EMADOC-1700519818-1894726
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Trelegy Ellipta

Fluticasone furoate / Umeclidinium / Vilanterol

Procedure no.: EMA/PAM/0000248964

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment			
Current step[1]	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	31 March 2025	31 March 2025
☐	CHMP comments	14 April 2025	n/a
☐	Updated CHMP Rapporteur AR	16 April 2025	n/a
☒	CHMP outcome	25 April 2025	25 April 2025

Table of contents

1. Introduction

On 30 January 2025, the MAH submitted a completed paediatric study for Trelegy Ellipta, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study 214953: TRELEGY ELLIPTA General Drug Use Investigation (asthma) is a stand alone study. The final study report is being submitted within 6 months of the study completion, defined as end of data analysis (31 January 2025).

The MAH confirmed that the study is not a measure of the agreed Paediatric Investigation Plan for Fluticasone furoate/ Umeclidinium Bromide/ Vilanterol Trifenatate (EMEA-002153-PIP01-17) and thus a line listing is not included in this submission.

The MAH also confirmed that they are not proposing to update to the paediatric aspects of the product information based on the results of the study and no changes to the Product Information are considered necessary arising from the study conclusions.

2.2. Information on the pharmaceutical formulation used in the study

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)

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study number: **214953**
- Title: TRELEGY ELLIPTA General Drug Use Investigation (asthma)

2.3.2. Clinical study

Clinical study number and title

Study number: 214953

Title of the investigation: TRELEGY ELLIPTA (hereafter referred to as Trelegy) General Drug Use Investigation (asthma)

Description

Study 214953 was a non-interventional, observational post-marketing surveillance study conducted in Japan to assess the real-world safety and effectiveness of Trelegy in patients with bronchial asthma. The study included first-time Trelegy patients who were observed for one year after initiating treatment. Data collected encompassed study site and patient composition, patient characteristics, treatment administration, safety, effectiveness, and outcomes in specific patient subgroups.

Methods

Investigation methods: Central registration method.

Investigation period: June 2021 - November 2023

Study participants

This study included patients who were prescribed Trelegy for the first time for the treatment of diagnosed bronchial asthma, which is one of the indications of Trelegy outside of the EU eg. in the USA and Japan.

The registration of patients with bronchial asthma 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 initiation date of Trelegy treatment (or until the date of withdrawal/termination of treatment should this occur).

There were n=286 patients in the safety analysis set of which n= 281 were included in the effectiveness analysis set.

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).

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

Treatments

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)

Objectives

The objective of this study was to collect and assess information regarding the safety and effectiveness of Trelegy in asthma patients under actual use conditions.

Outcomes/endpoints

Safety:

-To collect information on the occurrence of the safety specifications under the actual use conditions.

- Cardiovascular events

Effectiveness considerations: Not defined.

Sample size

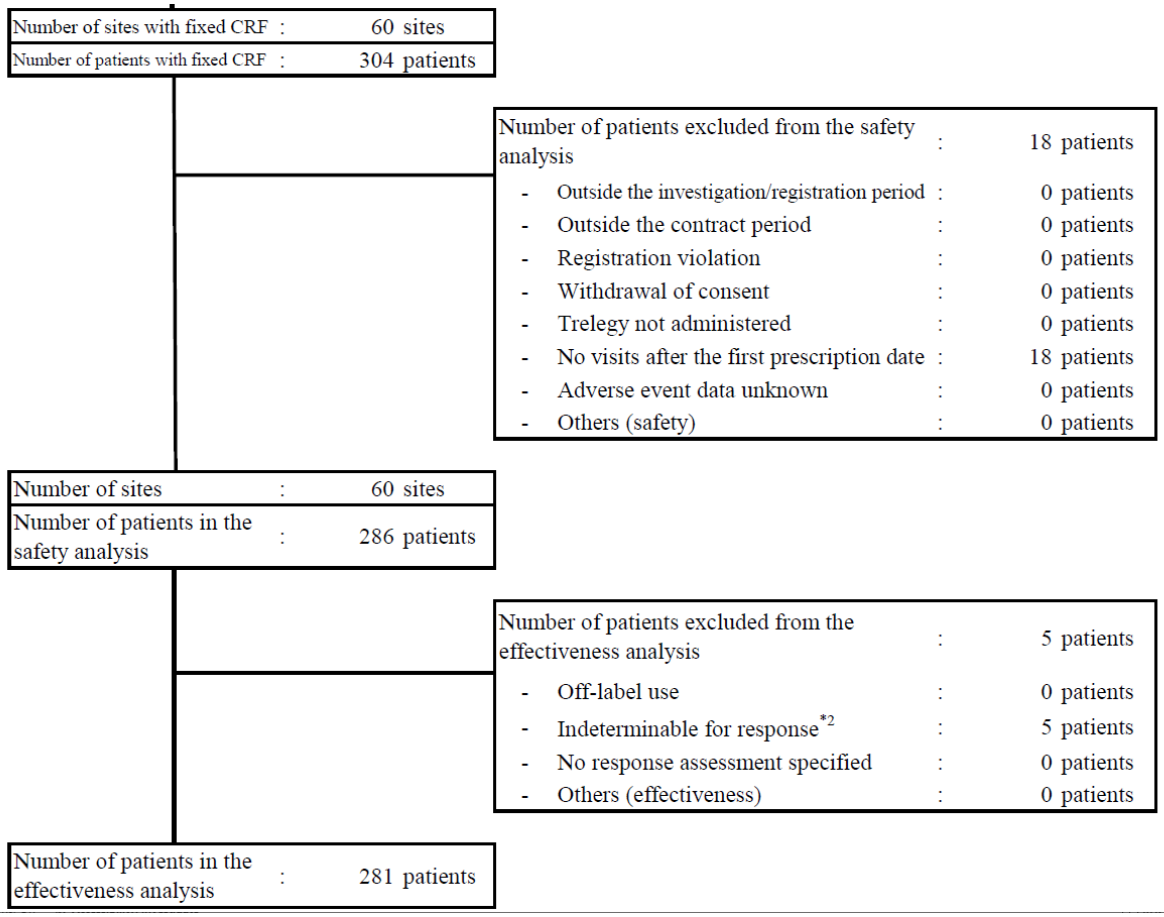
The study began with 62 Japanese sites and 314 registered patients but was adjusted to 60 sites and 304 patients after the initial CRF collection and consent withdrawal.

Randomisation and blinding (masking)

N/A

Results

Participant flow



Number analysed

Following exclusion of 18 patients who did not return after the first prescription, 286 patients were included in the safety analysis.

An additional 5 patients were excluded due to indeterminable responses, resulting in 281 patients in the effectiveness analysis.

Efficacy results

Effectiveness was 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) 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).

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 "pretreatment 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", "pretreatment medications", and "concomitant medications".

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

Respiratory Function Test (Peak Expiratory Flow [PEF])

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 was outlined.

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.

Respiratory Function Test (Spirometry)

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.

Asthma Control Test (ACT)

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.

Events Related to Exacerbation of Asthma

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.

Assessor's comments:

Trelegy Ellipta (fluticasone furoate/umeclidinium bromide/vilanterol trifenatate) is approved for the maintenance treatment of moderate to severe chronic obstructive pulmonary disease (COPD) in patients who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting β2-agonist or a combination of a long acting β2-agonist and a long-acting muscarinic antagonist in adult patients.

In other jurisdictions outside the EU, Trelegy is also indicated for the maintenance treatment of asthma in patients aged 18 years and older.

Effectiveness of Trelegy Ellipta in asthmatic patients under real-world conditions was evaluated in this observational post-marketing study which was conducted in Japan.

The effectiveness of Trelegy was evaluated in 281 patients, with 92.5% achieving a positive response based on improvements in subjective and clinical symptoms.

Clinical outcomes demonstrated sustained improvements, with increases in Peak Expiratory Flow (PEF), spirometry measures (FVC and FEV1), and Asthma Control Test (ACT) scores maintained above baseline levels. Asthma exacerbations were observed to have decreased from 25.6% pre-treatment to 5.0% post-treatment in real-world conditions.

Of note, the use of Trelegy Ellipta in asthmatic patients has been previously assessed in the EU and was refused by CHMP following assessment of the relevant variation(ref:EMEA/H/C/004363/X/0012/G).

The EMA considered that an improvement in lung function alone was not enough to show that Trelegy was suitable for treating asthma. The main study did not clearly show that the medicine was effective at reducing asthma attacks or controlling symptoms. Therefore, the Agency's opinion was that the benefits of Trelegy in the treatment of asthma did not outweigh its risks. Hence, the Agency recommended refusing the change to the marketing authorisation.

In this context, while the overall study conclusions are noted, on the basis of the nature of the study and its inherent limitations and limited sample size, it is highlighted that the data presented is not robust to support any changes to the approved indication and does not supersede the previous EMA conclusions following the assessment of the use of Trelegy Ellipta in asthmatic patients.

Safety results

There were 286 patients in the safety analysis set, 24 patients experienced ADRs, and the proportion of patients with ADRs was 8.4%.

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).

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

The occurrence of ADRs by gender was examined. 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.

The 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. 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.

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.

Age

The occurrence of ADRs by age was examined. 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.

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 the package leaflet.

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. 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.

In this study, "cardiovascular events" were defined as a safety specification.

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". The incidence based on person-year method [/100 person-year] was 0.95.

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)

Assessor's comments:

The MAH's conclusions arising from the review of this observational, non interventional, post-marketing study of real use of Trelegy Ellipta in asthmatic patients conducted in Japan are noted.

In the safety analysis of 286 patients, 8.4% of patients experienced ADRs most commonly "respiratory, thoracic, and mediastinal disorders" (5.2%), with "cough" and "dysphonia" reported at 2.4% each.

Higher ADR rates were observed in females and patients aged ≥65 years, but all events were non-serious and resolved or were resolving.

Most ADRs (75%) occurred within 60 days of treatment initiation. Cardiovascular events, such as non-serious "palpitations," were rare (0.7%) and resolved without requiring additional safety measures.

The safety data obtained in this study is generally in line with the established safety profile for the triple combination product and no new safety concerns have been identified.

Only n=2 paediatric patients were included in this study and while no specific discussion on paediatric safety has been provided, it is noted that the MAH concludes that no specific concerns were identified in specific populations, including children, elderly, or patients with renal or hepatic disorders. Specifically, no ADRs were reported in children.

No changes to the approved safety information are proposed by the MAH and this is agreed.

It is recommended that the ongoing safety of Trelegy Ellipta continues to be routinely monitored.

2.3.3. Discussion on clinical aspects

In this observational study, the MAH has provided an overview of the outcome of Study 214953 which was a General Drug Use Investigation post-marketing surveillance study of Trelegy Ellipta in the asthma indication.

Study 214953 was a non-interventional, observational post-marketing surveillance study conducted in Japan to assess the real-world safety and effectiveness of Trelegy in patients with bronchial asthma. The study included first-time Trelegy patients who were observed for one year after initiating treatment. Data collected encompassed study site and patient composition, patient characteristics, treatment administration, safety, effectiveness, and outcomes in specific patient subgroups.

Notwithstanding the inherent limitations of the data set, the findings observed in the study are noted.

Of note, the study was conducted in patients with asthma in Japan. The indication for use in asthma is only approved outside of the EU.

A previous variation application in which the MAH proposed an indication for Trelegy Ellipta in asthma was not accepted by CHMP on the basis that an improvement in lung function alone shown in the single pivotal study was not considered sufficient to justify the new indication. The main clinical study in that variation did not clearly demonstrate efficacy in reducing asthma attacks or controlling symptoms.

Of note, in this current submission, Study 21495 has been submitted by the MAH in accordance with Article 46 of regulation (EC) No 1901/2006, as amended however only 2 paediatric patients were listed as having been included. No specific safety or effectiveness concerns were identified. The MAH stated that no concerns were identified in specific populations, including children during the study and no ADRs were reported in children.

It is noted that the MAH is not proposing to update the product information for Trelegy Ellipta in respect of paediatric aspects and this is agreed. For reference, in April 2021, the MAH submitted notification of discontinuation of paediatric development which is covered by an agreed PIP Decision for Trelegy Ellipta. No further paediatric data are currently anticipated.

In general, no new safety signals were observed during the study.

It is recommended that the ongoing safety of Trelegy continues to be routinely monitored.

3. CHMP overall conclusion and recommendation

This study was submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended.

The MAH's submission of the data within the scope of Article 46 is considered acceptable although only 2 paediatric patients out of 286 patients were listed as having been included in the study.

The submitted study was conducted in patients with asthma in Japan where this indication is approved. Of note, Trelegy Ellipta is not approved for use in asthma in the EU. The use of Trelegy Ellipta in asthmatic patients has been previously assessed in the EU and was refused by CHMP following assessment of variation EMEA/H/C/004363/X/0012/G.

In this context, while the overall conclusions of Study 214953 are noted, the data are not robust to support any changes to the currently approved indication. The previous CHMP conclusions refusing the use of Trelegy Ellipta in asthmatic patients in the EU still remain.

Overall, no new safety concerns have been identified in this study and no updates to the product information have been proposed by the MAH. This is agreed.

It is recommended that the ongoing safety of Trelegy Ellipta continues to be routinely monitored.

☒ **Fulfilled:**

No regulatory action required.