the crude HR was 0.97 (95% CI: 0.73-1.30) and 0.98 (95% CI: 0.73-1.31), respectively, and the adjusted HR was 1.14 (95% CI: 0.79-1.63) and 1.14 (95% CI: 0.80-1.65), respectively. In supplementary analyses a), the crude HR was 0.91 (95% CI: 0.71-1.17) and the adjusted HR was 1.03 (95% CI: 0.75-1.42), 1.05 (95% CI: 0.76-1.45), and 1.06 (95% CI: 0.76-1.47), respectively, when BMI was not adjusted, when it was adjusted by imputing missing BMI using multiple imputation, or when it was adjusted by imputing missing BMI using the missing-indicator method. In the supplementary analysis b), the crude HR was 0.91 (95% CI: 0.71-1.17) and the adjusted HR was 1.05 (95% CI: 0.76-1.44), 1.07 (95% CI: 0.77-1.47) and 1.07 (95% CI: 0.77-1.48), respectively, when BMI was not adjusted, when it was adjusted by imputing missing BMI using multiple imputation, or when it was adjusted by imputing missing BMI using the missing-indicator method. In summary, the risk of hospitalization for CAP in Trelegy 100 group was below a prespecified level (HR>3), and there was no safety concern about hospitalization for CAP with Trelegy 100 treatment.

The crude incidence rates of hospitalization due to CAP in Trelegy 100 and MITT groups in the complete case analysis were 86.18 (95%CI: 75.74 – 98.07) [/1000 patient-years] and 110.28 (95%CI: 97.66 – 124.53) [/1000 patient-years] for overall users and 89.44 (95%CI: 73.71 – 108.52) [/1000 patient-years] and 105.30 (95%CI: 84.21 – 131.68) [/1000 patient-years] for incident users, respectively. The adjusted incidence rate was 227.24 (95%CI: 155.48 – 332.13) [/1000 patient-years] for overall users in Trelegy 100 group and 296.86 (95%CI: 200.38 – 439.78) [/1000 patient-years] in the MITT group; 182.74 (95%CI: 97.16 – 343.67) [/1000 patient-years] for incident users in Trelegy 100 group and 252.68 (95%CI: 128.85 – 495.49) [/1000 patient-years] in the MITT group. Based on the above, the incidence of hospitalization due to CAP in this study was similar to that in the MITT group, and there was no new concern about the incidence of pneumonia in patients receiving Trelegy 100.

As a result of identifying covariates for which the adjusted HR between covariate subgroups met a certain criterion (> 2 or < 0.5, and the asymptotic 95% confidence interval does not exceed 1), “history of hospitalization due to COPD exacerbation,” “history of hospitalization due to CAP,” and “history or complication of connective tissue disease” were identified in overall users in Trelegy 100 group, but there were no noteworthy differences between the two groups. Thus, it was considered unnecessary to take new measures to ensure proper use at this point in time.

Regarding the time to occurrence of hospitalization due to CAP, the cumulative crude incidence and cumulative adjusted incidence at 360 days were calculated. As a result, there were no noteworthy differences between the groups and no safety concerns about hospitalization due to CAP during treatment with Trelegy 100.

Thus, in this study, the occurrence status of hospitalization due to CAP under the actual use of Trelegy 100 was confirmed using the MDV hospital claims database, and there was no new concern about the safety of Trelegy 100 in relation to hospitalization due to CAP.

3.2. Efficacy Summary

Not applicable