In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

Note: Sample Case Report Form may be available upon request.

Title of the investigation	TRELEGY ELLIPTA General Drug Use Investigation (asthma)
Protocol No.	214953
Date of preparation	18 Apr 2025
Trade name	TRELEGY 100 ELLIPTA 14 doses TRELEGY 100 ELLIPTA 30 doses TRELEGY 200 ELLIPTA 14 doses TRELEGY 200 ELLIPTA 30 doses
Active ingredients	Fluticasone furoate (FF) Umeclidinium bromide (UMEC) Vilanterol trifenatate (VI)
Marketing Authorization Holder (MAH: Marketing Authorization Holder)	GlaxoSmithKline K.K.

1. Protocol Synopsis

Title of the investigation: TRELEGY ELLIPTA General Drug Use Investigation (asthma)	
Objectives	The objective of this investigation is to collect and assess information regarding the safety and effectiveness of Trelegy Ellipta (hereinafter referred to as "Trelegy") in asthma patients under the actual use conditions.
Safety specifications	Rationale: To collect information on the occurrence of the safety specifications under the actual use conditions. - Cardiovascular events
Effectiveness considerations	Not defined
Investigation methods	Central registration method
Target patients	This investigation will include patients who are prescribed Trelegy for the first time for the treatment of diagnosed bronchial asthma, which is one of the indications of Trelegy.
Investigation period	June 2021 - November 2023
Target number of patients	300 (as patient registration)
Observation period (treatment period)	The observation period (Trelegy treatment period) per patient will be 1 year after the first ever initiation of Trelegy treatment. If a patient has withdrawn from /terminated administration of Trelegy, it will be until the withdrawal/termination date.
Observation items	1. Information regarding medical institutions 2. Patient characteristics (at the initiation date of Trelegy treatment) 3. Pre-treatment medications for asthma (during 6 weeks prior to the initiation of Trelegy treatment) 4. Administration status of Trelegy 5. Concomitant medications 6. Concomitant therapies for asthma (except for medications) 7. Asthma management status of a patient (course of clinical symptoms) 1) Respiratory Function Test (Peak Expiratory Flow [PEF]) 2) Respiratory Function Test (Spirometry) 3) Asthma Control Test (ACT) 4) Events related to exacerbation of asthma 8. Overall assessment of effectiveness 9. Pregnancy 10. Adverse events (AEs)
Effectiveness assessment criteria	Effective, not effective, indeterminable
Remarks	Protocol revisions: 27 November 2020: Newly created 8 April 2021: Minor changes ((1) clarification of the time of completion of the investigation, (2) addition of outsources, and (3) addition of details on publication of investigation results)

2. Investigation Results

2.1. Number of Study Sites and Patient Composition

The registration of patients with bronchial asthma, which is one of the indications of Trelegy, was started in June 2021 using the central registration method (target number of patients: 300 registered patients). The observation period was 1 year from the first ever initiation date of Trelegy treatment. If a patient had withdrawn from/terminated administration of Trelegy, it was until the withdrawal/termination date.

Figure 1 shows the patient composition of this investigation.

2.2. Patient characteristics (composition)

Table 1 shows the characteristics of 286 patients in the safety analysis set: in terms of gender, there were more "female" patients, accounting for 56.3% (161/286 patients), and the mean ± standard deviation (SD) of the "age" of patients was 58.7 ± 16.7 years. Patients with comorbidities accounted for 58.0% (166/286 patients), and the proportion of patients with comorbidities of "renal function disorder", "hepatic function disorder", and "COPD" was 0.7% (2/286 patients), 1.4% (4/286 patients), and 9.1% (26/286 patients), respectively. The severity of bronchial asthma was "mild intermittent" in 15.7% (45/286 patients), "mild persistent" in 20.3% (58/286 patients), "moderate persistent" in 45.1% (129/286 patients), "severe persistent" in 16.8% (48/286 patients), and "most severe persistent" in 2.1% (6/286 patients). The type of asthma was "atopic" in 46.2% (132/286 patients), "non-atopic" in 36.0% (103/286 patients), and "unknown" in 17.8% (51/286 patients). The use of pre-treatment medications was "Yes" in 70.3% (201/286 patients) and "No" in 29.7% (85/286 patients). Table 2 shows the detailed breakdown of pre-treatment medications.

The composition of patients in the effectiveness analysis set were generally similar.

2.3. Administration status of Trelegy

Table 3 shows the administration status of Trelegy in the 286 patients in the safety analysis set: the daily dose of ICS [μg] (initial dose) was 100 [μg] (initial dose) in 25.2% (72/286 patients) and 200 [μg] (initial dose) in 74.8% (214/286 patients). The mean ± SD of the total number of days of treatment was 265.9 ± 138.6 days: the total number of days of treatment was < 28 days in 8.0% (23/286 patients), ≥ 28 and < 84 days in 12.6% (36/286 patients), ≥ 84 and < 168 days in 7.3% (21/286 patients), ≥ 168 and < 252 days in 4.9% (14/286 patients), ≥ 252 and < 365 days in 11.9% (34/286 patients), and ≥ 365 days in 55.2% (158/268 patients). The status of continuation of Trelegy treatment at the end of the observation period was "continued" in 62.2% (178/286 patients) and "withdrawn/terminated" in 37.8% (108/286 patients).

The administration status in the effectiveness analysis set was generally similar.

2.3.1. Status of Continuation of Trelegy Treatment and Reason for Withdrawal/Termination

Table 4 shows the duration of Trelegy treatment by reason for treatment withdrawal/termination in 108 patients who had withdrawn from/terminated treatment among the 286 patients in the safety analysis set. The most common reason for treatment withdrawal/termination was "no visits from the middle of the study" in 44 patients, followed by "factors related to effectiveness" in 25 patients, and "occurrence of AEs" in 23 patients (some patients had more than one reason).

2.4. Safety

2.4.1. Occurrence of Adverse Drug Reactions (ADRs)

Among the 286 patients in the safety analysis set, 24 patients experienced ADRs, and the proportion of patients with ADRs was 8.4% (Table 5).

The most common ADR by system organ class was "respiratory, thoracic and mediastinal disorders" in 5.2% (15/286 patients), followed by "general disorders and administration site conditions" in 1.0% (3/286 patients), and "cardiac disorders" and "gastrointestinal disorders" in 0.7% (2/286 patients). The type of ADRs in descending order of the number of patients was "cough" and "dysphonia" in 2.4% (7/286 patients) each, and "thirst" and "palpitations" in 0.7% (2/286 patients) each. Urinary retention was reported as a serious ADR in 0.3% (1/286 patients).

Table 6 shows the seriousness and outcome of each reported ADR. The outcome was "resolving" or "resolved" for all events. The outcome of the serious ADR "urinary retention" was "resolved".

Among 18 patients excluded from the safety analysis set, all patients had "no visits after the first prescription date", and no ADRs were reported.

2.4.2. Factors Affecting the Onset of ADRs

In 286 patients in the safety analysis set, univariate and multivariate analyses were performed by patient characteristics to explore possible factors affecting the safety of Trelegy.

When factors meeting the criterion for the unadjusted odds ratio of the occurrence of ADRs by patient characteristics, "The asymptotic 95% confidence interval does not cross 1 and the point estimate exceeds 2 or is less than 0.5", were explored using univariate analysis, "≥ 65 years" was identified as a factor meeting the given criterion (Table 7). Therefore, a multivariate analysis was performed in consideration of the results of the univariate analysis and variable selection with correlation in each item of patient characteristics. When factors meeting the criterion for the adjusted odds ratio were explored using multivariate analysis, "female" and "≥ 65 years" were identified as factors meeting the given criterion as shown in Table 8. The adjusted odds ratios were estimated for "gender", "age", "comorbidities", "history of smoking", "duration of asthma", "type of asthma", "pre-treatment medications", and "concomitant medications".

The results of investigation of each factor that met the criterion for the adjusted odds ratio in the multivariate analysis are shown below.

2.4.2.1. Gender

The occurrence of ADRs by gender was examined. As shown in Table 9, the proportion of patients with ADRs was higher in female patients. "Cough" was the ADR with the largest difference between genders, which is attributed to gender affecting the overall ADRs. The proportion of patients with "cough" was 3.7% (6/161 patients) in female patients and 0.8% (1/125 patients) in male patients.

As shown in Table 6, the confirmed outcome of each "cough" was "resolving" or "resolved", and in female patients, it was "resolving" in 1 patient and "resolved" in 5 patients.

"Cough" was reported in 0.5% (2/406 patients) of patients treated with FF/UMEC/VI 100/62.5/25 μg in a global phase III study with the treatment period of 24 weeks (up to 52 weeks), and is listed in "11.2 Other Adverse Reactions" of the package insert to call attention. [1, 2)] Of the 6 female patients who experienced cough, 5 patients were aged ≥ 65 years. Although it might be related to the

age (patients aged ≥ 65 years) as described below, the confirmed proportion of patients with "cough" in female patients in this investigation and the fact that the outcome of each ADR was "resolving" or "resolved" and all of them were non-serious warrant no new safety assurance measures, such as revision of the package insert.

ADRs other than "cough" that occurred more frequently in female patients than in male patients were "feeling abnormal", "palpitations", "glossitis", "nausea", "taste disorder", and "eczema". Of these ADRs, "palpitations" are listed in "11.2 Other Adverse Reactions" of the package insert, and "taste disorder" is listed as "abnormal taste" in the same section, with each being highlighted for caution. [1, 2)] As for "feeling abnormal", "glossitis", "nausea", and "eczema", since the proportion of patients with these ADRs was low, all of them were non-serious, and the outcomes are ‘resolving’ for ‘feeling abnormal’ and ‘resolved’ for "glossitis", "nausea", and "eczema", no new safety assurance measures, such as revision of the package insert, are considered necessary.

2.4.2.2. Age

The occurrence of ADRs by age was examined. As shown in Tables 10 and 11, the proportion of patients with "cough" and "dysphonia" in patients aged ≥ 65 years was 5.0% (6/119 patients) each, which was higher than 0.6% (1/167 patients) each for "cough" and "dysphonia" in patients aged < 65 years. That is one of the reasons why age was considered to be a factor contributing to the overall proportion of patients with ADRs.

As shown in Table 6, the confirmed outcome of "cough" and "dysphonia" was "resolving" or "resolved". In patients aged ≥ 65 years, the outcome of "cough" was "resolving" in 1 patient and "resolved" in 5 patients, and the outcome of "dysphonia" was "resolving" in 2 patients and "resolved" in 4 patients.

"Cough" was reported in 0.5% (2/406 patients) of patients treated with FF/UMEC/VI 100/62.5/25 μg in the global phase III study with the treatment period of 24 weeks (up to 52 weeks), and "dysphonia" was reported in 1.0% (4/406 patients) of patients treated with FF/UMEC/VI 100/62.5/25 μg and 0.7% (3/408 patients) of patients treated with FF/UMEC/VI 200/62.5/25 μg in the global phase III study and in 3.6%(4/111 patients) of patients in a Japanese phase III study with the treatment period of 52 weeks. These ADRs are listed in "11.2 Other Adverse Reactions" of the package insert to call attention. [1, 2)]

The confirmed proportion of patients with "cough" and "dysphonia" in patients aged ≥ 65 years in this investigation and the fact that the outcome of each ADR was "resolving" or "resolved" and all of them were non-serious warrant no new safety assurance measures, such as revision of the package insert.

ADRs other than "cough" and "dysphonia" that occurred more frequently in patients aged ≥ 65 years than in patients aged < 65 years were "Oropharyngeal discomfort", "palpitations", "glossitis", "nausea", "eczema", and "urinary retention". Of these ADRs, "palpitations" and "urinary retention" are listed in "11.2 Other Adverse Reactions" of the package insert, as is the case with "cough" and "dysphonia", to call attention. [1, 2)] As for "Oropharyngeal discomfort", "glossitis", "nausea", and "eczema", as the proportion of patients with these ADRs was low, all of them were non-serious, and the outcome of all these ADRs was "resolved", no new safety assurance measures, such as revision of the package insert, are considered necessary.

2.4.3. Time to Onset of ADRs

The time from the initiation of Trelegy treatment to the onset of ADRs was examined in 24 patients with ADRs reported among the 286 patients in the safety analysis set. As a result, 75.0% of ADRs were observed within 60 days after administration as shown in Table 12. As shown in Figure 2, the cumulative proportion of patients with ADRs was 4.60% at 30 days, 6.51% at 90 days, 7.86% at 180 days, 9.33% at 360 days, and 9.33% at 365 days.

2.4.4. Safety specifications

In this investigation, "cardiovascular events" were defined as a safety specification. Table 13 shows the occurrence of ADRs related to the safety specification in the 286 patients in the safety analysis set. The results of the examination of "cardiovascular events" that occurred in 0.7% (2/286 patients) are shown below.

2.4.4.1. Cardiovascular Events

Among the 286 patients in the safety analysis set, the proportion of patients with ADRs of events related to "cardiovascular events" was 0.7% (2/286 patients), and it was confirmed that all of them were non-serious "palpitations" and the outcome was "resolved" (Table 6). The incidence based on person-year method [/100 person-year] was 0.95 (Table 14).

2.5. Effectiveness

2.5.1. Effectiveness Assessment

Effectiveness was comprehensively assessed by the investigator as any of "effective" or "not effective" based on the course of subjective symptoms, and course of clinical symptoms (asthma management status), etc. from the initiation of Trelegy treatment to the end of the observation period. If the effectiveness could not be assessed by the investigator for some reason, it was assessed as "indeterminable." The proportion of patients in the effectiveness analysis set who were assessed as "effective" was calculated as the proportion of responders.

Among the 281 patients in the effectiveness analysis set, the proportion of responders was 92.5% (260/281 patients) (Table 15).

2.5.2. Factors Affecting the Effectiveness

In 281 patients in the effectiveness analysis set, univariate and multivariate analyses were performed by patient characteristics to explore possible factors affecting the effectiveness of Trelegy.

In the effectiveness assessment by patient characteristics, when factors meeting the criterion for the unadjusted odds ratio, "The asymptotic 95% confidence interval does not cross 1 and the point estimate exceeds 2 or is less than 0.5", were explored using univariate analysis, "≥ 65 years" and "pre-treatment medications (Yes)" ("Prior use of ICS, ICS/LABA, or ICS/LABA/LAMA" is included) were detected as such factors (Table 16). Therefore, a multivariate analysis was performed in consideration of the results of the univariate analysis and variable selection with correlation in each item of patient characteristics. The multivariate analysis did not identify any factor meeting the criterion for the adjusted odds ratio (Table 17). The adjusted odds ratios were estimated for "gender", "age", "comorbidities", "medical history in the past", "duration of asthma", "type of asthma", "pre-treatment medications", and "concomitant medications".

2.5.3. Asthma management status of a patient (course of clinical symptoms)

2.5.3.1. Respiratory Function Test (Peak Expiratory Flow [PEF])

Table 18 shows the mean ± SD of the PEF (L/min) at "the initiation of Trelegy treatment", "1 month after the initiation of Trelegy treatment", "3 months after the initiation of Trelegy treatment", "6 months after the initiation of Trelegy treatment", "1 year after the initiation of treatment", and "the end of the observation period" in patients included in the analysis (patients with available measurement results before and after treatment) among the 281 patients in the effectiveness analysis set. The PEF (morning) was 352.1 ± 126.9 (54 patients) at the initiation of Trelegy treatment, 398.4 ± 129.1 (38 patients) at 1 month after the initiation of Trelegy treatment, 392.9 ± 150.5 (36 patients) at 3 months after the initiation of Trelegy treatment, 397.7 ± 131.2 (38 patients) at 6 months after the initiation of Trelegy treatment, 387.8 ± 131.5 (41 patients) at 1 year after the initiation of Trelegy treatment, and 403.4 ± 132.6 (51 patients) at the end of the observation period.

The results of the PEF (evening) were slightly lower than the PEF (morning), but after the initiation of Trelegy treatment, the PEF (evening) remained at levels higher than that at the initiation of Trelegy treatment.

2.5.3.2. Respiratory Function Test (Spirometry)

Table 19 shows the mean ± SD of Spirometry (L) "before the initiation of Trelegy treatment", at "1 year after the initiation of Trelegy treatment", and at "the final measurement" in patients included in the analysis (patients with available measurement results before and after treatment) among the 281 patients in the effectiveness analysis set. The FVC was 2.668 ± 1.064 (66 patients) before the initiation of Trelegy treatment, 2.755 ± 1.013 (37 patients) at 1 year after the initiation of Trelegy treatment, and 2.872 ± 0.993 (66 patients) at the final measurement. The FEV1 was 2.003 ± 0.757 (66 patients) before the initiation of Trelegy treatment, 2.233 ± 0.780 (37 patients) at 1 year after the initiation of Trelegy treatment, and 2.247 ± 0.724 (66 patients) at the final measurement. After the initiation of Trelegy treatment, the FVC and FEV1 remained at levels higher than those at the initiation of Trelegy treatment.

2.5.3.3. Asthma Control Test (ACT)

Table 20 shows the ACT score at "the initiation of Trelegy treatment", "1 month after the initiation of Trelegy treatment", "3 months after the initiation of Trelegy treatment", "6 months after the initiation of Trelegy treatment", "1 year after the initiation of treatment", and "the end of the observation period" in patients included in the analysis (patients with available measurement results before and after treatment) among the 281 patients in the effectiveness analysis set. The mean ± SD of the ACT scores was 16.8 ± 5.0 (205 patients) at the initiation of Trelegy treatment, 20.7 ± 4.0 (143 patients) at 1 month after the initiation of Trelegy treatment, 21.9 ± 3.5 (125 patients) at 3 months after the initiation of Trelegy treatment, 22.3 ± 2.9 (121 patients) at 6 months after the initiation of Trelegy treatment, 22.0 ± 3.6 (120 patients) at 1 year after the initiation of Trelegy treatment, and 21.9 ± 3.7 (168 patients) at the end of the observation period. After the initiation of Trelegy treatment, the ACT score remained at levels higher than that at the initiation of Trelegy treatment.

2.5.3.4. Events Related to Exacerbation of Asthma

Table 21 and Table 22 show events related to exacerbation of asthma for 1 year prior to the initiation of Trelegy treatment and 1 year after the initiating treatment (or to the time point of withdrawal/termination). Among the 281 patients in the effectiveness analysis set, the proportion of events occurrence related to asthma exacerbation as of the end of treatment (including patients who received treatment for less than 1 year) was 25.6% (72/281 patients) and 5.0% (14/281 patients) before and after the initiation of treatment, respectively. Among patients treated for 1 year, the proportion was 25.8% (46/178 patients) and 6.2% (11/178 patients) before and after the initiation of treatment, respectively. The proportion of events occurrence related to asthma exacerbation was lower at the time of discontinuation and in cases administered for one year, compared to the incidence rate after the start of administration.

2.6. Patients with Specific Backgrounds

2.6.1. Safety

2.6.1.1. Children (aged < 15 years)

As shown in Table 1, there were no reports of use in children (aged < 15 years).

2.6.1.2. Elderly (aged ≥ 65 years)

Among the 286 patients in the safety analysis set, use in the elderly (aged ≥ 65 years) was reported in 119 patients (aged 65-89 years), and the proportion of patients with ADRs was 13.4% (16/119 patients). Table 23 shows reported events, and Table 24 shows the outcome of each event.

2.6.1.3. Pregnant and Parturient Women

As shown in Table 1, there were no reports of use in pregnant and parturient women.

2.6.1.4. Patients with Renal Function Disorder

Among the 286 patients in the safety analysis set, use in patients with renal function disorder was reported in 2 patients, but no ADRs were reported (Table 25).

2.6.1.5. Patients with Hepatic Function Disorder

Among the 286 patients in the safety analysis set, use in patients with hepatic function disorder was reported in 4 patients, but no ADRs were observed (Table 26).

2.6.1.6. Patients with COPD

Among the 286 patients in the safety analysis set, use in patients with COPD was reported in 26 patients, and the proportion of patients with ADRs was 7.7% (2/26 patients). Table 27 shows reported events, and Table 28 shows the outcome of each event.

2.6.2. Effectiveness

2.6.2.1. Children (aged < 15 years)

As shown in Table 1, there were no reports of use in children (aged < 15 years).

2.6.2.2. Elderly (aged ≥ 65 years)

Among the 281 patients in the effectiveness analysis set, use in the elderly (aged ≥ 65 years) was reported in 116 patients (aged 65-89 years), and the proportion of responders was 87.9% (102/116 patients) (Table 15).

2.6.2.3. Pregnant and Parturient Women

As shown in Table 1, there were no reports of use in pregnant and parturient women.

2.6.2.4. Patients with Renal Function Disorder

Among the 281 patients in the effectiveness analysis set, use in patients with renal function disorder was reported in 2 patients, and the proportion of responders was 100.0% (2/2 patients) (Table 15).

2.6.2.5. Patients with Hepatic Function Disorder

Among the 281 patients in the effectiveness analysis set, use in patients with hepatic function disorder was reported in 4 patients, and the proportion of responders was 100.0% (4/4 patients) (Table 15).

3. Summary of the General Drug Use Investigation

3.1. Safety Summary

Among the 286 patients in the safety analysis set, the proportion of patients with ADRs was 8.4% (24/286 patients). The proportion of patients with ADRs in the global phase III and Japanese phase III studies were 5.9% (48/814 patients) and 14.4% (16/111 patients), respectively. The patient characteristics and investigation methods, etc. of this investigation are different from these studies, and the treatment period in each study was 24 weeks (up to 52 weeks) in the global phase III study and 52 weeks in the Japanese phase III study,[1)] rendering difficulties in making a strict comparison. Nevertheless, the proportion of patients with ADRs in this investigation was within the range expected from that in the global phase III and Japanese phase III studies, and therefore there appear to be no new concerns.

The type of ADRs in descending order of the number of patients was cough (2.4%, 7/286 patients), dysphonia (2.4%, 7/286 patients), etc., and many ADRs were already observed in the global phase III and Japanese phase III studies.[1)] Moreover, in this investigation, there seem to be no ADRs requiring safety assurance measures, such as revision of the package insert.

For factors affecting the onset of ADRs, univariate and multivariate analyses were performed to explore factors meeting the criterion for the unadjusted/adjusted odds ratios of the occurrence of ADRs by patient characteristics, "The asymptotic 95% confidence interval does not cross 1 and the point estimate exceeds 2 or is less than 0.5". As a result, "≥ 65 years" was identified by univariate analysis. Therefore, a multivariate analysis was performed in consideration of the results of the univariate analysis and variable selection with correlation in each item of patient characteristics, and identified "female" and "≥ 65 years" as factors meeting the given criterion. When the proportion of patients with each ADR by gender was examined, the proportion of patients with "cough" was higher in female patients than in male patients. However, since "cough" is ADR that has been observed in 0.5% (2/406 cases) of the FF/UMEC/VI 100/62.5/25 μg group in the global phase III trial, and is already listed in the package insert.,[1, 2)] and based on the proportion of patients with this ADR and the

fact that it was a non-serious ADR, no new safety assurance measures, such as revision of the package insert, were considered necessary. In addition, when the occurrence of ADRs by age was examined, the proportion of patients with "cough" and "dysphonia" was higher in patients aged ≥ 65 years than in patients aged < 65 years. However, since "cough" and "dysphonia" are ADRs that have been observed in the FF/UMEC/VI 100/62.5/25 μg group in the global phase III trial, with "cough" at 0.5% (2/406 cases) and "dysphonia" at 1.0% (4/406 cases) for the FF/UMEC/VI 100/62.5/25 μg group and 0.7% (3/408 cases) for the FF/UMEC/VI 200/62.5/25 μg group, and 3.6% (4/111 cases) in the Japanese phase III trial with a treatment period of 52 weeks and are already listed in the package insert,[1, 2)] and based on the proportion of patients with these ADRs and the fact that they were non-serious ADRs, no new safety assurance measures, such as revision of the package insert, were considered necessary.

In this investigation, "cardiovascular events" were defined as safety specification. Among the 286 patients in the safety analysis set, the proportion of patients with ADRs of events related to "cardiovascular events" was 0.7% (2/286 patients), and it was confirmed that all of them were non-serious "palpitations". The proportion of patients with cardiovascular events in the Japanese phase III study (12 months) was 4.5%. The sample size of patients in the safety analysis set required to confirm the frequency of occurrence of cardiovascular events in post-marketing surveillance with estimation accuracy that enabled a power of ≥ 80% for the 4.5% threshold in case the real risk existed at 2 times or more than the threshold was calculated to be 222. In this investigation, 286 patients, which exceeded 222 patients, were included in the safety analysis, and the proportion of patients with cardiovascular events was 0.7%. Therefore, there were no safety concerns regarding "palpitations" during Trelegy treatment. Since "palpitations" were also reported by 0.9% (1/111 patients) of patients in the Japanese phase III study,[1)] there appeared to be no concern about the frequency of "palpitations" in this investigation, although it is difficult to make a rigorous comparison because of the differences in patient characteristics, investigation methods, etc. In addition, since "palpitations" are already listed in "11.2 Other Adverse Reactions" of the package insert, no new safety assurance measures were considered necessary.[2)]

Similarly, no new safety assurance measures were considered necessary from the viewpoint of the safety in patients with specific backgrounds (children, pregnant and parturient women, patients with renal function disorder, patients with COPD, and patients with hepatic function disorder). From the viewpoint of the safety in the elderly, no new safety assurance measures, such as revision of the package insert, were considered necessary, as described above, based on the proportion of patients with and type of ADRs that occurred in the elderly.

In summary, this investigation confirmed the safety of Trelegy under actual use conditions and revealed no new safety concerns.

3.2. Effectiveness Summary

Among the 281 patients in the effectiveness analysis set, the proportion of responders was 92.5% (260/281 patients).

In the effectiveness assessment by patient characteristics, univariate and multivariate analyses were performed to explore factors meeting the criterion for the unadjusted/adjusted odds ratios of the effectiveness assessment by patient characteristics, "The asymptotic 95% confidence interval does not cross 1 and the point estimate exceeds 2 or is less than 0.5". As a result, while "≥ 65 years" and "pre-treatment medications (Yes)" ("Prior use of ICS, ICS/LABA, or ICS/LABA/LAMA" is included)

were detected as factors by univariate analysis, the multivariate analysis that included "age", etc. as estimation factors identified no factor meeting the given criterion.

In the global phase III study, a mean change from baseline in FEV1 trough value at Week 24 of treatment was defined as the primary endpoint, and it was 0.130 ± 0.371 L (mean at baseline: 2.076 ± 0.6762 L) in the FF/UMEC/VI 100/62.5/25 μg group and 0.171 ± 0.3195 L (mean at baseline: 1.985 ± 0.6912 L) in the FF/UMEC/VI 200/62.5/25 μg group.[1,2)] Although a rigorous comparison cannot be made because of the differences in patient characteristics, investigation methods, etc., no new measures to ensure the proper use of Trelegy for the effectiveness related to the respiratory function tests were considered necessary, because in this investigation, the mean change ± SD in FEV1 from the initiation of treatment at Year 1 was 0.243 ± 0.286 L (mean at the initiation of Trelegy treatment: 2.003 ± 0.757 L) and after Trelegy treatment, the PEF and FVC remained at levels higher than those at the initiation of Trelegy treatment. Moreover, for the assessment of ACT scores and events related to exacerbation of asthma, this investigation did not use the same items and definitions as those in the global phase III study. Japanese cohort for The global phase III study used the 7-item Asthma Control Questionnaire (ACQ-7), an objective indicator of asthma control, and showed a Clinically meaningful improvement at Week 24 compared to the baseline.[3)] In the global phase III study, moderate/severe asthma exacerbations are defined as shown in the table below, and the proportion of patients with such asthma exacerbations at Weeks 1 to 52 of treatment was 27% (109/406 patients) for FF/UMEC/VI 100/62.5/25 group and 27% (112/408 cases) for the FF/UMEC/VI 200/62.5/25 μg group.[4)]

Moderate asthma exacerbation

- A worsening of asthma symptoms, a deterioration of lung function, or an exacerbation requiring the use of a rescue bronchodilator for ≥ 2 days, which is not as severe as requiring the use of a systemic corticosteroid for ≥ 3 days(or a ≥ 2-fold increase in the dose of a systemic corticosteroid used as maintenance therapy) or hospitalization.
- An event that requires a temporary change in therapy to prevent progression to severe exacerbation.

Severe asthma exacerbation

- Use of systemic corticosteroids (tablet, suspension for injection, or intravenous injection) for ≥ 3 days (for patients receiving systemic corticosteroids as maintenance therapy, a ≥ 2-fold increase in the dose of the systemic corticosteroids for ≥ 3 days is required), or hospitalization or emergency room visit for asthma that requires systemic corticosteroids.

In this investigation, the ACT score remained at levels higher than that at the initiation of Trelegy treatment after Trelegy treatment, and the proportion of events occurrence related to asthma exacerbation in the 281 patients in the effectiveness analysis set was 25.6% (72/281 patients) before the initiation of treatment and 5.0% (14/281 patients) after the initiation of treatment at the end of treatment (including patients treated for less than 1 year).. Therefore, no new measures to ensure the proper use of Trelegy for the effectiveness related to the ACT score or exacerbation events were considered necessary, although a strict comparison cannot be made due to the differences in patient characteristics, investigation methods, definitions of asthma exacerbation, etc. between this investigation and the global phase III study.

No particular concerns were identified in terms of the effectiveness in children, elderly, pregnant and parturient women, patients with renal function disorder, or patients with hepatic function disorder.

In summary, this investigation revealed no new issues or questions about the effectiveness of Trelegy.

4. References

1) GlaxoSmithKline K.K. Interview Form of TRELEGY 100 ELLIPTA 14 doses/TRELEGY 100 ELLIPTA 30 doses/TRELEGY 200 ELLIPTA 14 doses/TRELEGY 200 ELLIPTA 30 doses (Version 8). Revised in September 2024
2) GlaxoSmithKline K.K. TRELEGY 100 ELLIPTA 14 doses/TRELEGY 100 ELLIPTA 30 doses/TRELEGY 200 ELLIPTA 14 doses/TRELEGY 200 ELLIPTA 30 doses (Version 4; September 2023)
3) Nakamura Y, et al. Efficacy and safety of once-daily, single-inhaler fluticasone furoate/umeclidinium/vilanterol versus fluticasone furoate/vilanterol in Japanese patients with inadequately controlled asthma: the CAPTAIN study. Curr Med Res Opin. 2021 Sep;37(9):1657-1665.
4) Summary Technical Documentation. Data source: CTD 2.7. Clinical Summary. https://www.pmda.go.jp/drugs/2020/P20201201001/index.html (accessed on 29 August 2024)

As of 29 May 2024

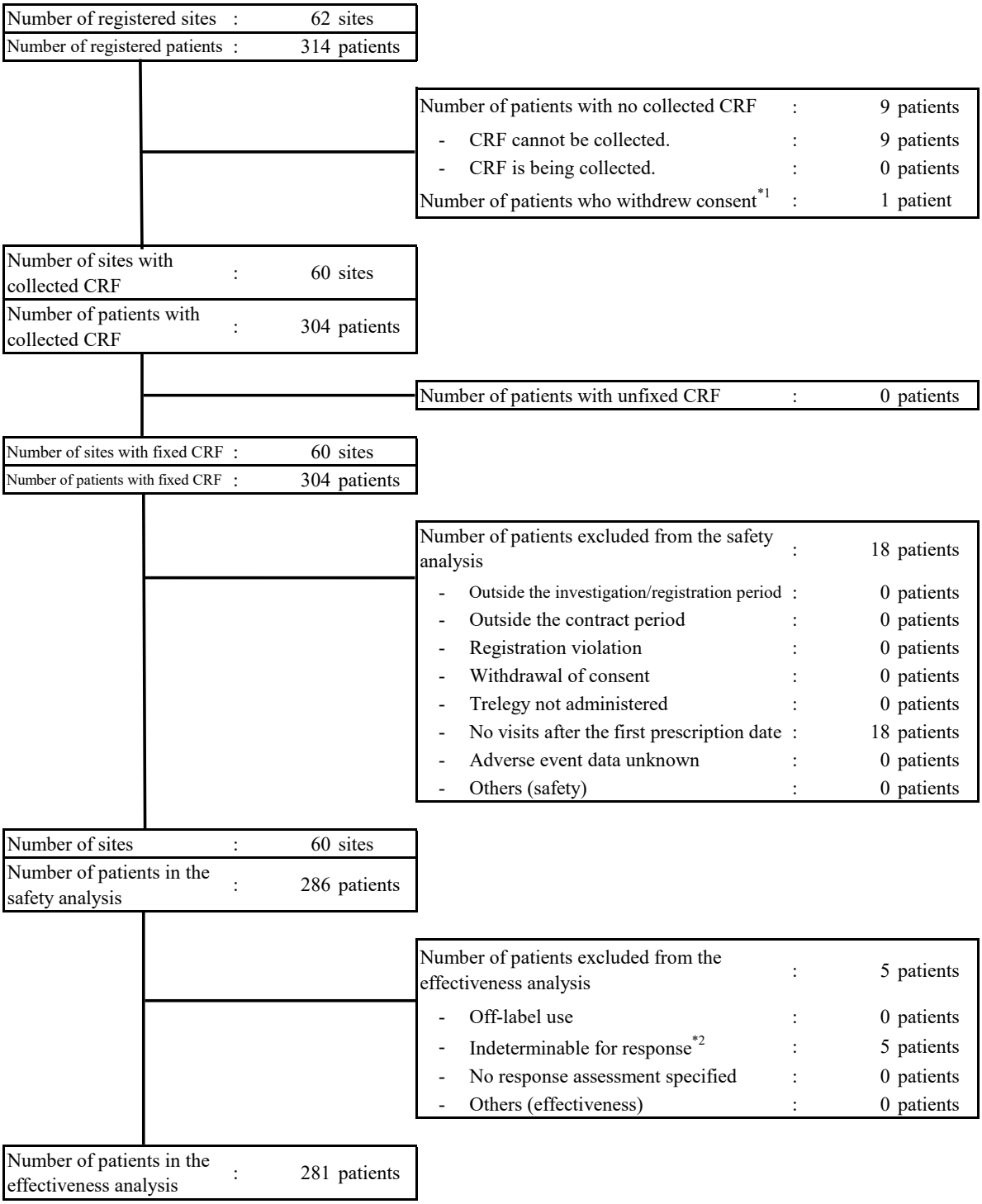


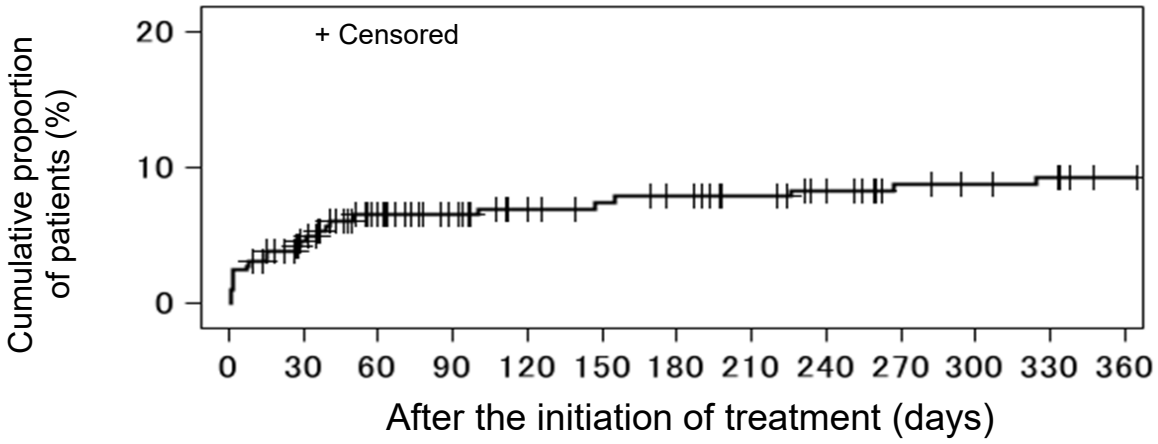
Figure 1 Patient Composition

*1: Patients who withdrew their consent before the collection of CRF.
*2: Patients assessed by the investigator as indeterminable for response for the following reasons: "The patient discontinued treatment after only one inhalation", "The patient changed to a local clinic", "The patient discontinued treatment early due to cough", "No visits", and "The patient could use Trelegy only for 3 days".

Figure 2 Cumulative Proportion of Patients with Adverse Drug Reactions

As of 29 May 2024

Number of patients in the safety analysis



After the initiation of treatment (days)	30	90	180	360	365
Number of patients at risk	254	220	201	175	175
Cumulative number of patients with ADRs	13	18	21	24	24
Cumulative proportion of patients	4.60	6.51	7.86	9.33	9.33

Table 1 Patient Composition

As of 29 May 2024

Patients in the safety analysis, patients in the effectiveness analysis

Item of patient characteristics		Number of patients in the safety analysis		Number of patients in the effectiveness analysis	
		Number of patients investigated	Composition (%)	Number of patients investigated	Composition (%)
Total		286	100.0	281	100.0
Gender	Male	125	43.7	124	44.1
	Female	161	56.3	157	55.9
Age 1 [years]	< 15	0	0.0	0	0.0
Mean ± SD: 58.7 ± 16.7/58.5 ± 16.8	15 ≤ to < 65	167	58.4	165	58.7
Minimum: 16/16	65 ≤	119	41.6	116	41.3
Median: 59.5/59.0					
Maximum: 89/89					
Age 2 [years]	< 65	167	58.4	165	58.7
	65 ≤	119	41.6	116	41.3
Age 3 [years]	< 12	0	0.0	0	0.0
	12 ≤ to < 18	2	0.7	2	0.7
	18 ≤	284	99.3	279	99.3
Weight [kg]	< 40	7	2.4	7	2.5
Mean ± SD: 62.52 ± 13.68/62.57 ± 13.70	40 ≤ to < 50	25	8.7	24	8.5
Minimum: 32.9/32.9	50 ≤ to < 60	46	16.1	46	16.4
Median: 62.00/62.00	60 ≤ to < 70	54	18.9	52	18.5
Maximum: 105.0/105.0	70 ≤ to < 80	34	11.9	34	12.1
	80 ≤	21	7.3	21	7.5
	Unknown	99	34.6	97	34.5
BMI	< 18.5	16	5.6	15	5.3
Mean ± SD: 24.21 ± 4.44/24.22 ± 4.44	18.5 ≤ to < 25	98	34.3	97	34.5
Minimum: 14.1/14.1	25 ≤	70	24.5	69	24.6
Median: 23.58/23.63	Unknown	102	35.7	100	35.6
Maximum: 38.1/38.1					
Reason for use	Bronchial asthma	286	100.0	281	100.0
	Others	0	0.0	0	0.0
Comorbidities	No	120	42.0	118	42.0
	Yes	166	58.0	163	58.0
Comorbidities (renal function disorder)	No	284	99.3	279	99.3
	Yes	2	0.7	2	0.7
Comorbidities (hepatic function disorder)	No	282	98.6	277	98.6
	Yes	4	1.4	4	1.4
Comorbidities (COPD)	No	260	90.9	255	90.7
	Yes	26	9.1	26	9.3
Comorbidities (others)	No	134	46.9	132	47.0
	Yes	152	53.1	149	53.0
Medical history	No	263	92.0	259	92.2
	Yes	23	8.0	22	7.8
Pregnancy (female only)	No	161	100.0	157	100.0
	Yes	0	0.0	0	0.0
History of smoking	No history of smoking	148	51.7	146	52.0
	Ex-smoker and not current smoker	29	10.1	29	10.3
	Current smoker	91	31.8	88	31.3
	Unknown	18	6.3	18	6.4
Duration of asthma [years]	≤ 2	65	22.7	64	22.8
	2 < to ≤ 5	45	15.7	43	15.3
	5 < to ≤ 10	46	16.1	46	16.4
	10 <	102	35.7	100	35.6
	Unknown	28	9.8	28	10.0
Severity	Mild intermittent	45	15.7	43	15.3
	Mild persistent	58	20.3	57	20.3
	Moderate persistent	129	45.1	127	45.2
	Severe persistent	48	16.8	48	17.1
	Most severe persistent	6	2.1	6	2.1
Type of asthma	Atopic	132	46.2	130	46.3
	Non-atopic	103	36.0	101	35.9
	Unknown	51	17.8	50	17.8
Pre-treatment medications	No	85	29.7	85	30.2
	Yes	201	70.3	196	69.8
Prior use of ICS, ICS/LABA, or ICS/LABA/LAMA	No	95	33.2	94	33.5
	Yes	191	66.8	187	66.5

*: The "mean ± SD", "minimum", "median", and "maximum" in each patient factor are shown in the order of "patients in the safety analysis"/"patients in the effectiveness analysis".

Table 2 Patient Characteristics (Pre-treatment Medications)

As of 29 May 2024

Patients in the safety analysis, patients in the effectiveness analysis

Drug category/drug name		Number of patients in the safety analysis		Number of patients in the effectiveness analysis	
		Number of patients	Percentage (%)	Number of patients	Percentage (%)
Inhaled corticosteroid alone (ICS)		7	2.4	7	2.5
Inhaled corticosteroid/long-acting beta 2 agonist combination (ICS/LABA)		182	63.6	178	63.3
	Relvar	89	31.1	88	31.3
	Symbicort	47	16.4	45	16.0
	Adoair	25	8.7	24	8.5
	Flutiform	21	7.3	21	7.5
	Atectura	0	0.0	0	0.0
	Others	0	0.0	0	0.0
	Unknown	0	0.0	0	0.0
Inhaled corticosteroid/long-acting beta 2 agonist /long-acting anticholinergic drug .combination (ICS/LABA/LAMA)		2	0.7	2	0.7
	Enerzair	1	0.3	1	0.4
	Others	1	0.3	1	0.4
	Unknown	0	0.0	0	0.0
Oral steroid		8	2.8	8	2.8
Long-acting beta 2 agonist alone (LABA)		8	2.8	8	2.8
Leukotriene receptor antagonist		93	32.5	92	32.7
Theophylline sustained-release preparation		19	6.6	18	6.4
Long-acting anticholinergic drug		39	13.6	39	13.9
Anti-IgE antibody		0	0.0	0	0.0
Anti-IL-5 antibody		1	0.3	1	0.4
Anti-IL-5 receptor α antibody		0	0.0	0	0.0
Anti-IL-4/13 receptor antibody		1	0.3	1	0.4
Antiallergic agents other than leukotriene receptor antagonists		23	8.0	23	8.2
Others		17	5.9	16	5.7
Unknown		0	0.0	0	0.0

Table 3 Administration Status

As of 29 May 2024

Patients in the safety analysis, patients in the effectiveness analysis

Item/Category		Number of patients in the safety analysis		Number of patients in the effectiveness analysis	
		Number of patients	Percentage (%)	Number of patients	Percentage (%)
ICS daily dose [μg] (initial dose)	100	72	25.2	70	24.9
	200	214	74.8	211	75.1
ICS daily dose [μg] (maximum dose)	100	67	23.4	65	23.1
	200	219	76.6	216	76.9
ICS mean daily dose [μg/day]	100	67	23.4	65	23.1
Sample size: 286/281	100 < to < 200	21	7.3	21	7.5
Mean ± SD: 171.8 ± 43.6/172.0 ± 43.5	200	198	69.2	195	69.4
Minimum: 100/100	200 <	0	0.0	0	0.0
Median: 200.0/200.0					
Maximum: 200/200					
Total number of days of treatment [days]	< 28	23	8.0	19	6.8
Sample size: 286/281	28 ≤ to < 84	36	12.6	35	12.5
Mean ± SD: 265.9 ± 138.6/270.4 ± 135.5	84 ≤ to < 168	21	7.3	21	7.5
Minimum: 2/2	168 ≤ to < 252	14	4.9	14	5.0
Median: 365.0/365.0	252 ≤ to < 365	34	11.9	34	12.1
Maximum: 365/365	365 ≤	158	55.2	158	56.2
ICS total dose [μg]	< 2800	9	3.1	6	2.1
Sample size: 286/281	2800 ≤ to < 8400	30	10.5	28	10.0
Mean ± SD: 45373.8 ± 26845.7/46142.7 ± 26448.5	8400 ≤ to < 16800	25	8.7	25	8.9
Minimum: 200/200	16800 ≤ to < 25200	15	5.2	15	5.3
Median: 41900.0/44000.0	25200 ≤ to < 36500	13	4.5	13	4.6
Maximum: 73000/73000	36500 ≤	194	67.8	194	69.0
Status of continuation of Trelegy treatment at the end of the observation period	Treatment continued	178	62.2	178	63.3
	Treatment	108	37.8	103	36.7
Concomitant medications	No	82	28.7	82	29.2
	Yes	204	71.3	199	70.8
Combination therapies	No	285	99.7	280	99.6
	Yes	1	0.3	1	0.4

*: The "sample size", "mean ± SD", "minimum", "median", and "maximum" are shown in the order of "patients in safety analysis"/"patients in effectiveness analysis".

Table 4 Duration of Trelegy Treatment by Reason for Treatment Withdrawal/Termination

As of 29 May 2024

Number of patients in the safety analysis

		Duration of Trelegy treatment until treatment withdrawal/termination (days)													
		≤ 30	30 < to ≤ 60	60 < to ≤ 90	90 < to ≤ 120	120 < to ≤ 150	150 < to ≤ 180	180 < to ≤ 210	210 < to ≤ 240	240 < to ≤ 270	270 < to ≤ 300	300 < to ≤ 330	330 < to ≤ 365	Unknown	Total
Number of patients who withdrew from/terminated treatment		28	18	16	13	3	3	5	5	6	3	2	6	0	108
Reason for treatment withdrawal/termination*	Occurrence of adverse events	10	3	3	2	1	0	0	0	1	1	2	0	0	23
	Pregnancy	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Factors related to effectiveness	6	3	2	4	1	3	2	3	0	0	0	1	0	25
	No visits after the first prescription date	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	No visits from the middle of the study	11	6	7	6	1	0	3	2	4	1	0	3	0	44
	Patient's personal reason other than stated above	3	5	4	2	0	0	0	0	1	1	0	2	0	18
	Physician's judgment other than stated above	0	1	0	0	0	0	0	0	0	0	0	0	0	1
	Unknown	0	0	0	0	0	0	0	0	0	0	0	0	0	0

*Includes overlaps.

Table 5 Occurrence of Adverse Drug Reactions by Seriousness

As of 29 May 2024

Number of patients in the safety analysis

	Total		Serious	
Number of patients investigated	286			
Number of patients with ADRs	24		1	
Proportion of patients with ADRs, etc. (%)	8.4		0.3	
Type of ADRs, etc.	Number of patients with ADRs (%)			
Respiratory, thoracic and mediastinal disorders	15	(5.2)	0	-
Cough	7	(2.4)	0	-
Dysphonia	7	(2.4)	0	-
Oropharyngeal discomfort	1	(0.3)	0	-
General disorders and administration site conditions	3	(1.0)	0	-
Thirst	2	(0.7)	0	-
Feeling abnormal	1	(0.3)	0	-
Cardiac disorders	2	(0.7)	0	-
Palpitations	2	(0.7)	0	-
Gastrointestinal disorders	2	(0.7)	0	-
Glossitis	1	(0.3)	0	-
Nausea	1	(0.3)	0	-
Infections and infestations	1	(0.3)	0	-
Oropharyngeal candidiasis	1	(0.3)	0	-
Nervous system disorders	1	(0.3)	0	-
Taste disorder	1	(0.3)	0	-
Skin and subcutaneous tissue disorders	1	(0.3)	0	-
Eczema	1	(0.3)	0	-
Renal and urinary disorders	1	(0.3)	1	(0.3)
Urinary retention	1	(0.3)	1	(0.3)

MedDRA/J (27.0)

Table 6 Outcome of Adverse Drug Reactions by Seriousness (by Event)

As of 29 May 2024

Number of patients in the safety analysis

	Serious												Non-serious											
	Death		Sequelae		Not resolved		Resolving		Resolved		Unknown		Death		Sequelae		Not resolved		Resolving		Resolved		Unknown	
Number of patients investigated	286												286											
Number of patients with ADRs	0		0		0		0		1		0		0		0		0		5		18		0	
Type of ADRs, etc.	Number of patients with ADRs (%)												Number of patients with ADRs (%)											
Respiratory, thoracic and mediastinal disorders	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	3	(1.0)	12	(4.2)	0	-
Cough	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	1	(0.3)	6	(2.1)	0	-
Dysphonia	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	2	(0.7)	5	(1.7)	0	-
Oropharyngeal discomfort	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	1	(0.3)	0	-
General disorders and administration site conditions	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	2	(0.7)	1	(0.3)	0	-
Thirst	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	1	(0.3)	1	(0.3)	0	-
Feeling abnormal	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	1	(0.3)	0	-	0	-
Cardiac disorders	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	2	(0.7)	0	-
Palpitations	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	2	(0.7)	0	-
Gastrointestinal disorders	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	2	(0.7)	0	-
Glossitis	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	1	(0.3)	0	-
Nausea	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	1	(0.3)	0	-
Infections and infestations	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	1	(0.3)	0	-
Oropharyngeal candidiasis	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	1	(0.3)	0	-
Nervous system disorders	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	1	(0.3)	0	-
Taste disorder	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	1	(0.3)	0	-
Skin and subcutaneous tissue disorders	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	1	(0.3)	0	-
Eczema	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	1	(0.3)	0	-
Renal and urinary disorders	0	-	0	-	0	-	0	-	1	(0.3)	0	-	0	-	0	-	0	-	0	-	0	-	0	-
Urinary retention	0	-	0	-	0	-	0	-	1	(0.3)	0	-	0	-	0	-	0	-	0	-	0	-	0	-

MedDRA/J (27.0)

If more than one event with the same SOT and PT occurred in the same patient, it was tabulated for each of the SOC and the PT in the order of priority of (1) serious > non-serious and (2) death > sequelae > not resolved > resolving > resolved > unknown.

Table 7 Logistic Regression Analysis by Univariate Analysis (Safety)

As of 29 May 2024

Number of patients in the safety analysis
Odds ratio estimated by univariate logistic regression

Item/Category			Number of patients investigated	Number of patients with ADRs	Proportion of patients with ADRs (%)	Unadjusted odds ratio		
						Point estimate	95% CI	
Total		base category	286	24	8.4		Lower limit	Upper limit
Gender	Male	*	125	9	7.2	-	-	-
	Female		161	15	9.3	1.324	0.559	3.134
Age 1 [years]	< 15		0	0	-	-	-	-
	15 ≤ to < 65	*	167	8	4.8	-	-	-
	65 ≤		119	16	13.4	3.087	1.275	7.474
Age 2 [years]	< 65	*	167	8	4.8	-	-	-
	65 ≤		119	16	13.4	3.087	1.275	7.474
Age 3 [years]	< 12		0	0	-			
	12 ≤ to < 18	*	2	0	0.0			
	18 ≤		284	24	8.5			
BMI	< 18.5		16	2	12.5	1.413	0.276	7.228
	18.5 ≤ to < 25	*	98	9	9.2	-	-	-
	25 ≤		70	6	8.6	0.927	0.314	2.735
Weight [kg]	< 40		7	0	0.0			
	40 ≤ to < 50		25	4	16.0			
	50 ≤ to < 60	*	46	6	13.0			
	60 ≤ to < 70		54	3	5.6			
	70 ≤ to < 80		34	2	5.9			
	80 ≤		21	2	9.5			
Reason for use	Bronchial asthma	*	286	24	8.4	-	-	-
	Others		0	0	-	-	-	-
Comorbidities	No	*	120	11	9.2	-	-	-
	Yes		166	13	7.8	0.842	0.364	1.950
Comorbidities (renal function disorder)	No	*	284	24	8.5			
	Yes		2	0	0.0			
Comorbidities (hepatic function disorder)	No	*	282	24	8.5			
	Yes		4	0	0.0			
Comorbidities (COPD)	No	*	260	22	8.5	-	-	-
	Yes		26	2	7.7	0.902	0.200	4.069
Comorbidities (others)	No	*	134	12	9.0	-	-	-
	Yes		152	12	7.9	0.871	0.378	2.011
Medical history	No	*	263	20	7.6	-	-	-
	Yes		23	4	17.4	2.559	0.794	8.249
Pregnancy (female only)	No	*	161	15	9.3	-	-	-
	Yes		0	0	-	-	-	-
History of smoking	No history of smoking	*	148	12	8.1	-	-	-
	Ex-smoker and not current smoker		29	2	6.9	0.840	0.178	3.967
	Current smoker		91	10	11.0	1.399	0.579	3.384
Duration of asthma [years]	≤ 2	*	65	7	10.8	-	-	-
	2 < to ≤ 5		45	5	11.1	1.036	0.307	3.495
	5 < to ≤ 10		46	2	4.3	0.377	0.075	1.902
	10 <		102	10	9.8	0.901	0.325	2.498
Severity	Mild intermittent		45	5	11.1			
	Mild persistent		58	7	12.1			
	Moderate persistent	*	129	11	8.5			
	Severe persistent		48	1	2.1			
	Most severe persistent		6	0	0.0			
Type of asthma	Atopic	*	132	9	6.8	-	-	-
	Non-atopic		103	11	10.7	1.634	0.650	4.106
Pre-treatment medications	No	*	85	7	8.2	-	-	-
	Yes		201	17	8.5	1.029	0.411	2.581
Prior use of ICS, ICS/LABA, or ICS/LABA/LAMA	No	*	95	7	7.4	-	-	-
	Yes		191	17	8.9	1.228	0.491	3.072
Concomitant medications	No	*	82	8	9.8	-	-	-
	Yes		204	16	7.8	0.787	0.323	1.917
Combination therapies	No	*	285	24	8.4	-	-	-
	Yes		1	0	0.0	-	-	-

Table 8 Multivariate Analysis (Safety)

As of 29 May 2024

Number of patients in the safety analysis
Odds ratio estimated by multivariate logistic regression

Item/Category			Number of patients investigated	Number of patients with ADRs	Proportion of patients with ADRs (%)	Adjusted odds ratio		
						Point estimate	95% CI	
Total		base category	286	24	8.4		Lower limit	Upper limit
Gender	Male	*	125	9	7.2	-	-	-
	Female		161	15	9.3	3.510	1.023	12.049
Age 2 [years]	< 65	*	167	8	4.8	-	-	-
	65 ≤		119	16	13.4	3.658	1.140	11.741
Comorbidities	No	*	120	11	9.2	-	-	-
	Yes		166	13	7.8	0.889	0.265	2.980
Comorbidities (COPD)	No	*	260	22	8.5	-	-	-
	Yes		26	2	7.7	0.224	0.023	2.148
History of smoking	No history of smoking	*	148	12	8.1	-	-	-
	Ex-smoker and not current smoker		29	2	6.9	0.976	0.102	9.366
	Current smoker		91	10	11.0	3.110	0.862	11.216
Duration of asthma [years]	≤ 2	*	65	7	10.8	-	-	-
	2 < to ≤ 5		45	5	11.1	0.872	0.183	4.165
	5 < to ≤ 10		46	2	4.3	0.150	0.015	1.459
	10 <		102	10	9.8	0.695	0.164	2.942
Type of asthma	Atopic	*	132	9	6.8	-	-	-
	Non-atopic		103	11	10.7	1.359	0.476	3.875
Pre-treatment medications	No	*	85	7	8.2	-	-	-
	Yes		201	17	8.5	0.726	0.188	2.806
Concomitant medications	No	*	82	8	9.8	-	-	-
	Yes		204	16	7.8	0.652	0.195	2.179

Table 9 Occurrence of Adverse Drug Reactions by Affecting Factor

As of 29 May 2024

Number of patients in the safety analysis

	Gender									
	Male				Female			Total		
	Total		Serious		Total	Serious		Total	Serious	
Number of patients investigated	125				161			286		
Number of patients with ADRs	9		1		15	0		24	1	
Proportion of patients with ADRs, etc. (%)	7.2		0.8		9.3	0.0		8.4	0.3	
Type of ADRs, etc.	Number of patients with ADRs (%)				Number of patients with ADRs (%)			Number of patients with ADRs (%)		
Respiratory, thoracic and mediastinal disorders	6	(4.8)	0		9	(5.6)	0	15	(5.2)	0
Cough	1	(0.8)	0		6	(3.7)	0	7	(2.4)	0
Dysphonia	4	(3.2)	0		3	(1.9)	0	7	(2.4)	0
Oropharyngeal discomfort	1	(0.8)	0		0		0	1	(0.3)	0
General disorders and administration site conditions	1	(0.8)	0		2	(1.2)	0	3	(1.0)	0
Thirst	1	(0.8)	0		1	(0.6)	0	2	(0.7)	0
Feeling abnormal	0		0		1	(0.6)	0	1	(0.3)	0
Cardiac disorders	0		0		2	(1.2)	0	2	(0.7)	0
Palpitations	0		0		2	(1.2)	0	2	(0.7)	0
Gastrointestinal disorders	0		0		2	(1.2)	0	2	(0.7)	0
Glossitis	0		0		1	(0.6)	0	1	(0.3)	0
Nausea	0		0		1	(0.6)	0	1	(0.3)	0
Infections and infestations	1	(0.8)	0		0		0	1	(0.3)	0
Oropharyngeal candidiasis	1	(0.8)	0		0		0	1	(0.3)	0
Nervous system disorders	0		0		1	(0.6)	0	1	(0.3)	0
Taste disorder	0		0		1	(0.6)	0	1	(0.3)	0
Skin and subcutaneous tissue disorders	0		0		1	(0.6)	0	1	(0.3)	0
Eczema	0		0		1	(0.6)	0	1	(0.3)	0
Renal and urinary disorders	1	(0.8)	1	(0.8)	0		0	1	(0.3)	1 (0.3)
Urinary retention	1	(0.8)	1	(0.8)	0		0	1	(0.3)	1 (0.3)

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Table 10 Occurrence of Adverse Drug Reactions by Affecting Factor

As of 29 May 2024

Number of patients in the safety analysis

	Age 1 [years]									
	< 15		15 ≤ to < 65		65 ≤		Total			
	Total	Serious	Total	Serious	Total	Serious	Total		Serious	
Number of patients investigated	0		167		119		286			
Number of patients with ADRs	0	0	8	0	16	1	24		1	
Proportion of patients with ADRs, etc. (%)	-	-	4.8	0.0	13.4	0.8	8.4		0.3	
Type of ADRs, etc.	Number of patients with ADRs (%)		Number of patients with ADRs (%)		Number of patients with ADRs (%)		Number of patients with ADRs (%)			
Respiratory, thoracic and mediastinal disorders	0	0	2 (1.2)	0	13 (10.9)	0	15 (5.2)		0	
Cough	0	0	1 (0.6)	0	6 (5.0)	0	7 (2.4)		0	
Dysphonia	0	0	1 (0.6)	0	6 (5.0)	0	7 (2.4)		0	
Oropharyngeal discomfort	0	0	0	0	1 (0.8)	0	1 (0.3)		0	
General disorders and administration site conditions	0	0	3 (1.8)	0	0	0	3 (1.0)		0	
Thirst	0	0	2 (1.2)	0	0	0	2 (0.7)		0	
Feeling abnormal	0	0	1 (0.6)	0	0	0	1 (0.3)		0	
Cardiac disorders	0	0	1 (0.6)	0	1 (0.8)	0	2 (0.7)		0	
Palpitations	0	0	1 (0.6)	0	1 (0.8)	0	2 (0.7)		0	
Gastrointestinal disorders	0	0	0	0	2 (1.7)	0	2 (0.7)		0	
Glossitis	0	0	0	0	1 (0.8)	0	1 (0.3)		0	
Nausea	0	0	0	0	1 (0.8)	0	1 (0.3)		0	
Infections and infestations	0	0	1 (0.6)	0	0	0	1 (0.3)		0	
Oropharyngeal candidiasis	0	0	1 (0.6)	0	0	0	1 (0.3)		0	
Nervous system disorders	0	0	1 (0.6)	0	0	0	1 (0.3)		0	
Taste disorder	0	0	1 (0.6)	0	0	0	1 (0.3)		0	
Skin and subcutaneous tissue disorders	0	0	0	0	1 (0.8)	0	1 (0.3)		0	
Eczema	0	0	0	0	1 (0.8)	0	1 (0.3)		0	
Renal and urinary disorders	0	0	0	0	1 (0.8)	1 (0.8)	1 (0.3)		1	(0.3)
Urinary retention	0	0	0	0	1 (0.8)	1 (0.8)	1 (0.3)		1	(0.3)

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Table 11 Occurrence of Adverse Drug Reactions by Affecting Factor

As of 29 May 2024

Number of patients in the safety analysis

	Age 2 [years]											
	< 65			65 ≤			Total					
	Total		Serious	Total		Serious	Total			Serious		
Number of patients investigated	167			119			286					
Number of patients with ADRs	8		0	16		1	24			1		
Proportion of patients with ADRs, etc. (%)	4.8		0.0	13.4		0.8	8.4			0.3		
Type of ADRs, etc.	Number of patients with ADRs (%)			Number of patients with ADRs (%)			Number of patients with ADRs (%)					
Respiratory, thoracic and mediastinal disorders	2	(1.2)	0	13	(10.9)	0	15	(5.2)		0		
Cough	1	(0.6)	0	6	(5.0)	0	7	(2.4)		0		
Dysphonia	1	(0.6)	0	6	(5.0)	0	7	(2.4)		0		
Oropharyngeal discomfort	0		0	1	(0.8)	0	1	(0.3)		0		
General disorders and administration site conditions	3	(1.8)	0	0		0	3	(1.0)		0		
Thirst	2	(1.2)	0	0		0	2	(0.7)		0		
Feeling abnormal	1	(0.6)	0	0		0	1	(0.3)		0		
Cardiac disorders	1	(0.6)	0	1	(0.8)	0	2	(0.7)		0		
Palpitations	1	(0.6)	0	1	(0.8)	0	2	(0.7)		0		
Gastrointestinal disorders	0		0	2	(1.7)	0	2	(0.7)		0		
Glossitis	0		0	1	(0.8)	0	1	(0.3)		0		
Nausea	0		0	1	(0.8)	0	1	(0.3)		0		
Infections and infestations	1	(0.6)	0	0		0	1	(0.3)		0		
Oropharyngeal candidiasis	1	(0.6)	0	0		0	1	(0.3)		0		
Nervous system disorders	1	(0.6)	0	0		0	1	(0.3)		0		
Taste disorder	1	(0.6)	0	0		0	1	(0.3)		0		
Skin and subcutaneous tissue disorders	0		0	1	(0.8)	0	1	(0.3)		0		
Eczema	0		0	1	(0.8)	0	1	(0.3)		0		
Renal and urinary disorders	0		0	1	(0.8)	1	(0.8)	1	(0.3)	1	(0.3)	
Urinary retention	0		0	1	(0.8)	1	(0.8)	1	(0.3)	1	(0.3)	

MedDRA/J (27.0)

Table 12 Time to Onset of Adverse Drug Reactions

As of 29 May 2024

Number of patients in the safety analysis

	Time to onset of ADRs (days)[*1]													Total number of patients (%)[*3]	
	≤30	30 < to ≤60	60 < to ≤90	90 < to ≤120	120 < to ≤150	150 < to ≤180	180 < to ≤210	210 < to ≤240	240 < to ≤270	270 < to ≤300	300 < to ≤330	330 < to ≤365	Unknown[*2]		
Number of patients in the safety analysis	286	258	240	224	211	208	205	200	195	189	186	184		286	(100.0)
Type of ADRs, etc.	Number of patients with ADRs by type														
Respiratory, thoracic and mediastinal disorders	8	4	0	1	0	0	0	1	0	0	1	0	0	15	(5.2)
Cough	5	1	0	1	0	0	0	0	0	0	0	0	0	7	(2.4)
Dysphonia	2	3	0	0	0	0	0	1	0	0	1	0	0	7	(2.4)
Oropharyngeal discomfort	1	0	0	0	0	0	0	0	0	0	0	0	0	1	(0.3)
General disorders and administration site conditions	3	0	0	0	0	0	0	0	0	0	0	0	0	3	(1.0)
Thirst	2	0	0	0	0	0	0	0	0	0	0	0	0	2	(0.7)
Feeling abnormal	1	0	0	0	0	0	0	0	0	0	0	0	0	1	(0.3)
Cardiac disorders	1	1	0	0	0	0	0	0	0	0	0	0	0	2	(0.7)
Palpitations	1	1	0	0	0	0	0	0	0	0	0	0	0	2	(0.7)
Gastrointestinal disorders	1	1	0	0	0	0	0	0	0	0	0	0	0	2	(0.7)
Glossitis	0	1	0	0	0	0	0	0	0	0	0	0	0	1	(0.3)
Nausea	1	0	0	0	0	0	0	0	0	0	0	0	0	1	(0.3)
Infections and infestations	0	0	0	0	0	1	0	0	0	0	0	0	0	1	(0.3)
Oropharyngeal candidiasis	0	0	0	0	0	1	0	0	0	0	0	0	0	1	(0.3)
Nervous system disorders	0	0	0	0	1	0	0	0	0	0	0	0	0	1	(0.3)
Taste disorder	0	0	0	0	1	0	0	0	0	0	0	0	0	1	(0.3)
Skin and subcutaneous tissue disorders	1	0	0	0	0	0	0	0	0	0	0	0	0	1	(0.3)
Eczema	1	0	0	0	0	0	0	0	0	0	0	0	0	1	(0.3)
Renal and urinary disorders	0	0	0	0	0	0	0	0	1	0	0	0	0	1	(0.3)
Urinary retention	0	0	0	0	0	0	0	0	1	0	0	0	0	1	(0.3)
Number of patients with ADRs	13	5	0	1	1	1	0	1	1	0	1	0	0	24	(8.4)
(%)[*4]	(54.2)	(20.8)	(0.0)	(4.2)	(4.2)	(4.2)	(0.0)	(4.2)	(4.2)	(0.0)	(4.2)	(0.0)		-	-
Cumulative number of patients with ADRs	13	18	18	19	20	21	21	22	23	23	24	24	0	-	-
(%)[*5]	(54.2)	(75.0)	(75.0)	(79.2)	(83.3)	(87.5)	(87.5)	(91.7)	(95.8)	(95.8)	(100.0)	(100.0)		-	-

*1: When an ADR with the same preferred term (PT) occurred multiple times in the same patient, the number of days of treatment until the first onset of the ADR was used for tabulation. MedDRA/J (27.0)

*2: Patients with unknown date of onset of ADRs were tabulated as those with unknown time to onset of ADRs.

*3: Th overlapping data of patients from unit dose and frequency of daily, and type of ADRs were excluded from tabulation.

*4: (Number of patients with ADRs/total number of patients)*100

*5: (Cumulative number of patients with ADRs/total number of patients)*100

Table 13 Occurrence of Adverse Drug Reactions (Cardiovascular Events) by Safety Specification

As of 29 May 2024

Number of patients in the safety analysis

[Cardiovascular Events]

	Total		Serious	
Number of patients investigated	286			
Number of patients with ADRs	2		0	
Proportion of patients with ADRs, etc. (%)	0.7		0.0	
Type of ADRs, etc.	Number of patients with ADRs (%)			
Cardiac disorders	2	(0.7)	0	-
Palpitations	2	(0.7)	0	-

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Table 14 Occurrence of Adverse Drug Reactions by Safety Specification (Person-year Method)

As of 29 May 2024

Number of patients in the safety analysis

Number of patients in the safety analysis	286					
Safety specifications	Number of patients with ADRs	Proportion of patients (%)	95% CI	Total person-years	Incidence [/100 person-years]	95% CI [/100 person-years]
Cardiovascular events	2	0.7	0.08, 2.50	210.35	0.95	0.12, 3.43

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The person-year is based on the time to onset of the first ADR (PT).

Table 15 Proportion of Responders by Patient Characteristics

As of 29 May 2024

Number of patients in the effectiveness analysis

Item of patient characteristics		Number of patients investigated	Number of responders	Number of non-responders	Proportion of responders (%)
Total		281	260	21	92.5
Gender	Male	124	114	10	91.9
	Female	157	146	11	93.0
Age 1 [years]	< 15	0	0	0	-
Mean ± SD: 58.5 ± 16.8	15 ≤ to < 65	165	158	7	95.8
Minimum: 16	65 ≤	116	102	14	87.9
Median: 59.0					
Maximum: 89					
Age 2 [years]	< 65	165	158	7	95.8
	65 ≤	116	102	14	87.9
Age 3 [years]	< 12	0	0	0	-
	12 ≤ to < 18	2	2	0	100.0
	18 ≤	279	258	21	92.5
Weight [kg]	< 40	7	7	0	100.0
Mean ± SD: 62.57 ± 13.70	40 ≤ to < 50	24	22	2	91.7
Minimum: 32.9	50 ≤ to < 60	46	43	3	93.5
Median: 62.00	60 ≤ to < 70	52	48	4	92.3
Maximum: 105.0	70 ≤ to < 80	34	32	2	94.1
	80 ≤	21	18	3	85.7
	Unknown	97	90	7	92.8
BMI	< 18.5	15	14	1	93.3
Mean ± SD: 24.22 ± 4.44	18.5 ≤ to < 25	97	91	6	93.8
Minimum: 14.1	25 ≤	69	63	6	91.3
Median: 23.63	Unknown	100	92	8	92.0
Maximum: 38.1					
Reason for use	Bronchial asthma	281	260	21	92.5
	Others	0	0	0	-
Comorbidities	No	118	111	7	94.1
	Yes	163	149	14	91.4
Comorbidities (renal function disorder)	No	279	258	21	92.5
	Yes	2	2	0	100.0
Comorbidities (hepatic function disorder)	No	277	256	21	92.4
	Yes	4	4	0	100.0
Comorbidities (COPD)	No	255	236	19	92.5
	Yes	26	24	2	92.3
Comorbidities (others)	No	132	125	7	94.7
	Yes	149	135	14	90.6
Medical history	No	259	239	20	92.3
	Yes	22	21	1	95.5
Pregnancy (female only)	No	157	146	11	93.0
	Yes	0	0	0	-
History of smoking	No history of smoking	146	135	11	92.5
	Ex-smoker and not current smoker	29	28	1	96.6
	Current smoker	88	80	8	90.9
	Unknown	18	17	1	94.4
Duration of asthma [years]	≤ 2	64	58	6	90.6
	2 < to ≤ 5	43	41	2	95.3
	5 < to ≤ 10	46	43	3	93.5
	10 <	100	93	7	93.0
	Unknown	28	25	3	89.3
Severity	Mild intermittent	43	40	3	93.0
	Mild persistent	57	50	7	87.7
	Moderate persistent	127	119	8	93.7
	Severe persistent	48	45	3	93.8
	Most severe persistent	6	6	0	100.0
Type of asthma	Atopic	130	124	6	95.4
	Non-atopic	101	91	10	90.1
	Unknown	50	45	5	90.0
Pre-treatment medications	No	85	84	1	98.8
	Yes	196	176	20	89.8
Prior use of ICS, ICS/LABA, or ICS/LABA/LAMA	No	94	93	1	98.9
	Yes	187	167	20	89.3

Table 16 Logistic Regression Analysis by Univariate Analysis (Effectiveness)

As of 29 May 2024

Number of patients in the effectiveness analysis
Odds ratio estimated by univariate logistic regression

Item/Category			Number of patients investigated	Number of responders	Proportion of responders	Unadjusted odds ratio		
						Point estimate	95% CI	
Total		base category	281	260	92.5		Lower limit	Upper limit
Gender	Male	*	124	114	91.9	-	-	-
	Female		157	146	93.0	1.164	0.478	2.837
Age 1 [years]	< 15		0	0	-	-	-	-
	15 ≤ to < 65	*	165	158	95.8	-	-	-
	65 ≤		116	102	87.9	0.323	0.126	0.827
Age 2 [years]	< 65	*	165	158	95.8	-	-	-
	65 ≤		116	102	87.9	0.323	0.126	0.827
Age 3 [years]	< 12		0	0	-			
	12 ≤ to < 18	*	2	2	100.0			
	18 ≤		279	258	92.5			
BMI	< 18.5		15	14	93.3	0.923	0.103	8.252
	18.5 ≤ to < 25	*	97	91	93.8	-	-	-
	25 ≤		69	63	91.3	0.692	0.214	2.244
Weight [kg]	< 40		7	7	100.0			
	40 ≤ to < 50		24	22	91.7			
	50 ≤ to < 60	*	46	43	93.5			
	60 ≤ to < 70		52	48	92.3			
	70 ≤ to < 80		34	32	94.1			
	80 ≤		21	18	85.7			
Reason for use	Bronchial asthma	*	281	260	92.5	-	-	-
	Others		0	0	-	-	-	-
Comorbidities	No	*	118	111	94.1	-	-	-
	Yes		163	149	91.4	0.671	0.262	1.718
Comorbidities (renal function disorder)	No	*	279	258	92.5			
	Yes		2	2	100.0			
Comorbidities (hepatic function disorder)	No	*	277	256	92.4			
	Yes		4	4	100.0			
Comorbidities (COPD)	No	*	255	236	92.5	-	-	-
	Yes		26	24	92.3	0.966	0.212	4.398
Comorbidities (others)	No	*	132	125	94.7	-	-	-
	Yes		149	135	90.6	0.540	0.211	1.381
Medical history	No	*	259	239	92.3	-	-	-
	Yes		22	21	95.5	1.757	0.225	13.751
Pregnancy (female only)	No	*	157	146	93.0	-	-	-
	Yes		0	0	-	-	-	-
History of smoking	No history of smoking	*	146	135	92.5	-	-	-
	Ex-smoker and not current smoker		29	28	96.6	2.281	0.283	18.383
	Current smoker		88	80	90.9	0.815	0.315	2.111
Duration of asthma [years]	≤ 2	*	64	58	90.6	-	-	-
	2 < to ≤ 5		43	41	95.3	2.121	0.407	11.037
	5 < to ≤ 10		46	43	93.5	1.483	0.351	6.264
	10 <		100	93	93.0	1.374	0.440	4.292
Severity	Mild intermittent		43	40	93.0			
	Mild persistent		57	50	87.7			
	Moderate persistent	*	127	119	93.7			
	Severe persistent		48	45	93.8			
	Most severe persistent		6	6	100.0			
Type of asthma	Atopic	*	130	124	95.4	-	-	-
	Non-atopic		101	91	90.1	0.440	0.154	1.255
Pre-treatment medications	No	*	85	84	98.8	-	-	-
	Yes		196	176	89.8	0.105	0.014	0.794
Prior use of ICS, ICS/LABA, or ICS/LABA/LAMA	No	*	94	93	98.9	-	-	-
	Yes		187	167	89.3	0.090	0.012	0.680
Concomitant medications	No	*	82	79	96.3	-	-	-
	Yes		199	181	91.0	0.382	0.109	1.334
Combination therapies	No	*	280	260	92.9	-	-	-
	Yes		1	0	0.0	-	-	-

Table 17 Multivariate Analysis (Effectiveness)

As of 29 May 2024

Number of patients in the effectiveness analysis
Odds ratio estimated by multivariate logistic regression

Item/Category			Number of patients investigated	Number of responders	Proportion of responders	Adjusted odds ratio		
						Point estimate	95% CI	
							Lower limit	Upper limit
Total		base category	281	260	92.5			
Gender	Male	*	124	114	91.9	-	-	-
	Female		157	146	93.0	1.215	0.291	5.076
Age 2 [years]	< 65	*	165	158	95.8	-	-	-
	65 ≤		116	102	87.9	0.244	0.055	1.074
Comorbidities	No	*	118	111	94.1	-	-	-
	Yes		163	149	91.4	1.959	0.479	8.022
Comorbidities (COPD)	No	*	255	236	92.5	-	-	-
	Yes		26	24	92.3	0.541	0.083	3.542
History of smoking	No history of smoking	*	146	135	92.5	-	-	-
	Ex-smoker and not current smoker		29	28	96.6	0.957	0.080	11.489
	Current smoker		88	80	90.9	1.419	0.293	6.876
Duration of asthma [years]	≤ 2	*	64	58	90.6	-	-	-
	2 < to ≤ 5		43	41	95.3	1.808	0.236	13.846
	5 < to ≤ 10		46	43	93.5	2.154	0.273	17.021
	10 <		100	93	93.0	2.071	0.377	11.389
Type of asthma	Atopic	*	130	124	95.4	-	-	-
	Non-atopic		101	91	90.1	0.587	0.155	2.224
Pre-treatment medications	No	*	85	84	98.8	-	-	-
	Yes		196	176	89.8	0.250	0.026	2.439
Concomitant medications	No	*	82	79	96.3	-	-	-
	Yes		199	181	91.0	0.184	0.021	1.647

Table 18　Respiratory Function Test Values over Time (PEF)

As of 29 May 2024

Number of patients in the effectiveness analysis

Parameter	Timing	Number of patients	Mean	SD	Minimum	25th percentile	Median	75th percentile	Maximum	95% CI of mean change
PEF (morning)	At the initiation of treatment	54	352.1	126.9	54	260.0	357.0	440.0	639	-
	1 month after the initiation of treatment	38	398.4	129.1	199	280.0	396.0	490.0	644	-
	3 months after the initiation of treatment	36	392.9	150.5	105	259.0	386.0	510.0	682	-
	6 months after the initiation of treatment	38	397.7	131.2	91	330.0	391.0	480.0	720	-
	1 year after the initiation of treatment	41	387.8	131.5	116	289.0	394.0	460.0	685	-
	End of the observation period*	51	403.4	132.6	116	289.0	406.0	498.0	685	-
Change in PEF (morning)	1 month after the initiation of treatment	38	30.9	48.4	-40	8.0	14.0	41.0	180	15.0-46.8
	3 months after the initiation of treatment	36	49.3	55.6	-30	10.0	35.0	69.5	180	30.5-68.1
	6 months after the initiation of treatment	38	57.8	69.1	-10	10.0	35.0	100.0	300	35.1-80.5
	1 year after the initiation of treatment	41	50.5	54.1	-20	12.0	40.0	70.0	240	33.5-67.6
	End of the observation period*	51	47.5	55.5	-40	10.0	35.0	70.0	240	31.9-63.1
PEF (evening)	At the initiation of treatment	34	358.3	115.1	150	280.0	366.0	450.0	600	-
	1 month after the initiation of treatment	22	376.6	133.7	176	248.0	392.0	470.0	610	-
	3 months after the initiation of treatment	19	392.3	147.7	209	250.0	370.0	490.0	640	-
	6 months after the initiation of treatment	25	380.0	113.6	210	290.0	380.0	430.0	630	-
	1 year after the initiation of Trelegy treatment	26	371.9	98.4	215	255.0	390.0	410.0	630	-
	End of the observation period*	33	400.6	114.1	215	320.0	400.0	480.0	640	-
Change in PEF (evening)	1 month after the initiation of treatment	22	21.2	35.8	-60	0.0	14.0	30.0	110	5.3-37.0
	3 months after the initiation of treatment	19	35.6	48.8	-40	5.0	20.0	40.0	150	12.1-59.2
	6 months after the initiation of treatment	25	35.2	44.1	-40	6.0	20.0	50.0	140	17.0-53.5
	1 year after the initiation of treatment	26	37.3	40.8	-40	10.0	25.0	70.0	140	20.9-53.8
	End of the observation period*	33	39.6	41.8	-40	10.0	26.0	70.0	140	24.7-54.4

* At the end of the observation period (1 year after the initiation of treatment or at the withdrawal/termination of treatment if treatment with Trelegy is withdrawn/terminated)

Of the patients in the effectiveness analysis set, the following patients were included in the analysis:
- Patients with respiratory function test data before and after the initiation of Trelegy treatment
- Patients with all data on the presence or absence of use of short-acting beta 2 agonist (SABA) at the initiation of Trelegy treatment and after the initiation of treatment

Table 19　Respiratory Function Test Values over Time (FEV1, FVC)

As of 29 May 2024

Number of patients in the effectiveness analysis

Parameter	Timing	Number of patients	Mean	SD	Minimum	25th percentile	Median	75th percentile	Maximum	95% CI of mean change
FVC	Before the initiation of treatment	66	2.668	1.064	0.88	1.730	2.720	3.270	5.01	-
	1 year after the initiation of treatment	37	2.755	1.013	1.26	2.040	2.660	3.010	4.99	-
	At the final measurement*	66	2.872	0.993	1.26	2.090	2.785	3.480	4.99	-
Change in FVC	1 year after the initiation of treatment	37	0.214	0.410	-0.67	0.060	0.130	0.310	1.88	0.078-0.351
	At the final measurement*	66	0.204	0.390	-0.79	0.050	0.135	0.310	1.88	0.108-0.300
FEV1	Before the initiation of treatment	66	2.003	0.757	0.58	1.340	2.065	2.560	3.66	-
	1 year after the initiation of treatment	37	2.233	0.780	0.97	1.490	2.320	2.690	4.31	-
	At the final measurement*	66	2.247	0.724	0.97	1.780	2.340	2.690	4.31	-
Change in FEV1	1 year after the initiation of treatment	37	0.243	0.286	-0.15	0.090	0.120	0.330	1.17	0.147-0.338
	At the final measurement*	66	0.244	0.309	-0.34	0.080	0.150	0.380	1.42	0.168-0.320

* Including patients treated for less than 1 year

Of the patients in the effectiveness analysis set, the following patients were included in the analysis:
- Patients with respiratory function test data before and after the initiation of Trelegy treatment
- Patients with all data on the presence or absence of use of short-acting beta 2 agonist (SABA) at the initiation of Trelegy treatment and after the initiation of treatment

Table 20 ACT Scores over Time

As of 29 May 2024

Number of patients in the effectiveness analysis

Parameter	Timing	Number of patients	Mean	SD	Minimum	25th percentile	Median	75th percentile	Maximum	95% CI of mean change
ACT score	At the initiation of treatment	205	16.8	5.0	5	13.0	18.0	21.0	25	-
	1 month after the initiation of treatment	143	20.7	4.0	7	19.0	22.0	24.0	25	-
	3 months after the initiation of treatment	125	21.9	3.5	8	20.0	23.0	25.0	25	-
	6 months after the initiation of treatment	121	22.3	2.9	10	21.0	23.0	25.0	25	-
	1 year after the initiation of treatment	120	22.0	3.6	8	21.0	23.0	25.0	25	-
	End of the observation period*	168	21.9	3.7	8	20.0	23.0	25.0	25	-
Change in ACT score	1 month after the initiation of treatment	143	4.1	4.2	-5	1.0	3.0	7.0	15	3.4-4.8
	3 months after the initiation of treatment	125	4.9	5.1	-4	1.0	4.0	9.0	16	4.0-5.8
	6 months after the initiation of treatment	121	5.7	5.0	-3	1.0	5.0	10.0	16	4.8-6.6
	1 year after the initiation of Trelegy treatment	120	5.8	5.4	-8	1.0	5.0	10.0	17	4.8-6.8
	End of the observation period*	168	5.3	5.4	-10	1.0	4.0	9.5	17	4.5-6.1

* At the end of the observation period (1 year after the initiation of treatment or at the withdrawal/termination of treatment if treatment with Trelegy is withdrawn/terminated)

Of the patients in the effectiveness analysis set, those with ACT score data before and after the initiation of Trelegy treatment were included in the analysis.

Table 21 Events Related to Exacerbation of Asthma

As of 29 May 2024

Number of patients in the effectiveness analysis
[At the end of treatment (including patients treated for less than 1 year)]

		Before the initiation of treatment		After the initiation of treatment	
Number of patients	Number of patients investigated	Number of patients with "Yes"	%	Number of patients with "Yes"	%
Experienced any of the following events:	281	72	25.6	14	5.0
Hospitalization due to exacerbation of asthma	281	9	3.2	1	0.4
Treatment at emergency room due to exacerbation of asthma	281	9	3.2	1	0.4
Oral corticosteroid use (3 days or more) due to exacerbation of asthma	281	41	14.6	12	4.3
Unscheduled visit to an outpatient clinic due to exacerbation of asthma	281	50	17.8	12	4.3
Experience of one day off from work (including home activities) or school due to exacerbation of asthma	281	19	6.8	3	1.1

Of the patients in the effectiveness analysis, those with all data on the presence or absence of "events related to exacerbation of asthma" before and after the initiation of Trelegy treatment were included in the analysis.

Table 22 Events Related to Exacerbation of Asthma

As of 29 May 2024

Number of patients in the effectiveness analysis
[Patients treated for 1 year]

		Before the initiation of treatment		After the initiation of treatment	
Number of patients	Number of patients investigated	Number of patients with "Yes"	%	Number of patients with "Yes"	%
Experienced any of the following events:	178	46	25.8	11	6.2
Hospitalization due to exacerbation of asthma	178	7	3.9	1	0.6
Treatment at emergency room due to exacerbation of asthma	178	6	3.4	0	0.0
Oral corticosteroid use (3 days or more) due to exacerbation of asthma	178	25	14.0	9	5.1
Unscheduled visit to an outpatient clinic due to exacerbation of asthma	178	31	17.4	9	5.1
Experience of one day off from work (including home activities) or school due to exacerbation of asthma	178	12	6.7	3	1.7

Of the patients in the effectiveness analysis, those with all data on the presence or absence of "events related to exacerbation of asthma" before and after the initiation of Trelegy treatment were included in the analysis.

Table 23 Occurrence of Adverse Drug Reactions in Patients with Specific Backgrounds (Elderly)

As of 29 May 2024

Number of patients in the safety analysis

[Elderly]

	Specific background (elderly)											
	Yes				No				Total			
	Overall ADRs		Serious ADRs		Overall ADRs		Serious ADRs		Overall ADRs		Serious ADRs	
Number of patients investigated	119				167				286			
Number of patients with ADRs	16		1		8		0		24		1	
Proportion of patients with ADRs, etc. (%)	13.4		0.8		4.8		0.0		8.4		0.3	
Type of ADRs, etc.	Number of patients with ADRs (%)				Number of patients with ADRs (%)				Number of patients with ADRs (%)			
Respiratory, thoracic and mediastinal disorders	13	(10.9)	0	-	2	(1.2)	0	-	15	(5.2)	0	-
Cough	6	(5.0)	0	-	1	(0.6)	0	-	7	(2.4)	0	-
Dysphonia	6	(5.0)	0	-	1	(0.6)	0	-	7	(2.4)	0	-
Oropharyngeal discomfort	1	(0.8)	0	-	0	-	0	-	1	(0.3)	0	-
General disorders and administration site conditions	0	-	0	-	3	(1.8)	0	-	3	(1.0)	0	-
Thirst	0	-	0	-	2	(1.2)	0	-	2	(0.7)	0	-
Feeling abnormal	0	-	0	-	1	(0.6)	0	-	1	(0.3)	0	-
Cardiac disorders	1	(0.8)	0	-	1	(0.6)	0	-	2	(0.7)	0	-
Palpitations	1	(0.8)	0	-	1	(0.6)	0	-	2	(0.7)	0	-
Gastrointestinal disorders	2	(1.7)	0	-	0	-	0	-	2	(0.7)	0	-
Glossitis	1	(0.8)	0	-	0	-	0	-	1	(0.3)	0	-
Nausea	1	(0.8)	0	-	0	-	0	-	1	(0.3)	0	-
Infections and infestations	0	-	0	-	1	(0.6)	0	-	1	(0.3)	0	-
Oropharyngeal candidiasis	0	-	0	-	1	(0.6)	0	-	1	(0.3)	0	-
Nervous system disorders	0	-	0	-	1	(0.6)	0	-	1	(0.3)	0	-
Taste disorder	0	-	0	-	1	(0.6)	0	-	1	(0.3)	0	-
Skin and subcutaneous tissue disorders	1	(0.8)	0	-	0	-	0	-	1	(0.3)	0	-
Eczema	1	(0.8)	0	-	0	-	0	-	1	(0.3)	0	-
Renal and urinary disorders	1	(0.8)	1	(0.8)	0	-	0	-	1	(0.3)	1	(0.3)
Urinary retention	1	(0.8)	1	(0.8)	0	-	0	-	1	(0.3)	1	(0.3)

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Table 24 Outcome of Adverse Drug Reactions in Patients with Specific Backgrounds (Elderly)

As of 29 May 2024

Number of patients in the safety analysis
[Elderly]

	Specific background (elderly)																							
	Yes						No						Total					
	Death	Sequelae	Not resolved	Resolving	Resolved	Unknown	Death	Sequelae	Not resolved	Resolving	Resolved	Unknown	Death	Sequelae	Not resolved	Resolving	Resolved	Unknown
Number of patients investigated	119						167						286					
Number of patients with ADRs	0	0	0	3	13	0	0	0	0	2	6	0	0	0	0	5	19	0
Type of ADRs, etc.	Number of patients with ADRs (proportion of patients with ADRs [*])						Number of patients with ADRs (proportion of patients with ADRs [*])						Number of patients with ADRs (proportion of patients with ADRs [*])					
Respiratory, thoracic and mediastinal disorders	0 -	0 -	0 -	3 (2.5)	10 (8.4)	0 -	0 -	0 -	0 -	0 -	2 (1.2)	0 -	0 -	0 -	0 -	3 (1.0)	12 (4.2)	0 -
Cough	0 -	0 -	0 -	1 (0.8)	5 (4.2)	0 -	0 -	0 -	0 -	0 -	1 (0.6)	0 -	0 -	0 -	0 -	1 (0.3)	6 (2.1)	0 -
Dysphonia	0 -	0 -	0 -	2 (1.7)	4 (3.4)	0 -	0 -	0 -	0 -	0 -	1 (0.6)	0 -	0 -	0 -	0 -	2 (0.7)	5 (1.7)	0 -
Oropharyngeal discomfort	0 -	0 -	0 -	0 -	1 (0.8)	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
General disorders and administration site conditions	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	2 (1.2)	1 (0.6)	0 -	0 -	0 -	0 -	2 (0.7)	1 (0.3)	0 -
Thirst	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.6)	1 (0.6)	0 -	0 -	0 -	0 -	1 (0.3)	1 (0.3)	0 -
Feeling abnormal	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.6)	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -	0 -
Cardiac disorders	0 -	0 -	0 -	0 -	1 (0.8)	0 -	0 -	0 -	0 -	0 -	1 (0.6)	0 -	0 -	0 -	0 -	0 -	2 (0.7)	0 -
Palpitations	0 -	0 -	0 -	0 -	1 (0.8)	0 -	0 -	0 -	0 -	0 -	1 (0.6)	0 -	0 -	0 -	0 -	0 -	2 (0.7)	0 -
Gastrointestinal disorders	0 -	0 -	0 -	0 -	2 (1.7)	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	2 (0.7)	0 -
Glossitis	0 -	0 -	0 -	0 -	1 (0.8)	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
Nausea	0 -	0 -	0 -	0 -	1 (0.8)	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
Infections and infestations	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.6)	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
Oropharyngeal candidiasis	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.6)	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
Nervous system disorders	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.6)	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
Taste disorder	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.6)	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
Skin and subcutaneous tissue disorders	0 -	0 -	0 -	0 -	1 (0.8)	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
Eczema	0 -	0 -	0 -	0 -	1 (0.8)	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
Renal and urinary disorders	0 -	0 -	0 -	0 -	1 (0.8)	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
Urinary retention	0 -	0 -	0 -	0 -	1 (0.8)	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -

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If more than one event with the same preferred term (PT) occurred in the same patient, it was tabulated in the order of priority of (1) serious > non-serious and (2) death > sequelae > not resolved > resolving > resolved > unknown.

*: Percentage of each outcome in each seriousness

Table 25 Occurrence of Adverse Drug Reactions in Patients with Specific Backgrounds (Renal Function Disorder)

As of 29 May 2024

Number of patients in the safety analysis

[Renal function disorder]

	Specific background (renal function disorder)											
	Yes				No				Total			
	Overall ADRs		Serious ADRs		Overall ADRs		Serious ADRs		Overall ADRs		Serious ADRs	
Number of patients investigated	2				284				286			
Number of patients with ADRs	0		0		24		1		24		1	
Proportion of patients with ADRs, etc. (%)	0.0		0.0		8.5		0.4		8.4		0.3	
Type of ADRs, etc.	Number of patients with ADRs (%)				Number of patients with ADRs (%)				Number of patients with ADRs (%)			
Respiratory, thoracic and mediastinal disorders	0	-	0	-	15	(5.3)	0	-	15	(5.2)	0	-
Cough	0	-	0	-	7	(2.5)	0	-	7	(2.4)	0	-
Dysphonia	0	-	0	-	7	(2.5)	0	-	7	(2.4)	0	-
Oropharyngeal discomfort	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
General disorders and administration site conditions	0	-	0	-	3	(1.1)	0	-	3	(1.0)	0	-
Thirst	0	-	0	-	2	(0.7)	0	-	2	(0.7)	0	-
Feeling abnormal	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Cardiac disorders	0	-	0	-	2	(0.7)	0	-	2	(0.7)	0	-
Palpitations	0	-	0	-	2	(0.7)	0	-	2	(0.7)	0	-
Gastrointestinal disorders	0	-	0	-	2	(0.7)	0	-	2	(0.7)	0	-
Glossitis	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Nausea	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Infections and infestations	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Oropharyngeal candidiasis	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Nervous system disorders	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Taste disorder	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Skin and subcutaneous tissue disorders	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Eczema	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Renal and urinary disorders	0	-	0	-	1	(0.4)	1	(0.4)	1	(0.3)	1	(0.3)
Urinary retention	0	-	0	-	1	(0.4)	1	(0.4)	1	(0.3)	1	(0.3)

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Table 26 Occurrence of Adverse Drug Reactions in Patients with Specific Backgrounds (Hepatic Function Disorder)

As of 29 May 2024

Number of patients in the safety analysis

[Hepatic function disorder]

	Specific background (hepatic function disorder)											
	Yes				No				Total			
	Overall ADRs		Serious ADRs		Overall ADRs		Serious ADRs		Overall ADRs		Serious ADRs	
Number of patients investigated	4				282				286			
Number of patients with ADRs	0		0		24		1		24		1	
Proportion of patients with ADRs, etc. (%)	0.0		0.0		8.5		0.4		8.4		0.3	
Type of ADRs, etc.	Number of patients with ADRs (%)				Number of patients with ADRs (%)				Number of patients with ADRs (%)			
Respiratory, thoracic and mediastinal disorders	0	-	0	-	15	(5.3)	0	-	15	(5.2)	0	-
Cough	0	-	0	-	7	(2.5)	0	-	7	(2.4)	0	-
Dysphonia	0	-	0	-	7	(2.5)	0	-	7	(2.4)	0	-
Oropharyngeal discomfort	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
General disorders and administration site conditions	0	-	0	-	3	(1.1)	0	-	3	(1.0)	0	-
Thirst	0	-	0	-	2	(0.7)	0	-	2	(0.7)	0	-
Feeling abnormal	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Cardiac disorders	0	-	0	-	2	(0.7)	0	-	2	(0.7)	0	-
Palpitations	0	-	0	-	2	(0.7)	0	-	2	(0.7)	0	-
Gastrointestinal disorders	0	-	0	-	2	(0.7)	0	-	2	(0.7)	0	-
Glossitis	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Nausea	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Infections and infestations	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Oropharyngeal candidiasis	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Nervous system disorders	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Taste disorder	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Skin and subcutaneous tissue disorders	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Eczema	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Renal and urinary disorders	0	-	0	-	1	(0.4)	1	(0.4)	1	(0.3)	1	(0.3)
Urinary retention	0	-	0	-	1	(0.4)	1	(0.4)	1	(0.3)	1	(0.3)

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Table 27 Occurrence of Adverse Drug Reactions in Patients with Specific Backgrounds (COPD)

As of 29 May 2024

Number of patients in the safety analysis

[COPD]

	Specific background (COPD)											
	Yes				No				Total			
	Overall ADRs		Serious ADRs		Overall ADRs		Serious ADRs		Overall ADRs		Serious ADRs	
Number of patients investigated	26				260				286			
Number of patients with ADRs	2		0		22		1		24		1	
Proportion of patients with ADRs, etc. (%)	7.7		0.0		8.5		0.4		8.4		0.3	
Type of ADRs, etc.	Number of patients with ADRs (%)				Number of patients with ADRs (%)				Number of patients with ADRs (%)			
Respiratory, thoracic and mediastinal disorders	2	(7.7)	0	-	13	(5.0)	0	-	15	(5.2)	0	-
Cough	0	-	0	-	7	(2.7)	0	-	7	(2.4)	0	-
Dysphonia	2	(7.7)	0	-	5	(1.9)	0	-	7	(2.4)	0	-
Oropharyngeal discomfort	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
General disorders and administration site conditions	0	-	0	-	3	(1.2)	0	-	3	(1.0)	0	-
Thirst	0	-	0	-	2	(0.8)	0	-	2	(0.7)	0	-
Feeling abnormal	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Cardiac disorders	0	-	0	-	2	(0.8)	0	-	2	(0.7)	0	-
Palpitations	0	-	0	-	2	(0.8)	0	-	2	(0.7)	0	-
Gastrointestinal disorders	0	-	0	-	2	(0.8)	0	-	2	(0.7)	0	-
Glossitis	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Nausea	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Infections and infestations	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Oropharyngeal candidiasis	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Nervous system disorders	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Taste disorder	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Skin and subcutaneous tissue disorders	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Eczema	0	-	0	-	1	(0.4)	0	-	1	(0.3)	0	-
Renal and urinary disorders	0	-	0	-	1	(0.4)	1	(0.4)	1	(0.3)	1	(0.3)
Urinary retention	0	-	0	-	1	(0.4)	1	(0.4)	1	(0.3)	1	(0.3)

MedDRA/J (27.0)

Table 28 Outcome of Adverse Drug Reactions in Patients with Specific Backgrounds (COPD)

As of 29 May 2024

Number of patients in the safety analysis
[COPD]

	Specific background (COPD)																					
	Yes						No						Total					
	Death	Sequelae	Not resolved	Resolving	Resolved	Unknown	Death	Sequelae	Not resolved	Resolving	Resolved	Unknown	Death	Sequelae	Not resolved	Resolving	Resolved	Unknown
Number of patients investigated	26						260						286					
Number of patients with ADRs	0	0	0	1	1	0	0	0	0	4	18	0	0	0	0	5	19	0
Type of ADRs, etc.	Number of patients with ADRs (proportion of patients with ADRs [*])						Number of patients with ADRs (proportion of patients with ADRs [*])						Number of patients with ADRs (proportion of patients with ADRs [*])					
Respiratory, thoracic and mediastinal disorders	0 -	0 -	0 -	1 (3.8)	1 (3.8)	0 -	0 -	0 -	0 -	2 (0.8)	11 (4.2)	0 -	0 -	0 -	0 -	3 (1.0)	12 (4.2)	0 -
Cough	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.4)	6 (2.3)	0 -	0 -	0 -	0 -	1 (0.3)	6 (2.1)	0 -
Dysphonia	0 -	0 -	0 -	1 (3.8)	1 (3.8)	0 -	0 -	0 -	0 -	1 (0.4)	4 (1.5)	0 -	0 -	0 -	0 -	2 (0.7)	5 (1.7)	0 -
Oropharyngeal discomfort	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.4)	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
General disorders and administration site conditions	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	2 (0.8)	1 (0.4)	0 -	0 -	0 -	0 -	2 (0.7)	1 (0.3)	0 -
Thirst	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.4)	1 (0.4)	0 -	0 -	0 -	0 -	1 (0.3)	1 (0.3)	0 -
Feeling abnormal	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.4)	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -	0 -
Cardiac disorders	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	2 (0.8)	0 -	0 -	0 -	0 -	0 -	2 (0.7)	0 -
Palpitations	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	2 (0.8)	0 -	0 -	0 -	0 -	0 -	2 (0.7)	0 -
Gastrointestinal disorders	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	2 (0.8)	0 -	0 -	0 -	0 -	0 -	2 (0.7)	0 -
Glossitis	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.4)	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
Nausea	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.4)	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
Infections and infestations	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.4)	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
Oropharyngeal candidiasis	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.4)	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
Nervous system disorders	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.4)	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
Taste disorder	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.4)	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
Skin and subcutaneous tissue disorders	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.4)	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
Eczema	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.4)	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
Renal and urinary disorders	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.4)	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -
Urinary retention	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	0 -	1 (0.4)	0 -	0 -	0 -	0 -	0 -	1 (0.3)	0 -

MedDRA/J (27.0)

If more than one event with the same preferred term (PT) occurred in the same patient, it was tabulated in the order of priority of (1) serious > non-serious and (2) death > sequelae > not resolved > resolving > resolved > unknown.

*: Percentage of each outcome in each seriousness

TRELEGY ELLIPTA
General Drug Use Investigation
(asthma)

Protocol

GlaxoSmithKline K.K.

Prepared: 8 April 2021 (Ver 1.1)

<Table of Contents>

1. Objectives

The objective of this investigation is to collect and assess information regarding the safety and effectiveness of Trelegy Ellipta (hereinafter referred to as "Trelegy") in asthma patients under the actual use conditions.

2. Safety Specifications

In this investigation, the safety specification will be defined as follows;

- Cardiovascular events

3. Target Population

This investigation will include patients who are prescribed Trelegy for the first time for the treatment of diagnosed bronchial asthma, which is one of the indications of Trelegy.

4. Target Sample Size and Rationale

Target number of patients: 300 (as patient registration)

1) Rationale:

Cardiovascular events are important identified risk in RMP and the proportion of patients experiencing any cardiovascular events in the Japanese long-term clinical trial (12 months) was 4.5%. To confirm the frequency of occurrence of cardiovascular events with estimation accuracy that enables a power of ≥80% for the 4.5% threshold in case the real risk exists at 2 times or more than the threshold, sample size of 222 subject for safety analysis will be required. Therefore, a Drug Use Investigation (DUI) of 300 subjects considered enough to confirm it.

5. Planned Number of Medical Institutions by Department

Approximately 60 medical institutions, mainly the departments of internal medicine and respiratory medicine

6. Investigation Period

1) Implementation of the investigation

Investigation period: June 2021 - November 2023

Observation period:

The observation period per patient will be 1 year from the first ever initiation date of Trelegy treatment. If a patient has withdrawn from /terminated administration of Trelegy, it will be until the withdrawal/termination date.

Planned registration period: June 2021 - August 2022

If the number of enrolled patients has reached the target sample size, registration may be terminated even prior to the end of the above-mentioned planned registration period.

2) End of the investigation

Final Statistical Analysis Completed: July 2024

Final Report Completed: January 2025

7. Investigation Methods

In this investigation, the electronic data capture (EDC) system will be used for patient registration and data collection.

1) Request and contract for the investigation
   (1) The medical representative (MR) will explain the objectives, target population, investigation items, investigation methods, etc. to the physicians expected to be investigator of the investigation, etc. at the medical institutions where Trelegy has been adopted or delivered, and MR will request them to cooperate with the investigation.
   (2) When cooperation to the investigation has been obtained, the written contract should be concluded with the heads (e.g. directors, etc.) of the medical institutions before starting the investigation.
2) Issuance of user ID and password
   The investigator will receive user ID and the password which needed to enter data to the EDC system, after the contract.
3) Obtaining consent
   The investigator will conduct informed consent to the patient after the own decision of prescribing Trelegy under usual clinical practice.
   The investigator will explain about participation in the investigation and publication of the investigation results sufficiently to a patient (and/or patient's representative) using the Informed Consent Form (ICF) and obtain his/her (and/or person's representative's) signature or name/seal and date of consent. Once consent is obtained from a patient (and/or patient's representative), investigator will put that information into the Registration Form by marking in a checkbox for consent "Yes". The obtained ICF should not be submitted to MR.
   If a patient (and/or patient's representative) withdraws his/her consent during the investigation period, the investigator will fill in necessary information in a notification form of consent withdrawal which prepared by the sponsor and submits it to MR.
4) Registration of target population
   The investigation will be conducted using a central registration method.
   (1) The investigator will enter patient information, etc. into the registration form for "3. Target Population" who initiate Trelegy treatment after making a contract, and then register patient via the EDC system within 14 days from the prescription date of Trelegy treatment (the prescription date of the treatment will be regarded as Day 1). The personal information such as patient's name, address, date of birth, number of medical chart, patient initials should not be entered in the registration form.
   (2) When the number of registered patients has reached to the contracted number of patients with the medical institution, the investigator will stop further patient registration for the investigation.
5) Data collection and data entry in the EDC system
   (1) The investigator will confirm for the investigation items, such as the characteristics of registered patient etc.
   (2) The investigator will confirm data of Asthma Control Test (ACT) at the initiation of Trelegy treatment*, at the timing of 1, 3, and 6 months after the initiation of treatment and at the end of observation period (1 year after the initiation of treatment or at the withdrawal/termination of treatment if treatment with Trelegy is withdrawn/terminated) and enter those information to the EDC system, if tests are performed.
   * at the initiation of Trelegy: the day of starting Trelegy or the last visit before starting Trelegy.
   (3) The investigator will confirm the course of clinical symptoms and assess overall effectiveness at the end of observation period (1 year after the initiation of treatment or at

the withdrawal/termination of treatment if treatment with Trelegy is withdrawn/terminated).

(4) The investigator will review the information regarding safety and enter all adverse events (AEs) (e.g., a disease, symptom, abnormal laboratory value) and pregnancy, etc. observed during the observation period in EDC system.

(5) The investigator will enter the information of the registered patients obtained at the end of the observation period and send data via the EDC system. The personal information such as patient's name, address, date of birth, number of medical chart, patient initials should not be entered in the EDC system.

8. Investigation Items

The investigator will collect the information regarding the following items, etc. as far as possible and enter it in the EDC system.

1) Information regarding medical institutions
   Name of medical institution, department and investigator

2) Patient characteristics (at the initiation date of Trelegy treatment)
   Identification number, gender, year of birth or age, prescribed date for the treatment, confirmation of informed consent, reason for use of Trelegy, type of asthma, duration of asthma, severity* prior to start treatment, height, body weight, history of smoking, presence/absence and the name of comorbidities (renal function disorder, hepatic function disorder, cardiovascular disorder, COPD, and others) and medical history in the past.
   To protect the confidentiality of personal information of patient, the identification number should be a unique number assigned to an individual patient by the investigator, etc.
   In this investigation, the reason for use of Trelegy will be defined as a disease for which Trelegy is mainly used. Any disease/symptom except for asthma which is present before the initiation of Trelegy treatment will be handled as a “comorbidity”, had been cured before initiation will be handled as a “medical history in the past”.
   *Categorization of severity prior to start treatment follows "Asthma prevention and management guideline Japan 2018"

3) Pre-treatment medications for asthma (during 6 weeks prior to the initiation of Trelegy treatment)
   Presence or absence of medications for asthma during 6 weeks prior to the initiation of Trelegy treatment, name and category of medications, one day dose of Inhaled Corticosteroid (ICS) (if medicine contains ICS)

4) Administration status of Trelegy
   Unit dose and frequency of daily dose during the observation period, date of start and end of treatment, reason if dose and dosage changed, reasons if a patient has withdrawn from/terminated treatment

5) Concomitant medications
   Presence or absence of concomitant medications during the observation period, name of medications, and reason for the medications

6) Concomitant therapies for asthma (except for medications)
   Presence or absence of concomitant therapies for asthma, name of therapies

7) Asthma management status of a patient (course of clinical symptoms)

   (1) Respiratory Function Test (Peak Expiratory Flow [PEF])
   PEF result measured at the initiation of Trelegy treatment, at the timing of 1, 3, and 6 month after the initiation of treatment and at the end of observation period (1 year after the

initiation of treatment or at the withdrawal/termination of treatment if treatment with Trelegy is withdrawn/terminated), measurement date, measured timing of the day (morning/evening), presence and absence of use of short-acting beta 2 agonist (SABA) within 6 hours before measuring PEF score, type of peak flow meter used

(2) Respiratory Function Test (Spirometry)
Spirometry results performed at the initiation of treatment with Trelegy and during the observation period; the date of Spirometry performed, forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) , presence and absence of use of short-acting beta 2 agonist (SABA) within 6 hours before Spirometry

(3) Asthma Control Test (ACT)
The ACT score recorded by patients at the initiation of Trelegy treatment, at the timing of 1, 3, and 6 month after the initiation of treatment and at the end of observation period (1 year after the initiation of treatment or at the discontinuation of treatment if treatment with Trelegy is discontinued), the date of ACT performed

(4) Events related to exacerbation of asthma
Presence or absence of following events related to exacerbation of asthma for 1 year prior to the initiation of Trelegy treatment and 1 year after the initiating treatment (or to the time point of withdrawal/termination);

- Hospitalization due to exacerbation of asthma
- Treatment at emergency room due to exacerbation of asthma
- Oral corticosteroid use (3days or more) due to exacerbation of asthma
- Unscheduled visit to a medical institution due to exacerbation of asthma
- Experience of one day off from work (including home activities) or school due to exacerbation of asthma

The investigator enters the test results and details of above (1) to (3) in EDC system, if those tests are performed.

8) Overall assessment of effectiveness
Effectiveness will be comprehensively assessed by any of “effective” or “not effective” based on the course of subjective symptoms, and course of clinical symptoms (asthma management status), etc. from the initiation of Trelegy treatment to the end of the observation period. If effectiveness cannot be determined for some reasons, it should be assessed as “indeterminable”, and the reason should be entered in the EDC system.

9) Pregnancy
(For female patients) whether registered patient is pregnant during the observation period or not, and expected delivery date
In addition, the follow-up investigation will be conducted for a mother and her foetus as far as possible regarding the course of delivery, spontaneous abortion, elective abortion and AEs, etc.

10) Adverse Events (AEs)
Presence or absence of AEs after initiation of Trelegy treatment, diagnosis or symptoms, onset date, outcome of AEs, outcome date, seriousness, reason for assessing as serious, relationship with Trelegy, factors suspected of being related to AEs except for Trelegy

(1) To grasp the information of safety specification and ADRs, the investigator will enter the information of all AEs (e.g., a disease, symptom, abnormal laboratory value), seriousness and outcome of AEs occurring after the initiation of Trelegy treatment, regardless of whether or not the Trelegy is related. Please see "Adverse Event (p.8)" for the details of AE, ADR and seriousness. The relationship to Trelegy will be assessed by any of “related”

or “not related” by considering whether the possibility of a reasonable relationship to Trelegy is present or not.

Among the reported AEs, those corresponding to the events in the standard search formula (SMQ) [1] of “cardiovascular events” in the MedDRA[2] which introduced by ICH are handled as "safety specification".

AEs assessed as “related” to Trelegy will be handled as suspected “adverse drug reactions (ADRs)” that are caused by Trelegy.

9. Analysis Items and Methods

The detailed analysis plan will be stated in the Statistical Analysis Plan separately.

1) Analysis items
   (1) Patient composition-related matters
      i). Number of registered patients, number of patients whose Case Report Form (CRF) is collected and number of patients whose CRF data fixed
      ii). Numbers of patients included in the safety and effectiveness analysis sets, number of patients excluded from analysis and the reason for exclusion
   (2) Safety-related matters
      i). Occurrence of ADRs and infections (type, degrees and proportion of patients with ADRs, etc.)
      ii). Occurrence of events defined as safety specification
   (3) Effectiveness-related matters
      i). Responder rate based on the overall assessment of effectiveness
      The proportion of responders is the proportion of patients assessed as “effective”.
      ii). Distribution and changes of respiratory function test results
      iii). Distribution and changes of ACT score by each questionnaire items, total ACT score and changes in asthma control status
      iv). The proportion of events occurrence related to asthma exacerbation
2) Analysis methods
   (1) Safety
      i). Proportion of patients with ADRs will be calculated at 1-month, 3-month, 6-month and 1-year, and overall period.
      ii). Incidence rates per 100 Patient Years of follow-up will be calculated along with 95% exact Poisson confidence intervals using chi-square distribution around the estimate.
   (2) Effectiveness
      i). Proportion of responders in overall assessment will be calculated
      ii). For comparison of the scores, etc., the summary statistics for values at the time of measurement and changes from baseline, i.e. vs at 1-month, 3-month, 6-month and at the end of observation period (1 year after the initiation of treatment or at the discontinuation of treatment if treatment with Trelegy is discontinued) will be calculated.

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1 Standardised MedDRA Queries (SMQ) is standard search formula developed to retrieval data from a MedDRA-coded database. The group of related terms for defined medical condition or area of interest.

2 Medical Dictionary for Regulatory Activities (MedDRA). MedDRA is international medical terminology developed by International Council for Harmonisation of Technical. AEs are managed by cording into MedDRA terms (symptoms, diagnoses, physical signs, values of laboratory test, etc.).

(3) Consideration of covariates

i). Logistic regression model will be used to search for factors affecting safety (proportion of patients with ADRs) and effectiveness (proportion of responders).

10. Organizational Structure

Same as the one described in the Risk Management Plan (RMP)

11. Name, Address of the Outsourcees, and the Scope of Outsourced Operations

1) Registration, Data management

Outsourcee: CIMIC Co., Ltd

1-1-1 Shibaura, Minato-ku, Tokyo, Japan

Scope: patient registration, development of the EDC system, data cleaning and other related operations

Scope: data entry from CRFs, re-investigation, other related operations

2) Statistical analysis

Outsourcee: The Institute of Japanese Union of Scientists & Engineers

5-10-11 Sendagaya, Shibuya-ku, Tokyo, Japan

Scope: statistical analysis, other related operations

12. Scheduled Timing to Be a Milestone for Assessing the Status and Results of the Investigation, or Reporting to the Pharmaceuticals and Medical Devices Agency (PMDA) and Rationale

- At the time of Periodic Safety Reports: consideration will be comprehensively given to the safety and effectiveness information.
- At the time of re-examination application: the final report will be prepared/submitted, based on the results of tabulation and analysis obtained from the fixed data of all collected CRFs.

13. Additional Measures that Potentially to Be Taken Depending on the Investigation Results, and the Decision Criteria for the Commence

The RMP including the following, will be reviewed at the timings to be a milestone.

- Regarding the safety specification, if the proportion of occurrence, peak occurrence period and risk factors become visible as an ADR caused by Trelegy, the necessity for revising to the Package Insert and investigation materials will be considered as appropriate.
- Including whether a new issue in the safety specification is present or not, the necessity for changes in the content of plan in the present investigation will be considered.
- The necessity for creating the Risk Minimization Plan for a new issue in the safety specification will be considered.

14. Publication of the Investigation Results

The information regarding the results of the investigation will be provided to clinical sites, including publication as a final report, and as an interim report as appropriate, for the purpose of “proper use” and “safety assurance.

Result which reported to PMDA will be disclosed when requested based on the Information Disclosure Law. In addition, the summaries of the results of the investigation will be disclosed in the websites designated by PMDA or international authorities, and in ClinicalTrials.gov, GSK Clinical Study Register and GSK homepage. In either case, no privacy information about patient or investigator will be disclosed.

15. Other Requirements

1) Protocol Revision
   In the progress of the investigation, the number of patients excluded from analysis, occurrence of unexpected/serious ADRs, large increase in occurrence of specific ADRs and validity of the investigation items, etc. will be timely grasped during the investigation period, and the protocol will be reviewed and revised if necessary.
   If the content of the protocol of the investigation has been changed, the written submission should be made to the PMDA in advance, except for minor changes.
2) Measures to be taken if issues and concerns are detected
   If issues, etc. have been detected from the results of assessment/analysis during the investigation period or after completion of the investigation, consideration will be given on whether or not the Post-marketing Studies should be newly conducted, as appropriate.

16. Attachments

1)	Trelegy Ellipta General DUI Implementation Guidance	Attachment1
2)	Trelegy Ellipta General DUI Registration Form	Attachment2
3)	Trelegy Ellipta General DUI Case Report Form (CRF)	Attachment3
4)	Asthma Control Test (ACT)	Attachment4

Requests when Adverse Events occur

- For patients who experienced AEs, further detailed investigation may be conducted, if necessary. In such a case, your cooperation would be appreciated.
- If you find your patient experience AEs, please contact to the medical representative (MR) of GlaxoSmithKline K.K. promptly.

Adverse Events (AEs)

1. Adverse Events (AEs)

The term "AE" means any untoward medical occurrence in a patient administered a medical product and which does not necessarily have to have a relationship to this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory value, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Examples regarded as an AE:

- Exacerbation of any chronic or intermittent symptom being present before the start of this investigation (including increase in frequency or severity of symptoms). Any case where a target disease and an underlying disease worsens **unexpectedly**.
- Any symptom being newly detected or diagnosed after the start of treatment (included as an AE if it has been detected or diagnosed after the treatment, even though it may have already been present before the start of the study).
- Any sign, symptom, or sequela originating from a suspected interaction.
- Any sign, symptom, or sequela originating from a suspected overdose of medical product or concomitant drugs (An overdose itself should not be reported as an AE or serious AE) However, a deliberate overdose intended for suicide/self-injury should be reported, regardless of the presence/absence of a sequela.
- Any abnormal laboratory value (haematological test, biochemical test, urine test) or any other abnormal safety assessment item (eg. electrocardiogram, X-ray test, measurement of vital signs) (including worsening from baseline) when an investigator judges a patient's condition as clinically significant **beyond the expectable range** based on medical and scientific judgment.

Examples not regarded as an AE:

- Any progress, sign or symptom of a target disease or disorder and an **expected** disease or disorder.
- Any medical or surgical treatment (eg. endoscopy, appendicectomy). The symptom which needs these treatments should be regarded as an AE.
- Any case where no unfavourable medical occurrence happens (social and /or hospitalisation in convenience, etc.).
- Any disease and condition, if identified or detected before the start of the study, the changes in them are within the expected range of daily changes or does not worsen.
- Any change in abnormal laboratory values and any other safety assessment items, etc. related to a target disease or an underlying disease.

2. Adverse Drug Reactions (ADRs)

All noxious and unintended responses to a medical product related to any dose should be considered ADRs. The phase "response to a medical product" means that a causal relationship between a medical product and an AE is at least a reasonable possibility. Unlike an AE, an ADR features the fact that a relationship between a medical product and occurrence of an AE is suspected.

3. Serious Adverse Events (SAEs) or Adverse Drug Reactions (SADRs)
   An SAE or SADR is any untoward medical occurrence that at any dose:
   1) results in death
   2) is life-threatening[3]
   3) requires inpatient hospitalisation or prolongation of existing hospitalisation
   4) results in persistent or significant disability/incapacity
   5) is a congenital anomaly/birth defect
   6) is another event or reaction, if judged to be a medically important[4]

3 The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

4 Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of other important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias; convulsions that do not result in an inpatient hospitalisation; the development of drug dependency; the development of drug abuse.