Cost-effectiveness evaluation of fluticasone furoate/umeclidinium bromide/vilanterol trifenatate (Trelegy Ellipta) by the academic group [Version 1.3]

[November 12, 2020]

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Table of abbreviations

Abbreviations	Formal expression
ACT	Appropriate Comparator Therapy
ASMR	Amelioration du Service Médical Rendu
AUD	Australian dollar
CAD	Canadian dollar
CADTH	Canadian Agency for Drugs and Technologies in Health
CAT	COPD Assessment Test
CDEC	Canadian Drug Expert Committee
CEA	Cost-Effectiveness Analysis
CFB	Change from Baseline
CI	Confidence Interval
CMA	Cost-Minimization Analysis
COPD	Chronic Obstructive Pulmonary Disease
CUA	Cost-Utility Analysis
EOS	Eosinophil granulocyte
EQ-5D	EuroQol 5 Dimension
ESC	Economics Subcommittee
FEV_1	Forced Expiratory Volume in one second
FF	Fluticasone Furoate
FVC	Forced Vital Capacity
G-BA	Gemeinsame Bundesausschuss
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HAS	Haute Autorité de Santé
HTA	Health Technology Assessment
HRQL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
ICS	Inhaled corticosteroid
IQWiG	Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LABA	Long-Acting Beta2-Agonist
LAMA	Long-Acting Muscarinic Antagonist
MCID	Minimum Clinically Important Difference
MITT	Multiple Inhaler Triple Therapy
mMRC	modified Medical Research Council
MMRM	Mixed effect Models for Repeated Measures
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QALY	Quality-Adjusted Life Year
QOL	Quality of Life
RCT	Randomized Controlled Trial
RR	Relative Risk
SE	Standard Error
SGRQ	St George's Respiratory Questionnaire
SMC	Scottish Medicines Agency
SMR	Service Médical Rendu
SR	Systematic Review
UMEC	Umeclidinium
VI	Vilanterol

0. Analytical framework

The evaluated product is fluticasone furoate/umeclidinium bromide/vilanterol trifenatate (Trelegy 100 Ellipta 14 doses, Trelegy 100 Ellipta 30 doses) (FF/UMEC/VI) and the manufacturer is GlaxoSmithKline K.K. FF/UMEC/VI is a therapeutic agent for chronic obstructive pulmonary disease (chronic bronchitis/emphysema) (COPD) and was selected as a target product of the cost-effectiveness evaluation at Central Social Insurance Medical Council on May 15, 2019. The market size of FF/UMEC/VI is 23.6 billion yen and the category of the cost-effectiveness evaluation is H1 (The market size is 10 billion yen or more). The analytical framework of FF/UMEC/V was established as shown in Table 0-1 after the Expert Committee of Cost-Effectiveness evaluation on September 12, 2019 and October 4, 2019.

Table 0-1 Analytical framework

<table>
<tr><td>Population</td><td>The target disease is chronic obstructive pulmonary disease (chronic bronchitis/emphysema) (COPD). In this evaluation, the following subpopulations of A-L will be analyzed in principle, but the presence and extent of additional benefit will first be assessed based on the results of subgroup analyses of the IMPACT trial (or other literature, if available).
<table>
<tr><th rowspan="2">Prior therapy</th><th rowspan="2">Details of the prior therapy</th><th colspan="2">Eosinophil count</th><th rowspan="2">Comparator</th></tr>
<tr><th>< 100/μL</th><th>≥ 100/μL</th></tr>
<tr><td rowspan="3">Triple therapy</td><td rowspan="3">MITT (triple therapy with inhalation of 2 drug products)</td><td>A</td><td>B</td><td>MITT (triple therapy with inhalation of 2 drug products)</td></tr>
<tr><td>C</td><td>D</td><td>ICS/LABA</td></tr>
<tr><td>E</td><td>F</td><td>LAMA/LABA</td></tr>
<tr><td>Dual therapy</td><td>ICS/LABA</td><td>G</td><td>H</td><td>ICS/LABA</td></tr>
<tr><td colspan="2">Prior therapy: Dual therapy (LAMA/LABA) or monotherapy (LAMA)</td><td>I</td><td>J</td><td>LAMA/LABA</td></tr>
<tr><td>monotherapy</td><td>LAMA</td><td>K</td><td>L</td><td>ICS/LABA</td></tr>
<tr><td>Other</td><td></td><td colspan="2">Non analyzed</td><td></td></tr>
</table>
Eosinophil count 100/μL will be the main analysis with a cutoff of 100/μL, and a sensitivity analysis of 150/μL will also be performed.</td></tr>
<tr><td>Comparator</td><td>For the price of comparator, the least expensive inhalant that contains the relevant two components should be used in accordance with the description in 4.1.3 of Guideline for Analysis of Cost-Effectiveness Evaluation by the Central Social Insurance Medical Council, 2nd Version, "If single comparator cannot be determined based on item "4.1", the comparator(s) should be selected considering the comparators in randomized controlled trials (RCTs), referred technology when</td></tr>
</table>

	determining the official price, cost-effectiveness, and other factors, based on agreement in consultation.".
Reason for selection of comparator	It is appropriate to select ICS/LABA and LAMA/LABA, which are usually used for a dual therapy, as a comparator. However, when comparing triple therapy, MITT (triple therapy with inhalation of 2 drug products) should be used.
Other perspective in addition to public healthcare payer	Yes (Details:) ☒ No
Outcome and the reason if QALY is not used.	Not applicable
Other	Not applicable

1. Summary of other HTA agency reviews

1.1 Summary

The manufacturer reported the results of the evaluation of FF/UMEC/VI by health technology assessment (HTA) organizations in the UK, France, Germany, Canada, and Australia. In response to this, the academic group conducted a survey on the evaluation results of FF/UMEC/VI at these agencies and compared the results with those reported by the manufacturer. The evaluation status was summarized in Tables 1-1 and 1-2.
Next, the academic group reviewed the details of economic evaluation of FF/UMEC/VI in these countries. The economic evaluation of FF/UMEC/VI was conducted only by CADTH in Canada and PBAC in Australia. Details of the cost-effectiveness evaluation were summarized and compared with details of the report by the manufacturer (Table1-3 and 1-4).

Table 1-1 Evaluation Status

Country	Organization	Evaluation results	
		Manufacturer	Academic group
UK	NICE	▪ **No assessment or recommendation** NICE has not completed a formal assessment of FF/UMEC/VI in COPD but has reviewed the evidence for local decision-making purposes. Guidance to decision makers: The acquisition cost of FF/UMEC/VI is less than that of other combinations of ICS/LABA plus LAMA in 2 inhalers. A 30-day supply of treatment with FF, UMEC, and VI costs £44.50 (excluding VAT) when the triple-therapy inhaler (FF/UMEC/VI) is prescribed. This compares with £49.50 (excluding VAT) when FF and VI are prescribed in a dual therapy inhaler (FF/VI 92/22 µgs) together with UMEC in a single-therapy inhaler (UMEC 55 µg).	**<No guidance on technology assessment, only summary of clinical evidence>** Indication: Adult patients with moderate to severe COPD who are not adequately treated with ICS/LABA. The drug cost of telergy is smaller than that of MITT (£44.5 and £49.5 per month for Telergy and MITT, respectively).
	SMC	▪ **Recommendation (Abbreviated submission)** FF/UMEC/VI was accepted for restricted use within NHS Scotland Indication under review: maintenance treatment in adult patients with moderate to severe COPD who are not adequately treated by a combination of an ICS and a LABA SMC restriction: in patients with severe COPD (FEV1 <50% predicted normal) A similar restriction is in place for other ICS/LABA containing treatments including Relvar, Symbicort, Fortair (not launched in Japan), and Trimbow (not launched in Japan).	**<Conditional recommendation>** ・ SMC restriction: Patients with severe COPD (%FEV_1 < 50%) ・ Indication: Maintenance therapy in adult patients with moderate to severe COPD who have not been adequately treated with ICS/LABA. ・ The drug cost of Trelegy is less than that of MITT.

		FF/UMEC/VI costs less than inhalers containing FF/VI 92/22 μg and UMEC 55 μg administered separately.	
France	HAS	**▪ Outcome of review** FF/UMEC/VI is a fixed combination which represents a therapeutic alternative in patients with severe COPD treated unsatisfactorily by the combination of an ICS and a LABA or by the combination of a LABA and a LAMA. FF/UMEC/VI has no place in the management of moderate COPD. **▪ SMR** Moderate: in treatment of severe COPD in adults treated unsatisfactorily by the combination of ICS/LABA or LABA/LAMA (reimbursable indication) Insufficient: in moderate COPD adults patients treated unsatisfactorily by the combination of ICS/LABA or LABA/LAMA (non reimbursable indication) **▪ ASMR** V: in the management of severe COPD patients	**<SMR: Moderate (Severe COPD), Insufficient (Moderate COPD), ASMR: V (Lack of clinical improvement), efficiency assessment: Not performed>** · Clinical benefit for management of adult patients with severe COPD, who are not sufficiently treated with ICS/LABA, is low and the benefit for the treatment strategy has not been demonstrated. · Clinical benefit is insufficient to justify reimbursement in the management of moderate COPD. · Although Trelegy was statistically superior to ICS/LABA and ICS/LABA in FEV_1, the difference was minimal.
Germany	IQWiG	**▪ No additional benefit** FF/UMEC/VI has been the subject of two benefit assessments; in ICS+LABA pretreated patients (launch label) in March 2018, and in LAMA+LABA pretreated patients (label extension) in November 2018. In both assessments, the Federal Joint Committee (G-BA) defined the Appropriate Comparator Therapy (ACT) as patient-individualized optimization of the existing therapy (either ICS+LABA or LAMA+LABA). For the benefit	**<No additional benefit>** · An appropriate comparator technology is MITT and there is no additional benefit in comparison to it.

		assessment in LAMA+LABA pretreated patients the G-BA also subsequently changed the ACT definition to ICS+LAMA+LABA triple therapy before publishing the assessment determination, as a result of changes in COPD guidelines. As a consequence, the comparators in FF/UMEC/VI trials (IMPACT study and FULFIL study) did not match the ACT definitions for the benefit assessments, therefore the decision of the G-BA was added benefit not proven.	
Canada	CADTH	▪ **Recommendation** The CADTH Canadian Drug Expert Committee (CDEC) recommended that FF/UMEC/VI was reimbursed for the long-term, once daily, maintenance treatment of COPD, including chronic bronchitis and/or emphysema, if the following criteria and condition were met: Criteria: 1) Patients should not be started on triple inhaled therapy as initial therapy for COPD. 2) For use in patients who are not controlled on optimal dual-inhaled therapy for COPD Condition: Drug plan cost of FF/UMEC/VI should not exceed the drug plan cost of treatment with any triple therapies reimbursed for COPD (LAMA/ LABA/ICS).	**<Conditional recommendation>** · A triple-drug therapy should not be used as an initial treatment for COPD. · It should be used when COPD is not controlled by optimal two-drug combination therapy. · The cost of Trelegy should not exceed the reimbursement price of MITT.
Australia	PBAC	▪ **Recommendation** The PBAC recommended the Authority Required (STREAMLINED) listing of FF/UMEC/VI in December 2017 for treatment of COPD in patients with FEV1 <50% predicted and history of repeated	**<Conditional recommendation>** · Limited to the treatment of patients with COPD who have a predicted FEV_1 of less than 50% and who experience repeated worsening

		exacerbations with significant symptoms despite maintenance with dual therapy LAMA and LABA, or ICS. The PBAC recommended an extension to the existing listing of FF/UMEC/VI in March 2019 for COPD, specifically the removal of the FEV1 threshold from the clinical criteria in the restriction.	of symptoms despite two-drug therapy (March 2017). • Expansion of Trelegy to an existing list and removal of the threshold of FEV_1 were recommended (March 2019).

Table 1-2 Status of economic evaluation

Country	Organization	Manufacturer	Academic analysis
UK	NICE	None	None
	SMC	None	None
France	HAS	NA (clinical effectiveness only)	None
Germany	IQWiG	NA (clinical effectiveness only)	None
Canada	CADTH	Present	Present
Australia	PBAC	Present	Present

Table 1-3 Details of cost-effectiveness analysis in Canada (CADTH)

Country	Canada	
	Manufacturer	Academic analysis
Organization	CADTH	
URL	https://www.cadth.ca/sites/default/files/cdr/complete/SR0562_cdr_complete_Trelegy_Ellipta_Aug_27_18.pdf https://www.cadth.ca/sites/default/files/cdr/pharmacoeconomic/SR0562_TrelegyEllipta_PE_Report.pdf	https://www.cadth.ca/fluticasone-furoateumeclidiniumvilanterol
Target technology	FF/UMEC/VI	FF/UMEC/VI
Evaluation results	Recommendation	Conditional recommendation
Details of the condition	The CADTH CDEC recommended that FF/UMEC/VI was reimbursed for the long-term, once daily, maintenance treatment of COPD, including chronic bronchitis and/or emphysema, if the following criteria and condition were met: Criteria: 1) Patients should not be started on triple inhaled therapy as initial therapy for COPD. 2) For use in patients who are not controlled on optimal dual-inhaled therapy for COPD. Condition: Drug plan cost of FF/UMEC/VI should not exceed the drug plan cost of treatment with any triple therapies reimbursed for COPD (LAMA/ LABA/ ICS).	• A triple-drug therapy should not be used as an initial treatment for COPD. • It should be used when COPD is not controlled by optimal two-drug combination therapy. • The cost of Trelegy should not exceed the reimbursement price of MITT.
Target disease	COPD	COPD
Usage and	Once-daily single-dose inhalation	Once-daily single-dose inhalation

Dosage		
Comparator	1) FF/VI 2) UMEC/VI 3) FP 250µg/ SAL 50µg + TIO 18µg 4) FP 500µg/ SAL 50µg + TIO 18µg	(1) FF/VI (2) UMEC/VI (3) FP 250µg/ SAL 50µg + TIO 18µg (4) FP 500µg/ SAL 50µg + TIO 18µg
ICER	**<GSK>** 1) CAD19,649/QALY (CAD2,598/0.1322QALYs) 2) CAD14,864/QALY (CAD1,801/0.1211QALYs) 3) Dominant (-CAD482/0.0050QALYs) 4) Dominant (-CAD1,670/0.028QALYs) **<CADTH>** 1) CAD21,189/QALY (CAD2,793/0.132QALYs) 2) CAD17,002/QALY (CAD2,065/0.121QALYs) 3) CAD137,990/QALY (CAD674/0.005QALYs) 4) Dominant (-CAD34/0.022QALYs)	**<Manufacturer>** (1) CAD19,649/QALY (2) CAD14,864/QALY (3) Dominant (4) Dominant **<CADTH>** (1) CAD21,189/QALY (2) CAD17,022/QALY (3) CAD137,990/QALY (4) Dominant

Table 1-4 Details of cost-effectiveness analysis in Australia (PBAC)

Country	Australia	
	Manufacturer	Academic analysis
Organization	PBAC	
URL	http://www.pbs.gov.au/industry/listing/elements/pbacmeetings/psd/2019-03/files/fluticasone-psd-arch-2019.pdf	http://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2017-12/fluticasone-psd-december-2017 https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2019-03/fluticasone-fuorate-psd-march-2019
Target technology	FF/UMEC/VI	FF/UMEC/VI
Evaluation results	Recommendation	Conditional recommendation
Details of the condition	The PBAC recommended the Authority Required (STREAMLINED) listing of FF/UMEC/VI in December 2017 for treatment of COPD in patients with FEV1 <50% predicted and history of repeated exacerbations with significant symptoms despite maintenance with dual therapy LAMA and LABA, or ICS. The PBAC recommended an extension to the existing listing of FF/UMEC/VI in March 2019 for COPD, specifically the removal of the FEV1 threshold from the clinical criteria in the restriction.	・ Limited to the treatment of patients with COPD who have a predicted FEV_1 of less than 50% and who experience repeated worsening of symptoms despite two-drug therapy (March 2017). ・ Expansion of Trelegy to an existing list and removal of the threshold of FEV_1 were recommended (March 2019).
Target disease	COPD	COPD

Usage and Dosage	Once-daily single-dose inhalation	Once-daily single-dose inhalation
Comparator	UMEC/VI	UMEC/VI
ICER	AUD15,000/QALY	**<Manufacturer>** AUD15,000/QALY **<ESC>** AUD15,000~AUD45,000/QALY

1.2 Review results

As a result of the review on the assessment of Trelegy by HTA organizations, details of the report by the manufacturer were generally appropriate except following points.

(1) The interpretation of evaluations by SMC, CADTH, and PBAC differed in terms of whether the results were "recommended" or "conditionally recommended.
(2) Some of the reported ICERs of FF/UMEC/VI by CADTH were different (the ICER for FF/UMEC/VI compared to UMEC/VI is CAD17,002/QALY in the manufacturer's report, but the correct value is CAD17,022/QALY).
(3) The reported ICERs of FF/UMEC/VI by PBAC were different (the manufacturer's report does not mention the revised results by ESC, but PBAC reports the revised ICER by ESC as AUD15,000~AUD45,000/QALY.).

1.3 Issues raised in HTA agencies

Considering the issues raised in the assessment process by HTA organizations, the issues that may be helpful for this evaluation was summarized as follows.

<NICE>

(1) It is not clear that the abrupt discontinuation of ICS in the LAMA/LABA arm of the IMPACT trial may have affected the outcome of exacerbations. That is, in the ICS/LABA arm, 38% of patients had been treated with ICS/LABA/LAMA prior to randomization, and treatment was stepped down.
(2) The IMPACT study showed a statistically significant difference in the SGRQ between the ICS/LABA/LAMA group and the dual therapy group. However, the difference was -1.8 points, which was less than the " minimal clinically important difference (MCID)" of -4 points in the total SGRQ score. However, a higher percentage of patients in the ICS/LABA/LAMA group had improved scores above the MCID (42% v.s. 34%) compared to dual therapy groups.

<IQWiG>

(1) In the LAMA/LABA arm of the IMPACT trial, ICS was abruptly stopped at the start of the trial, despite previous exacerbations. Treatment without ICS in the control group is different from the usual step-down in real practice and is not appropriate. It is doubtful that patients randomized to LAMA/LABA in the IMPACT trial received adequate treatment. Therefore, the IMPACT trial cannot be used to evaluate the efficacy of FF/UMEC/VI compared with LAMA/LABA.

<CADTH>

(1) Step-down from combination therapy including ICS may be considered in view of the patient's condition and avoidance of risks such as pneumonia due to ICS.
(2) There is uncertainty in the prediction of exacerbation occurrence and health-related quality of life based on the model submitted by the manufacturer.
(3) In the manufacturer's model, utilities are estimated based on an imprecise mapping algorithm, and superior results for FF/UMEC/VI compared with comparators have not been observed in the IMPACT trial.

<PBAC>

(1) The manufacturer requested that the drug price of FF/UMEC/VI be the same as that of MITT, but this was deemed unreasonable because the cost-effectiveness of triple therapy had not been evaluated in the past.
(2) The ESC believed that CEA could be implemented based on the IMPACT study.

2. Evaluation of additional benefit

2.1 Summary of additional benefit assessment by the manufacturer and review results

The manufacturer did not perform a systematic review (SR) on evaluation of additional benefit of FF/UMEC/VI and identified 5 manufacturer sponsored clinical studies of FF/UMEC/VI (Study 207608, Study 207609, Study 200812, IMPACT study, FULFIL study). 207608 and 207609 were used to examine additional benefit in populations A and B, and IMPACT was used in populations C-L. In addition to exacerbation specified in the analysis framework, the manufacturer used FEV_1 and SGRQ as outcome measures for the additional benefit assessment. In addition to populations A-L, the manufacturer also submitted additional benefit assessments for subpopulations by pretreatment (PT-1 to PT-5), subpopulations by blood eosinophil counts level (EOS-1 to EOS-4), and ITT populations (ITT-1 and ITT-2). As a result of the manufacturer's analysis, FF/UMEC/VI was found to have additional benefit in all populations except for populations A and B. For these, the following issues are raised.

<SR was not performed>
In accordance with the "Guideline for Analysis of Cost-Effectiveness Evaluation by the Central Social Insurance Medical Council, 2nd Version", a SR should be conducted to evaluate the presence of additional benefit[1]. On the other hand, the manufacturer did not conduct a SR and identified five studies, as there were no comparative studies other than the manufacturer sponsored RCTs that examined the clinical question in this evaluation. This made it difficult to assess the validity of the methodology and results of the systematic review.

<Setting of the target population>
The ITT population in IMPACT study may include various populations with different treatment effects in the target population due to study design issues. To consider the heterogeneity, it is reasonable to analyze the groups separately according to the clinical status of the previous treatment and eosinophil count, as per the analysis framework determined by the Expert Committee (Table 0-1). Therefore, academic group thought it is appropriate to assess the additional benefit based on the target populations A to L and to handle results of other target populations (PT-1 to PT-5, EOS-1 to EOS-4, ITT-1, ITT-2) presented by the manufacturer as reference information.

<Selection of clinical study>

【Population A, B】

The manufacturer employed 207608 and 207609 for additional benefit assessment in the populations A and B, while IMPACT study in the populations C to L. In contrast, the systematic review conducted by the academic group identified 200812 study as available for benefit assessment in populations A and B, and the FULFIL study in populations C-D, G-H, and K-L (see 2.2.8). However, the results based on these studies were not included in the manufacturer's report.

【Population C-F】
The manufacturer used the results of the subgroup analysis in IMPACT study for benefit assessment in the populations C-F. The clinical question in the population C-F is whether continuing triple therapy with FF/UMEC/VI has additional clinical benefit compared to stepping down to dual therapy for COPD patients receiving triple therapy as prior therapy (populations C and D: withdrawal of LAMA and switch to ICS/LABA, population E and F: withdrawal of LAMA and switch to ICS/LABA).
A response to a query on the manufacturer’s report (August 17, 2020) indicates “The GOLD 2020 guidelines recommend that the response to treatment step-up should be periodically reviewed and that treatment step-down should be considered if no clinical benefit is observed and/or adverse effects occur. The guideline also suggests that patients should be kept under close medical surveillance when treatment changes, especially step-down, are considered. (p.2)”. Therefore, benefit assessment in this population should include consideration of step-down in real practice, i.e., a step-down made only when considered clinically appropriate after a close examination of the patient's clinical condition. In the IMPACT study, due to the problems of the trial design, there was the possibility that patients receiving triple therapy as prior therapy might have been randomly assigned to the dual therapy regardless of the clinical indication for step-down. If some patients were randomized to the dual therapy despite the inappropriateness of step-down, the risk of exacerbation in the dual therapy group might be increased due to interruption of clinically inappropriate drugs, and the treatment effect of FF/UMEC/VI might be overestimated.
In addition, according to the response to the inquiry (August 17, 2020), "Patients in subgroup C-F were receiving triple therapy at the time of screening, but there was no information on what treatment they were receiving throughout the year prior to randomization. (p.2)". Therefore, it is not necessarily appropriate to use the IMPACT study to evaluate the additional benefit of FF/UMEC/VI compared to step-down to two-drug combination therapy in the C-F population.

【Population G-L】

As per the manufacturer's assessment, it is appropriate to conduct the assessment using the IMPACT study.

<Selection of outcome measures>

The manufacturer used a rate ratio of exacerbation, a difference between a change from baseline (CFB) in FEV_1, and a difference between CFB in SGRQ as outcome measures in the additional benefit assessment, stating that “Because COPD is a disease with diverse pathophysiological mechanisms and clinical features, outcomes of COPD drugs need to be assessed comprehensively with respect to exacerbation frequency, lung function, and SGRQ total score.”.
On the other hand, the decision of the Expert Committee on Cost-Effectiveness Evaluation stated that "Exacerbations should be used as the outcome measures for the additional benefit assessment.”. Therefore, in the additional benefit assessment by academic group, the treatment effect in avoiding exacerbations was used, in accordance with the decision of the Expert Committee, and the results of other endpoints were treated as reference information.

2.2 Systematic review by the academic group

2.2.1 Clinical questions

To assess the additional benefit of FF/UMEC/VI, a systematic review (SR) based on the clinical questions shown in Table 2-1 was conducted. The target population for the analysis was set up by dividing the population into 12 groups of A~L as shown in Table 2-1, but instead of constructing individual search formulas, a single search formula was constructed in accordance with Table 2-1. In the process of screening the literature identified by the search, the relevant literature was identified from the viewpoint of the possibility of examining the additional benefit of FF/UMEC/VI in A~L. Since the information on the clinical trials of FF/UMEC/VI were provided by the manufacturer, this systematic review was limited to the published literature.
The outcome measure was set as exacerbation, in accordance with the statement in the decision of the Expert Committee on Cost-Effectiveness Evaluation that "Exacerbation should be used as the outcome measure to assess additional benefit.”. Therefore, the results of other endpoints (FEV1 and SGRQ) were treated as reference information.

Table 2-1 Clinical questions of SR

<table>
<tr><td>Item</td><td>Setting in the assessment by academic group</td></tr>
<tr><td>Population</td><td>COPD</td></tr>
<tr><td>Intervention</td><td>FF/UMEC/VI</td></tr>
<tr><td>Comparator</td><td>
<table>
<tr><th rowspan="2">Prior therapy</th><th rowspan="2">Details of the prior therapy</th><th colspan="2">Eosinophil count</th><th rowspan="2">Comparator</th></tr>
<tr><th>< 100/μL</th><th>≥ 100/μL</th></tr>
<tr><td rowspan="3">Triple-drug therapy</td><td rowspan="3">MITT (triple-drug therapy with inhalation of 2 drug products)</td><td>A</td><td>B</td><td>MITT (triple-drug therapy with inhalation of 2 drug products)</td></tr>
<tr><td>C</td><td>D</td><td>ICS/LABA</td></tr>
<tr><td>E</td><td>F</td><td>LAMA/LABA</td></tr>
<tr><td>Dual-drug therapy</td><td>ICS/LABA</td><td>G</td><td>H</td><td>ICS/LABA</td></tr>
<tr><td colspan="2">Prior therapy: Dual-drug therapy (LAMA/LABA) or prior therapy with a single drug (LAMA)</td><td>I</td><td>J</td><td>LAMA/LABA</td></tr>
<tr><td>Single drug</td><td>LAMA</td><td>K</td><td>L</td><td>ICS/LABA</td></tr>
<tr><td>Other</td><td></td><td colspan="2">Not included in analysis</td><td></td></tr>
</table>
</td></tr>
<tr><td>Outcome</td><td>Exacerbation</td></tr>
<tr><td>Study design</td><td>A two-step SR was conducted.
(1) A systematic review to identify previously published systematic reviews that include clinical trials evaluating FF/UMEC/VI.
(2) A systematic review that identifies RCTs of FF/UMEC/VI that have been published since the most recent RCT in the previously reported systematic review in (1).</td></tr>
<tr><td>Literature search period</td><td>(1) Before the start of the Phase I study of FF/UMEC/VI (January 2013) ~ October/November 2019
(2) Approximate time since publication of the most recent RCT in the previously reported systematic review identified in (1) (January 2018) ~ November 2019</td></tr>
</table>

2.2.2 Implementation flow

To evaluate additional benefit of FF/UMEC/VI, a two-step SR was conducted with reference to the Minds Clinical Guidelines Development Manual [2]. In the first phase, a systematic review was conducted to identify previously published systematic reviews that included clinical trials that evaluated FF/UMEC/VI. In the second stage, a systematic review was conducted to identify RCTs of FF/UMEC/VI that were published after the most recent RCT in the previously reported systematic review identified in the first stage (Figure 2-1).

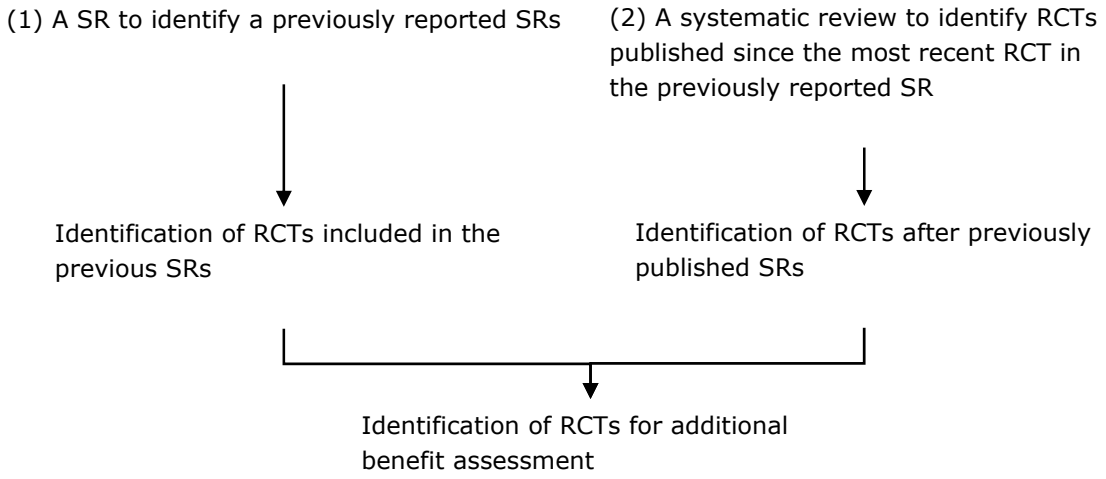


Figure 2-1 Flow of a systematic review

In the literature search process for the systematic review, a search formula was constructed by a medical information service/literature search expert by combining the criteria of disease and drug names, study design, and search period. Screening of the literature based on abstracts and subsequent identification of RCTs for additional benefit assessment was conducted by two independent reviewers in a blinded fashion. Literature was accepted or rejected according to predetermined inclusion and exclusion criteria, and any disagreements that arose during this process were resolved through consultation between the reviewers. The summary of the RCTs finally identified was summarized, and the duration of treatment, sample size, age, gender, rate ratio of exacerbations, hazard ratio of exacerbations, and the possibility of considering the analyzed populations A~L were summarized for each study.

2.2.3 Inclusion and exclusion criteria

The main inclusion and exclusion criteria for systematic reviews are listed below.

<Inclusion criteria>

- The target disease is COPD.
- Intervention includes a triple-drug therapy composed of ICS, LAMA, and LABA.
- Prespecified study design (The first step is a SR; the second step is an RCT).
- Published between the given starting point and October/November 2019.

<Exclusion criteria>

- A triple-drug therapy does not include FF/UMEC/VI.
- No comparative technology set in the analysis population A~L.
- Exacerbation is not included in the outcome.
- Not written in English or Japanese.

2.2.4 Database

PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, and Ichushi-Web were used for collection of the target studies.

2.2.5 Search formula

The search formula of the SR to identify previously reported SRs is shown below.

Search formula used for PubMed
Date of search: October 31, 2019
("Pulmonary Disease, Chronic Obstructive"[MH] OR "chronic obstructive pulmonary disease"[TIAB] OR "chronic obstructive pulmonary diseases"[TIAB] OR "chronic airflow obstruction"[TIAB] OR "chronic airflow obstructions"[TIAB] OR "chronic obstructive airway disease"[TIAB] OR "chronic obstructive airway diseases"[TIAB] OR "chronic obstructive lung disease"[TIAB] OR "chronic obstructive lung diseases"[TIAB]) AND ("Drug Combinations"[MH] OR "Drug Therapy, Combination"[MH] OR (triple[TIAB] AND (therapy[TIAB] OR combination[TIAB])) OR (("Adrenergic beta-2 Receptor Agonists"[MH] OR "LABA"[TIAB]) AND ("Long acting muscarinic antagonists"[TIAB] OR "LAMA"[TIAB] OR "Muscarinic Antagonists"[MH]) AND ("Adrenal Cortex Hormones"[MH] OR corticosteroid[TIAB] OR corticosteroids[TIAB])) OR (("fluticasone furoate"[NM] OR "fluticasone furoate"[TIAB] OR "GW685698"[TIAB]) AND ("vilanterol"[NM] OR vilanterol[TIAB] OR "GW642444M"[TIAB]) AND ("GSK573719"[NM] OR GSK573719[TIAB] OR Umeclidinium[TIAB])) OR "trelegy ellipta"[ALL]) AND systematic[SB] AND

(“2013/01/01”[PDAT] : “2019/12/31”[PDAT])
Number of literatures: 46

Search formula used for Embase
Date of search: November 7, 2019
((EMB.EXACT.EXPLODE("chronic obstructive lung disease")) OR ("chronic obstructive pulmonary disease") OR ("chronic airflow obstruction") OR ("chronic obstructive airway disease") OR "copd") AND ((EMB.EXACT.EXPLODE("fluticasone furoate plus umeclidinium plus vilanterol")) OR ("trelegy ellipta") OR (EMB.EXACT.EXPLODE("beta 2 adrenergic receptor stimulating agent")) OR ("adrenergic beta-2 receptor agonists") OR "laba" OR ("long acting muscarinic antagonist") OR "lama" OR EMB.EXACT.EXPLODE("corticosteroid") OR ("adrenal cortex hormones" OR "fluticasone") OR EMB.EXACT.EXPLODE("fluticasone")) AND ((EMB.EXACT.EXPLODE("drug combination") OR EMB.EXACT.EXPLODE("combination drug therapy")) OR ("drug combination therapy") OR "triple") AND (EMB.EXACT.EXPLODE("systematic review") OR "systematic") AND PD(2013-2019)
Number of literatures: 88

Search formula used for Cochrane
Date of search: November 1, 2019
#1 (COPD):ti,ab,kw OR ("chronic obstructive pulmonary disease"):ti,ab,kw OR ("chronic obstructive airway disease"):ti,ab,kw OR ("chronic obstructive lung disease"):ti,ab,kw (Word variations have been searched)
#2 MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
#3 ("LABA"):ti,ab,kw OR ("long acting beta agonists"):ti,ab,kw AND ("long acting beta agonist"):ti,ab,kw (Word variations have been searched)
#4 MeSH descriptor: [Adrenergic beta-Agonists] explode all trees
#5 ("LAMA"):ti,ab,kw OR ("Long acting muscarinic antagonists"):ti,ab,kw AND ("Long acting muscarinic antagonist"):ti,ab,kw (Word variations have been searched)
#6 MeSH descriptor: [Muscarinic Antagonists] explode all trees
#7 ("corticosteroid"):ti,ab,kw OR ("corticosteroids"):ti,ab,kw OR ("steroids"):ti,ab,kw (Word variations have been searched)
#8 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees
#9 (fluticasone furoate):ti,ab,kw (Word variations have been searched)
#10 (vilanterol):ti,ab,kw (Word variations have been searched)
#11 (umeclidinium):ti,ab,kw (Word variations have been searched)
#12 (triple):ti,ab,kw OR (combination):ti,ab,kw (Word variations have been searched)
#13 (#1 or #2) and (((#3 or #4) and (#5 or #6) and (#7 or #8)) or (#9 and #10 and #11)) and #12 with Publication Year from 2013 to 2019, in Reviews
Number of literatures: 9

Search formula used for Ichushi
Date of search: November 1, 2019
("肺疾患-慢性閉塞性"/TH or 慢性閉塞性肺疾患/TA or "慢性閉塞性気道疾患"/TA or "慢性気流閉塞"/TA or "COPD"/TA or "Chronic Obstructive Pulmonary Diseases"/TA or "Chronic Obstructive Pulmonary Disease"/TA or "Chronic Airflow Obstruction"/TA or "Chronic Obstructive Lung Diseases"/TA or "Chronic Obstructive Lung Disease"/TA) and (多剤併用/TA or 多数薬剤投与/TH or "多剤併用療法"/TH) and ("Adrenergic Beta-2 Receptor Agonists"/TH or "LABA"/TA or "Long-Acting Beta2 Agonist"/TA or β2/TA or "Muscarinic Antagonists"/TH or "LAMA"/TA or "Long-Acting Muscarinic Antagonists"/TA or ムスカリン/TA or 副腎皮質ホルモン/TH or corticosteroid/TA or (("Fluticasone Furoate"/TH or "fluticasone furoate"/TA or フルチカゾンフロアート/TA or フランカルボン酸フルチカゾン/TA or GW685698/TA) and ("Vilanterol"/TH or vilanterol/TA or GW642444M/TA or ビランテロール/TA) and (Umeclidinium/TH or umeclidinium/TA or GSK573719/TA or ウメクリジニウム/TA)) or "trelegy ellipta"/TA) and (PT=原著論文 and (メタアナリシス/TH or システマティックレビュー/TH)) and DT=2013:2019
Number of literatures: 1

The search formula of SR to identify RCTs published after the recent RCT in the previously reported SRs is shown below.

Search formula used for PubMed
Date of search: November 20, 2019
("Pulmonary Disease, Chronic Obstructive"[MH] OR "chronic obstructive pulmonary disease"[TIAB] OR "chronic obstructive pulmonary diseases"[TIAB] OR "chronic airflow obstruction"[TIAB] OR "chronic airflow obstructions"[TIAB] OR "chronic obstructive airway disease"[TIAB] OR "chronic obstructive airway diseases"[TIAB] OR "chronic obstructive lung disease"[TIAB] OR "chronic obstructive lung diseases"[TIAB]) AND ("Drug Combinations"[MH] OR "Drug Therapy, Combination"[MH] OR (triple[TIAB] AND (therapy[TIAB] OR chemotherapy[TIAB] OR combination[TIAB])) OR (("Adrenergic beta-2 Receptor Agonists"[MH] OR "LABA"[TIAB]) AND ("Long acting muscarinic antagonists"[TIAB] OR "LAMA"[TIAB] OR "Muscarinic Antagonists"[MH]) AND ("Adrenal Cortex Hormones"[MH] OR corticosteroid[TIAB] OR corticosteroids[TIAB])) OR (("fluticasone furoate"[NM] OR "fluticasone furoate"[TIAB] OR "GW685698"[TIAB]) AND ("vilanterol"[NM] OR vilanterol[TIAB] OR "GW642444M"[TIAB]) AND ("GSK573719"[NM] OR GSK573719[TIAB] OR Umeclidinium[TIAB])) OR "trelegy ellipta"[ALL]) AND (("Randomized Controlled Trial"[PT] OR "randomized controlled trial"[TI] OR "randomized controlled trials"[TI] OR "double blind"[TIAB] OR "Randomized Controlled Trials as Topic"[MH]) NOT systematic[SB]) AND ("2018/01/01"[PDAT] : "2019/12/31"[PDAT])
Number of literatures: 95

Search formula used for Embase
Date of search: November 1, 2019
(((EMB.EXACT.EXPLODE("chronic obstructive lung disease")) OR ("chronic obstructive pulmonary disease") OR ("chronic airflow obstruction") OR ("chronic obstructive airway disease") OR "copd") AND ((EMB.EXACT.EXPLODE("fluticasone furoate plus umeclidinium plus vilanterol")) OR ("trelegy ellipta") OR (EMB.EXACT.EXPLODE("beta 2 adrenergic receptor stimulating agent")) OR ("adrenergic beta-2 receptor agonists") OR "laba" OR ("long acting muscarinic antagonist") OR "lama" OR EMB.EXACT.EXPLODE("corticosteroid") OR ("adrenal cortex hormones" OR "fluticasone") OR EMB.EXACT.EXPLODE("fluticasone")) AND ((EMB.EXACT.EXPLODE("drug combination") OR EMB.EXACT.EXPLODE("combination drug therapy")) OR ("drug combination therapy") OR "triple")) AND (EMB.EXACT.EXPLODE("randomized controlled trial")) AND PD(2018-2019)
Number of literatures: 109

Search formula used for Cochrane
Date of search: November 1, 2019
#1 (COPD):ti,ab,kw OR ("chronic obstructive pulmonary disease"):ti,ab,kw OR ("chronic obstructive airway disease"):ti,ab,kw OR ("chronic obstructive lung disease"):ti,ab,kw (Word variations have been searched)
#2 MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
#3 ("LABA"):ti,ab,kw OR ("long acting beta agonists"):ti,ab,kw AND ("long acting beta agonist"):ti,ab,kw (Word variations have been searched)
#4 MeSH descriptor: [Adrenergic beta-Agonists] explode all trees
#5 ("LAMA"):ti,ab,kw OR ("Long acting muscarinic antagonists"):ti,ab,kw AND ("Long acting muscarinic antagonist"):ti,ab,kw (Word variations have been searched)
#6 MeSH descriptor: [Muscarinic Antagonists] explode all trees
#7 ("corticosteroid"):ti,ab,kw OR ("corticosteroids"):ti,ab,kw OR ("steroids"):ti,ab,kw (Word variations have been searched)
#8 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees
#9 (fluticasone furoate):ti,ab,kw (Word variations have been searched)
#10 (vilanterol):ti,ab,kw (Word variations have been searched)
#11 (umeclidinium):ti,ab,kw (Word variations have been searched)
#12 (triple):ti,ab,kw OR (combination):ti,ab,kw (Word variations have been searched)
#13 (#1 or #2) and (((#3 or #4) and (#5 or #6) and (#7 or #8)) or (#9 and #10 and #11)) and #12 with Publication Year from 2018 to 2019, in Randomized Controlled Trial
Number of literatures: 174

Search formula used for Ichushi
Date of search: November 1, 2019
("肺疾患-慢性閉塞性"/TH or 慢性閉塞性肺疾患/TA or "慢性閉塞性気道疾患"/TA or "慢性気流閉塞"/TA or "COPD"/TA or "Chronic Obstructive Pulmonary Diseases"/TA or "Chronic Obstructive Pulmonary Disease"/TA or "Chronic Airflow Obstruction"/TA or "Chronic Obstructive Lung Diseases"/TA or "Chronic Obstructive Lung Disease"/TA) and (多剤併用/TA or 多数薬剤投与/TH or "多剤併用療法"/TH) and ("Adrenergic Beta-2 Receptor Agonists"/TH or "LABA"/TA or "Long-Acting Beta2 Agonist"/TA or β2/TA or "Muscarinic Antagonists"/TH or "LAMA"/TA or "Long-Acting Muscarinic Antagonists"/TA or ムスカリン/TA or 副腎皮質ホルモン/TH or corticosteroid/TA or (("Fluticasone Furoate"/TH or "fluticasone furoate"/TA or フルチカゾンフロアート/TA or フランカルボン酸フルチカゾン/TA or GW685698/TA) and ("Vilanterol"/TH or vilanterol/TA or GW642444M/TA or ビランテロール/TA) and (Umeclidinium/TH or umeclidinium/TA or GSK573719/TA or ウメクリジニウム/TA)) or "trelegy ellipta"/TA) and PT=原著論文 and DT=2018:2019
Number of literatures: 6

2.2.6 Search results

The results of the SR were summarized in Figure 2-2, referring to the flowchart recommended by the PRISMA statement.

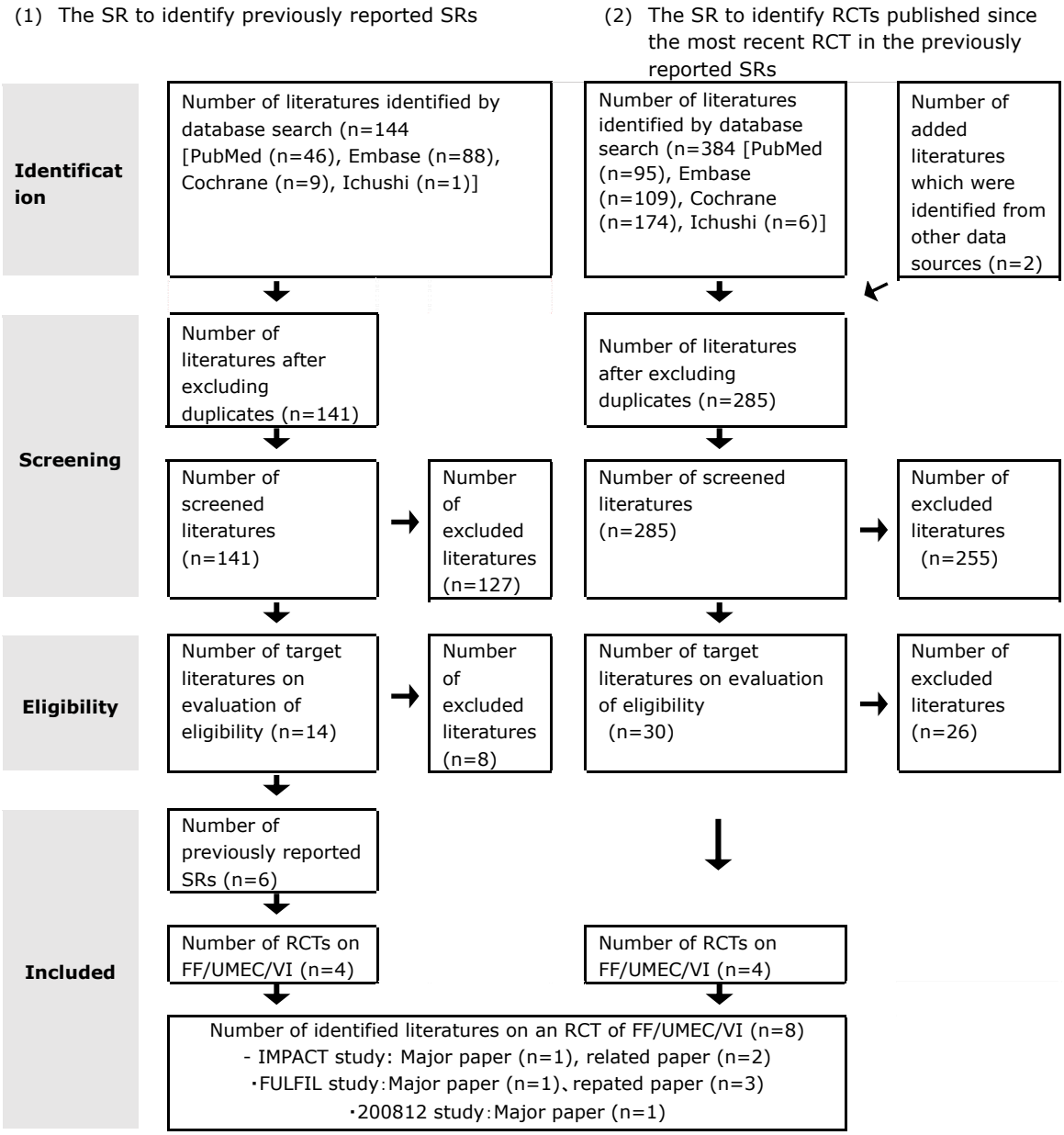


Figure 2-2 Flow chart of SR by the academic group

As a result of the SR to identify previously reported SRs, following 6 SRs were identified.

<A list of previously reported SRs>

1. Calzetta L, Cazzola M, Matera MG, Rogliani P. Adding a LAMA to ICS/LABA Therapy: A Meta-analysis of Triple Combination Therapy in COPD. Chest. 2019;155(4):758-770.
2. Cazzola M, Rogliani P, Calzetta L, Matera MG. Triple therapy versus single and dual long-acting bronchodilator therapy in COPD: a systematic review and meta-analysis. Eur Respir J. 2018;52(6).
3. Lai CC, Chen CH, Lin CYH, Wang CY, Wang YH. The effects of single inhaler triple therapy vs single inhaler dual therapy or separate triple therapy for the management of chronic obstructive pulmonary disease: a systematic review and meta-analysis of randomized controlled trials. Int J Chron Obstruct Pulmon Dis. 2019;14:1539-1548.
4. Langham S, Lewis J, Pooley N, et al. Single-inhaler triple therapy in patients with chronic obstructive pulmonary disease: a systematic review. Respir Res. 2019;20(1):242.
5. Zayed Y, Barbarawi M, Kheiri B, et al. Triple versus dual inhaler therapy in moderate-to-severe COPD: A systematic review and meta-analysis of randomized controlled trials. Clin Respir J. 2019;13(7):413-428.
6. Zheng Y, Zhu J, Liu Y, et al. Triple therapy in the management of chronic obstructive pulmonary disease: systematic review and meta-analysis. BMJ. 2018;363:k4388.

As a result of the review of these systematic reviews, the following four RCTs were identified as being consistent with this clinical question. A total of three RCTs on FF/UMEC/VI were identified: 1 and 4 are from the IMPACT trial, 2 from the FULFIL trial, and 3 from the 200812 trial.

<A list of RCTs in the previously reported SRs>

1. Lipson DA, Barnhart F, Brealey N, et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. N Engl J Med. 2018;378(18):1671-1680.
2. Lipson DA, Barnacle H, Birk R, et al. FULFIL Trial: Once-Daily Triple Therapy for Patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2017;196(4):438-446.
3. Bremner PR, Birk R, Brealey N, Ismaila AS, Zhu CQ, Lipson DA. Single-inhaler fluticasone furoate/umeclidinium/vilanterol versus fluticasone furoate/vilanterol plus umeclidinium using two inhalers for chronic obstructive pulmonary disease: a randomized non-inferiority study. Respir Res. 2018;19(1):19.
4. ClinicalTrials.gov. Registration information of IMPACT study (https://clinicaltrials.gov/ct2/show/NCT02164513)

A systematic review aimed at identifying RCTs published since the most recent RCT in the previously reported systematic review identified four randomized controlled trials. Of these, 1, 2, and 3 were post-hoc analyses of the FULFIL trial, and 4 were post-hoc analyses of the IMPACT trial.

<A list of RCTs that were published after the recent study in the previously reported SRs>

1. Naya I, Compton C, Ismaila AS, et al. Preventing clinically important deterioration with single-inhaler triple therapy in COPD. ERJ Open Res. 2018;4(4).
2. Halpin DMG, Birk R, Brealey N, et al. Single-inhaler triple therapy in symptomatic COPD patients: FULFIL subgroup analyses. ERJ Open Res. 2018;4(2).
3. Zheng J, Zhong N, Wang C, et al. The Efficacy and Safety of Once-daily Fluticasone Furoate/Umeclidinium/Vilanterol Versus Twice-daily Budesonide/Formoterol in a Subgroup of Patients from China with Symptomatic COPD at Risk of Exacerbations (FULFIL Trial). COPD. 2018;15(4):334-340.
4. Kato M, Tomii K, Hashimoto K, et al. The IMPACT Study - Single Inhaler Triple Therapy (FF/UMEC/VI) Versus FF/VI And UMEC/VI In Patients With COPD: Efficacy And Safety In A Japanese Population. Int J Chron Obstruct Pulmon Dis. 2019;14:2849-2861.

As a result of a series of systematic reviews, the three RCTs of FF/UMEC/VI identified were the IMPACT study, the FULFIL study, and the 200812 study. The studies 207608 and 207609 reported by the manufacturer were not identified in this systematic review because they had not been published as original papers.

2.2.7 Summary of clinical trials

Outline of the 3 RCTs (IMPACT study, FULFIL study, Study 200812) which were identified as a clinical study including FF/UMEC/VI were shown in Table 2-2. Outline of 4 papers of the post hoc analysis of IMPACT study and FULFIL study is shown in Table A-1 in Attachment.

Table 2-2 List of literatures

Study name	IMPACT	FULFIL	200812
Title of article	Once Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD	FULFIL trial: Once-Daily Triple Therapy for Patients with Chronic Obstructive Pulmonary Disease	Single-inhaler fluticasone furoate/umeclidinium/ vilanterol versus fluticasone furoate/vilanterol plus umeclidinium using two inhalers for chronic obstructive pulmonary disease: a randomized non-inferiority study
Author name	Lipson DA, et al.	Lipson DA, et al.	Bremner PR, et al.
Bibliographic information	N Engl J Med. 2018;378(18):1671-1680.	Am J Respir Crit Care Med. 2017;196(4):438-446.	Respir Res. 2018;19(1):19.
Test location	Multicenter (37 countries)	Multicenter (16 countries)	Multicenter (12 countries)
Study enrollment period	From June 2014 to July 2017	From January 2015 to April 2016	From June 2016 to March 2017
Target population	≥ 40 years old, diagnosed as COPD, has a history of smoking, CAT ≥ 10, $FEV_1/FVC < 0.7$, receiving a maintenance therapy, has a history of exacerbation within previous 12 months etc.	≥ 40 years old, diagnosed as COPD, CAT ≥ 10, receiving a maintenance therapy, has a history of exacerbation within previous 12 months etc.	≥ 40 years old, diagnosed as COPD, has a history of smoking, CAT ≥ 10, FEV1/FVC < 0.7, receiving a maintenance therapy, has a history of exacerbation within previous 12 months etc.
Key exclusion criteria	A patient who has asthma at present, a patient who has other respiratory diseases, a person who has experienced exacerbation before a	A patient who has asthma at present, a patient who has unabsorbed pneumonia/exacerbation etc.	A patient who has asthma at present, a patient who has other respiratory diseases etc.

	study or during a run-in period etc.		
Details of intervention method	FF/UMEC/VI group (n=4151)：FF/UMEC/VI 100 mcg/62.5mcg/25 mcg	FF/UMEC/VI group (n=911 24 weeks, n=210 52 weeks)：FF/UMEC/VI 100 mcg/62.5mcg/25 mcg	FF/UMEC/VI group (n=527)：FF/UMEC/VI 100 mcg/62.5mcg/25 mcg
Details of comparator	ICS/LABA group (n=4134)：FF/VI 100 mcg/25 mcg LAMA/LABA group (n=2070)：UMEC/VI 62.5 mcg/25 mcg	ICS/LABA group (n=899 24 weeks, n=220 52 weeks)：BUD/FOR 400mcg/12 mcg	MITT group (n=528)：FF/UMEC/VI 100 mcg/62.5 mcg/25 mcg
Study design	Phase III, RCT	Phase III, RCT	Phase III, RCT
Blinding method	Double-blind	Double-blind	Double-blind
Primary endpoint	Incidence of moderate/severe exacerbation event (52 weeks)	- Change in FEV_1 trough (24 weeks) - Change in FEV1 trough (52 weeks) - Change in SGRQ (24 weeks) - Change in SGRQ (52 weeks)	- Change in FEV1 trough (24 weeks)
Key secondary endpoints	- Change in FEV1 trough - Change in SGRQ - Time to first Incidence of moderate/severe exacerbation event - Incidence of moderate/severe exacerbation event (population with eosinophil count ≥ 150) - Time to first incidence of moderate/severe exacerbation event (population with	- Incidence of moderate/severe exacerbation event (24 weeks) - Incidence of moderate/severe exacerbation event (52 weeks) etc.	- Change in SGRQ (24 weeks) - Time to first Incidence of moderate/severe exacerbation event (24 weeks) etc.

	eosinophil count ≥ 150) - Incidence of severe exacerbation event etc.		
Statistical methods	- Incidence of exacerbation was analyzed with the generalized linear model assuming a negative binomial distribution - Amount of change was analyzed with MMRM - Time to event was analyzed with Cox proportional-hazards model	- Amount of change was analyzed with MMRM - Incidence of exacerbation was analyzed with the generalized linear model assuming a negative binomial distribution	- Amount of change was analyzed with MMRM - Time to event was analyzed with Cox proportional-hazards model

2.2.8 Availability for additional benefit assessment

The statistics of the three RCTs identified as clinical trials including FF/UMEC/VI (IMPACT, FULFIL, and 200812 trials) and the possibility of considering analytic population A~L in the assessment by academic group were summarized (Table 2-3). As a result, the data from the IMPACT study can be used for additional benefit assessment of the target population C~L. The data from the FULFIL study can potentially be used for additional benefit assessment of populations C, D, G, H, K, and L, and the data from the 200812 study can potentially be used for assessment of populations A and B.
However, because the results of these trials were not subjected to subgroup analyses consistent with the research questions of this analysis, it was not possible to examine the treatment effects of each analytic population from the published literature alone. Therefore, the additional usefulness in this analysis was based on the subgroup analysis of the IMPACT study submitted by the manufacturer. The data from both the FULFIL and 200812 studies showed that the results for the overall population were similar to those of the IMPACT study and other studies used in the evaluation.

Table 2-3 Statistics of clinical trials and the possibility of considering the population for analysis

Study	Treatment group	Treatment period (week)	Data					Rate ratio of exacerbation (FF/UMEC/VI vs comparator)			Hazard ratio of exacerbation (FF/UMEC/VI vs comparator)			Possibility of considering the population for analysis
			Sample size	Incidence of exacerbation	Mean age	Age SD	Proportion of male	Point estimate	95%CI lower limit	95%CI upper limit	Point estimate	95%CI lower limit	95%CI upper limit	
IMPACT	FF/UMEC/VI	52	4151	0.91	65.3	8.2	0.666	-	-	-	-	-	-	C-L
	ICS/LABA	52	4134	1.07	65.3	8.3	0.665	0.85	0.8	0.9	0.85	0.8	0.91	
	LAMA/LABA	52	2070	1.21	65.2	8.3	0.655	0.75	0.7	0.81	0.84	0.78	0.91	
FULFIL	FF/UMEC/VI	24	911	0.22	64.2	8.6	0.744	-	-	-	-	-	-	C,D,G,H,K,L
	ICS/LABA	24	899	0.34	63.7	8.7	0.737	0.65	0.49	0.86	-	-	-	
	ICS/LABA	52	220	0.36	63.7	8.7	0.737	0.56	0.37	0.85	-	-	-	
200812	FF/UMEC/VI	24	527	-	66.7	8.5	0.742	-	-	-	-	-	-	A,B
	MITT	24	528	-	65.9	8.8	0.746	-	-	-	0.87	0.68	1.12	

2.3 Results of additional benefit assessment

The target population in this analysis was established by dividing the population into 12 populations of A~L as shown in Table 0-1. The additional benefit of FF/UMEC/VI in the A~L population was assessed based on the manufacturer's report, the systematic review by the academic group, and additional literature review conducted as necessary. The results are shown in Tables 2-4 to 2-14.

Table 2-4 Evaluation of additional benefit (Population A and B)

Target population	Population A and B (Patients receiving triple therapy with two inhaled drugs, eosinophil count less than 100/μL for A and more than 100/μL for B)
Intervention	FF/UMEC/VI
Comparator	MITT
Outcome	Exacerbation
Presence or absence of additional benefit	☐ With additional benefit ■ "No additional benefit" or "Cannot be judged"
Data serving as the rationale for judgment	■ Meta-analysis of RCTs (Pooled analysis of several RCTs) ☐ Single RCT ☐ Prospective comparative observational studies ☐ Indirect comparison of RCT ☐ Comparison of single-arm studies ☐ No clinical study data
Reason for judging the presence or absence of additional benefit	● The manufacturer conducted an additional benefit assessment on the combined population of A-B. Treatment efficacy was assessed using the results of the combined analysis of the two non-inferiority trials (207608 and 207609). As an outcome measure, the incidence of moderate or severe exacerbations in each group was reported: 11% (80/729) in the FF/UMEC/VI group and 11% (77/731) in the MITT group. The manufacturer reported that FF/UMEC/VI had "no additional benefit" or " Cannot be judged" in this population. ● There was no statistically significant difference in exacerbation risk between treatment groups, and the similarity of point estimates of exacerbation rates does not indicate any additional benefit of FF/UMEC/VI compared with MITT.

Table 2-5 Evaluation of additional benefit (Population C)

Target population	Population C (Patients receiving triple therapy with two inhaled drugs, appropriate for step-down withdrawal from LAMA, and eosinophil count less than 100/μL)
Intervention	FF/UMEC/VI
Comparator	ICS/LABA
Outcome	Exacerbation
Presence or absence of additional benefit	☐ With additional benefit ☐ "No additional benefit" or "Cannot be judged" It was judged as unable to be analyzed.
Data serving as the rationale for judgment	☐ Meta-analysis of RCTs ・ Single RCT ☐ Prospective comparative observational studies ☐ Indirect comparison of RCT ☐ Comparison of single-arm studies ■ No clinical study data
Reason for judging the presence or absence of additional benefit	● Based on the subgroup analysis of the IMPACT study, the manufacturer reported the incidence rate of moderate or severe COPD exacerbations (case/person-year) in the FF/UMEC/VI group and the comparison group as 1.13 [0.99~1.28] and 1.37 [1.19~1.57], respectively. They also reported the rate ratio of moderate or severe COPD exacerbations as 0.83 [0.69~0.99] (p=0.044), and determined that FF/UMEC/VI had additional benefit. ● In the IMPACT study, there was the possibility that patients receiving triple therapy as pretreatment may have been randomly assigned to the dual therapy regardless of the clinical indication for step-down due to study design issues. If patients were randomized to the dual therapy despite the inappropriateness of step-down, the risk of exacerbation in the dual therapy group might be increased by interruption of clinically inappropriate drugs, and the treatment effect of FF/UMEC/VI might be overestimated. For this reason, it is not appropriate to use the IMPACT trial to assess additional benefit in this population. ● On the other hand, there are no clinical trials comparing the continued use of triple therapy with the withdrawal of LAMA and the use of ICS/LABA in patients on triple therapy for whom the clinical relevance of excluding LAMA has been confirmed. In the first place, clinicians

	are of the opinion that it is not common to exclude LAMA alone in a step-down in actual clinical practice. Therefore, since there are no data on LAMA withdrawal in these populations, the additional benefit of FF/UMEC/VI in these populations could not be considered and the study was classified as "unanalyzable”.

Table 2-6 Evaluation of additional benefit (Population D)

Target population	Population D (Patients receiving triple therapy in inhaled formulations, for whom a step-down procedure to wean off LAMA is appropriate, and have an eosinophil count of 100/μL or higher)
Intervention	FF/UMEC/VI
Comparator	ICS/LABA
Outcome	Exacerbation
Presence or absence of additional benefit	☐ With additional benefit ・ "No additional benefit" or "Cannot be judged" It was judged as unable to be analyzed.
Data serving as the rationale for judgment	☐ Meta-analysis of RCTs ・ Single RCT ☐ Prospective comparative observational studies ☐ Indirect comparison of RCT ☐ Comparison of single-arm studies ■ No clinical study data
Reason for judging the presence or absence of additional benefit	● Based on the subgroup analysis of the IMPACT study, the manufacturer reported the incidence rate of moderate or severe COPD exacerbations (case/person-year) in the FF/UMEC/VI group and the comparison group as 1.25 [1.16~1.34] and 1.46 [1.35~1.57], respectively. They also reported the rate ratio of moderate or severe COPD exacerbations as 0.86 [0.77~0.95] (p=0.003), and determined that FF/UMEC/VI had additional benefit. ● In the IMPACT study, there was the possibility that patients receiving triple therapy as pretreatment may have been randomly assigned to the dual therapy regardless of the clinical indication for step-down due to study design issues. If patients were randomized to the dual therapy despite the inappropriateness of step-down, the risk of exacerbation in the dual therapy group might be increased by interruption of clinically inappropriate drugs, and the treatment effect of FF/UMEC/VI might be overestimated. For this reason, it is not appropriate to use the IMPACT trial to assess additional benefit in this population. ● On the other hand, there are no clinical trials comparing the continued use of triple therapy with the withdrawal of LAMA and the use of ICS/LABA in patients on triple therapy for whom the clinical relevance of excluding

	LAMA has been confirmed. In the first place, clinicians are of the opinion that it is not common to exclude LAMA alone in a step-down in actual clinical practice. Therefore, since there are no data on LAMA withdrawal in these populations, the additional benefit of FF/UMEC/VI in these populations could not be considered and the study was classified as "unanalyzable".

Table 2-7 Evaluation of additional benefit (Population E)

Target population	Population E (Patients receiving triple therapy with two inhalation formulations, for whom a step-down from ICS is appropriate, and whose eosinophil count is less than 100/μL)
Intervention	FF/UMEC/VI
Comparator	LAMA/LABA
Outcome	Exacerbation
Presence or absence of additional benefit	☐ With additional benefit ■ "No additional benefit" or "Cannot be judged"
Data serving as the rationale for judgment	■ Meta-analysis of RCTs ☐ Single RCT ☐ Prospective comparative observational studies ☐ Indirect comparison of RCT ☐ Comparison of single-arm studies ☐ No clinical study data
Reason for judging the presence or absence of additional benefit	● Based on the subgroup analysis of the IMPACT study, the manufacturer reported the incidence rate of moderate or severe COPD exacerbations (case/person-year) in the FF/UMEC/VI group and the comparison group as 1.13 [0.99 to 1.28] and 1.45 [1.22 to 1.73], respectively. They also reported the rate ratio of moderate or severe COPD exacerbations as 0.78 [0.63 to 0.97] (p = 0.023), and determined that FF/UMEC/VI had additional benefit. ● In the IMPACT study, there was the possibility that patients receiving triple therapy as pretreatment may have been randomly assigned to the dual therapy regardless of the clinical indication for step-down due to study design issues. If patients were randomized to the dual therapy despite the inappropriateness of step-down, the risk of exacerbation in the dual therapy group might be increased by interruption of clinically inappropriate drugs, and the treatment effect of FF/UMEC/VI might be overestimated. For this reason, it is not appropriate to use the IMPACT trial to assess additional benefit in this population. ● According to the European Respiratory Society position on ICS discontinuation in COPD patients (May 2020), discontinuation of ICS is recommended for COPD patients without a history of frequent exacerbations[3].

	• The results of a meta-analysis of trials that evaluated the impact of stepping down from ICS (COSMIC, WISDOM, INSTEAD, and SUNSET trials) suggest that withdrawal from ICS is not necessarily associated with an increased risk of exacerbations[3]. It reported that the rate ratio of moderate or severe COPD exacerbations in the ICS withdrawal group compared with the ICS continuation group was 1.05 [0.97~1.13][3]. In addition, when the time to the first moderate or severe COPD exacerbation was analyzed, the hazard ratio of the ICS withdrawal group compared with the ICS continuation group was reported to be 1.04 [0.94~1.16][3]. Furthermore, an analysis of the proportion of patients who experienced at least one moderate or severe COPD exacerbation reported an odds ratio of 0.84 [0.63~1.14] in the ICS withdrawal group compared with the ICS continuation group[3]. • The results of the SUNSET study, which evaluated the effect of withdrawal from ICS from triple therapy, suggested that withdrawal from ICS was not necessarily associated with an increased risk of exacerbation[4]. It was reported that the rate ratio of moderate or severe COPD exacerbations in the ICS withdrawal group compared to the ICS continuation group was 1.08 [0.83~1.40][4]. • Based on the above, it cannot be said that the additional benefit of continuing FF/UMEC/VI therapy has been demonstrated in this population, i.e., those for whom step-down implementation is deemed appropriate based on clinically appropriate evaluation.

Table 2-8 Evaluation of additional benefit (Population F)

Target population	Population F (Patients receiving triple therapy with two inhalers, appropriate for step-down withdrawal from ICS, and eosinophil count ≥100/μL)
Intervention	FF/UMEC/VI
Comparator	LAMA/LABA
Outcome	Exacerbation
Presence or absence of additional benefit	☐ With additional benefit ■ "No additional benefit" or "Cannot be judged"
Data serving as the rationale for judgment	■ Meta-analysis of RCTs ☐ Single RCT ☐ Prospective comparative observational studies ☐ Indirect comparison of RCT ☐ Comparison of single-arm studies ☐ No clinical study data
Reason for judging the presence or absence of additional benefit	● Based on the subgroup analysis of the IMPACT study, the manufacturer reported the incidence rate of moderate or severe COPD exacerbations (case/person-year) in the FF/UMEC/VI group and the comparison group as 1.25 [1.16 to 1.34] and 1.86 [1.69 to 2.05], respectively. They also reported the rate ratio of moderate or severe COPD exacerbations as 0.67 [0.59 to 0.76] ($p < 0.001$), and determined that FF/UMEC/VI had additional benefit. ● In the IMPACT study, there was the possibility that patients receiving triple therapy as pretreatment may have been randomly assigned to the dual therapy regardless of the clinical indication for step-down due to study design issues. If patients were randomized to the dual therapy despite the inappropriateness of step-down, the risk of exacerbation in the dual therapy group might be increased by interruption of clinically inappropriate drugs, and the treatment effect of FF/UMEC/VI might be overestimated. For this reason, it is not appropriate to use the IMPACT trial to assess additional benefit in this population. ● According to the European Respiratory Society position on ICS discontinuation in COPD patients (May 2020), discontinuation of ICS is recommended for COPD patients without a history of frequent exacerbations[3].

	● The results of a meta-analysis of trials that evaluated the impact of stepping down from ICS (COSMIC, WISDOM, INSTEAD, and SUNSET trials) suggest that withdrawal from ICS is not necessarily associated with an increased risk of exacerbations[3]. It reported that the rate ratio of moderate or severe COPD exacerbations in the ICS withdrawal group compared with the ICS continuation group was 1.05 [0.97~1.13][3]. In addition, when the time to the first moderate or severe COPD exacerbation was analyzed, the hazard ratio of the ICS withdrawal group compared with the ICS continuation group was reported to be 1.04 [0.94~1.16][3]. Furthermore, an analysis of the proportion of patients who experienced at least one moderate or severe COPD exacerbation reported an odds ratio of 0.84 [0.63~1.14] in the ICS withdrawal group compared with the ICS continuation group[3]. ● The results of the SUNSET study, which evaluated the effect of withdrawal from ICS from triple therapy, suggested that withdrawal from ICS was not necessarily associated with an increased risk of exacerbation[4]. It was reported that the rate ratio of moderate or severe COPD exacerbations in the ICS withdrawal group compared to the ICS continuation group was 1.08 [0.83~1.40][4]. ● Based on the above, it cannot be said that the additional benefit of continuing FF/UMEC/VI therapy has been demonstrated in this population, i.e., those for whom step-down implementation is deemed appropriate based on clinically appropriate evaluation.

Table 2-9 Evaluation of additional benefit (Population G)

Target population	Population G (Patients receiving ICS/LABA combination therapy and eosinophil count less than 100/μL)
Intervention	FF/UMEC/VI
Comparator	ICS/LABA
Outcome	Exacerbation
Presence or absence of additional benefit	■ With additional benefit ☐ "No additional benefit" or "Cannot be judged"
Data serving as the rationale for judgment	☐ Meta-analysis of RCTs ■ Single RCT ☐ Prospective comparative observational studies ☐ Indirect comparison of RCT ☐ Comparison of single-arm studies ☐ No clinical study data
Reason for judging the presence or absence of additional benefit	● Based on the subgroup analysis of the IMPACT study, the manufacturer reported the incidence rate of moderate or severe COPD exacerbations (case/person-year) in the FF/UMEC/VI group and the comparison group as 0.65 [0.54 to 0.78] and 0.83 [0.70 to 0.98], respectively. They also reported the rate ratio of moderate or severe COPD exacerbations as 0.78 [0.61 to 1.00] (p = 0.050), and determined that FF/UMEC/VI had additional benefit. ● These results show a trend toward improvement in the FF/UMEC/VI group, although the p-value slightly exceeds 0.05. Considering the possible lack of power associated with the subgroup analysis, the additional benefit of FF/UMEC/VI in this population is indicated.

Table 2-10 Evaluation of additional benefit (Population H)

Target population	Population H (Patients receiving ICS/LABA combination therapy and eosinophil count ≥100/μL)
Intervention	FF/UMEC/VI
Comparator	ICS/LABA
Outcome	Exacerbation
Presence or absence of additional benefit	■ With additional benefit ☐ "No additional benefit" or "Cannot be judged"
Data serving as the rationale for judgment	☐ Meta-analysis of RCTs ■ Single RCT ☐ Prospective comparative observational studies ☐ Indirect comparison of RCT ☐ Comparison of single-arm studies ☐ No clinical study data
Reason for judging the presence or absence of additional benefit	● Based on the subgroup analysis of the IMPACT study, the manufacturer reported the incidence rate of moderate or severe COPD exacerbations (case/person-year) in the FF/UMEC/VI group and the comparison group as 0.73 [0.65 to 0.81] and 0.89 [0.80 to 0.98], respectively. They also reported the rate ratio of moderate or severe COPD exacerbations as 0.82 [0.71 to 0.95] (p = 0.008), and determined that FF/UMEC/VI had additional benefit. ● The improvement in exacerbations with statistical significance demonstrates the additional benefit of FF/UMEC/VI in this population.

Table 2-11 Evaluation of additional benefit (Population I)

Target population	Population I (Patients who are receiving only LAMA or a combination therapy with LAMA/LABA in addition to their eosinophil count of < 100/μL)
Intervention	FF/UMEC/VI
Comparator	LAMA/LABA
Outcome	Exacerbation
Presence or absence of additional benefit	☐ With additional benefit ■ "No additional benefit" or "Cannot be judged"
Data serving as the rationale for judgment	☐ Meta-analysis of RCTs ■ Single RCT ☐ Prospective comparative observational studies ☐ Indirect comparison of RCT ☐ Comparison of single-arm studies ☐ No clinical study data
Reason for judging the presence or absence of additional benefit	● Based on the subgroup analysis of the IMPACT study, the manufacturer reported the incidence rate of moderate or severe COPD exacerbations (case/person-year) in the FF/UMEC/VI group and the comparison group as 0.68 [0.53 to 0.87] and 0.50 [0.32 to 0.77], respectively. They also reported the rate ratio of moderate or severe COPD exacerbations as 1.37 [0.83 to 2.24] (p = 0.217), and determined that FF/UMEC/VI had additional benefit. ● Although not statistically significant, among the C-L subpopulations evaluated using the IMPACT study, the point estimate of the rate ratio of exacerbations exceeded 1 only in this population I, indicating a trend toward a higher incidence of exacerbations in the FF/UMEC/VI group. ● The benefit of adding steroids is not always clear clinically in this population, where steroid-free LAMA or LAMA/LABA is prescribed based on clinical judgment and eosinophil counts are low. From this perspective, the clinician's opinion that the higher rate of exacerbations in this population alone raises questions about the benefit of additional steroids is consistent with clinical practice. ● A post-hoc analysis of the IMPACT trial showed that there was no difference in the frequency of exacerbations between treatments in a patient

	population with low eosinophil counts[5]. ● Assuming that the exacerbation rate ratio data reported in the IMPACT trial is a posterior distribution of treatment effect (assuming a lognormal distribution) and interpreted in a Bayesian manner, the probability that the exacerbation rate ratio is less than 1 (FF/UMEC/VI is superior) is 81.06 The probability that the rate ratio of exacerbations is less than 1 (FF/UMEC/VI is superior) is 81.06%~100.0% in the other populations, while it is only 10.69% in the population I, which is relatively low (Table A-2). In addition, the probability that the rate ratio of exacerbations is less than 0.95 (i.e., the risk is reduced by 5% or more by FF/UMEC/VI) is only 7.42% in population I, compared to 71.09%~100.0% in the other populations (Table A-2). ● From the above, the additional benefit of FF/UMEC/VI in this population has been demonstrated.

Table 2-12 Evaluation of additional benefit (Population J)

Target population	Population J (Patients receiving LAMA monotherapy or LAMA/LABA combination therapy with eosinophil count ≥100/μL)
Intervention	FF/UMEC/VI
Comparator	LAMA/LABA
Outcome	Exacerbation
Presence or absence of additional benefit	■ With additional benefit ☐ "No additional benefit" or "Cannot be judged"
Data serving as the rationale for judgment	☐ Meta-analysis of RCTs ■ Single RCT ☐ Prospective comparative observational studies ☐ Indirect comparison of RCT ☐ Comparison of single-arm studies ☐ No clinical study data
Reason for judging the presence or absence of additional benefit	● Based on the subgroup analysis of the IMPACT study, the manufacturer reported the incidence rate of moderate or severe COPD exacerbations (case/person-year) in the FF/UMEC/VI group and the comparison group as 0.79 [0.69 to 0.91] and 0.98 [0.82 to 1.17], respectively. They also reported the rate ratio of moderate or severe COPD exacerbations as 0.81 [0.65 to 1.01] (p = 0.065), and determined that FF/UMEC/VI had additional benefit. ● These results show a trend toward improvement in the FF/UMEC/VI group, although the p-value slightly exceeds 0.05. Considering the possible lack of power associated with the subgroup analysis, the additional benefit of FF/UMEC/VI in this population is indicated.

Table 2-13 Evaluation of additional benefit (Population K)

Target population	Population K (Patients receiving LAMA monotherapy and eosinophil count less than 100/μL)
Intervention	FF/UMEC/VI
Comparator	ICS/LABA
Outcome	Exacerbation
Presence or absence of additional benefit	■ With additional benefit ☐ "No additional benefit" or "Cannot be judged"
Data serving as the rationale for judgment	☐ Meta-analysis of RCTs ■ Single RCT ☐ Prospective comparative observational studies ☐ Indirect comparison of RCT ☐ Comparison of single-arm studies ☐ No clinical study data
Reason for judging the presence or absence of additional benefit	● Based on the subgroup analysis of the IMPACT study, the manufacturer reported the incidence rate of moderate or severe COPD exacerbations (case/person-year) in the FF/UMEC/VI group and the comparison group as 0.58 [0.40 to 0.83] and 0.86 [0.62 to 1.19], respectively. They also reported the rate ratio of moderate or severe COPD exacerbations as 0.67 [0.41 to 1.09] (p = 0.104), and determined that FF/UMEC/VI had additional benefit. ● These results show a trend toward improvement in the FF/UMEC/VI group, although the p-value slightly exceeds 0.05. Considering the possible lack of power associated with the subgroup analysis, the additional benefit of FF/UMEC/VI in this population is indicated.

Table 2-14 Evaluation of additional benefit (Population L)

Target population	Population L (Patients receiving LAMA monotherapy and eosinophil count ≥100/μ)
Intervention	FF/UMEC/VI
Comparator	ICS/LABA
Outcome	Exacerbation
Presence or absence of additional benefit	■ With additional benefit ☐ "No additional benefit" or "Cannot be judged"
Data serving as the rationale for judgment	☐ Meta-analysis of RCTs ■ Single RCT ☐ Prospective comparative observational studies ☐ Indirect comparison of RCT ☐ Comparison of single-arm studies ☐ No clinical study data
Reason for judging the presence or absence of additional benefit	● Based on the subgroup analysis of the IMPACT study, the manufacturer reported the incidence rate of moderate or severe COPD exacerbations (case/person-year) in the FF/UMEC/VI group and the comparison group as 0.63 [0.50, 0.79] and 0.72 [0.59, 0.88], respectively. They also reported the rate ratio of moderate or severe COPD exacerbations as 0.87 [0.64 to 1.19] (p = 0.392), and determined that FF/UMEC/VI had additional benefit. ● These results show a trend toward improvement in the FF/UMEC/VI group, although the p-value slightly exceeds 0.05. Considering the possible lack of power associated with the subgroup analysis, the additional benefit of FF/UMEC/VI in this population is indicated.

Based on the results of the additional benefit assessment described above, it is appropriate to conduct a cost-effectiveness evaluation of FF/UMEC/VI as shown in Table 2-15.

Table 2-15 The results of additional benefit assessment

<table>
<tr><td rowspan="2">Prior therapy</td><td rowspan="2">Details of the prior therapy</td><td colspan="2">Eosinophil count</td><td rowspan="2">Comparator</td></tr>
<tr><td>< 100/μL</td><td>≥ 100/μL</td></tr>
<tr><td rowspan="3">Triple-drug therapy</td><td rowspan="3">MITT (triple-drug therapy with inhalation of 2 drug products)</td><td>A
No additional benefit.
CMA</td><td>B
No additional benefit.
CMA</td><td>MITT (triple-drug therapy with inhalation of 2 drug products)</td></tr>
<tr><td>C
Additional benefit is unknown.
Unable to be analyzed</td><td>D
Additional benefit is unknown.
Unable to be analyzed</td><td>ICS/LABA</td></tr>
<tr><td>E
It cannot to be said that additional benefit is indicated.
CMA</td><td>F
It cannot to be said that additional benefit is indicated.
CMA</td><td>LAMA/LABA</td></tr>
<tr><td>Dual-drug therapy</td><td>ICS/LABA</td><td>G
With additional benefit.
CEA</td><td>H
With additional benefit.
CEA</td><td>ICS/LABA</td></tr>
<tr><td colspan="2">Prior therapy:
Dual-drug therapy (LAMA/LABA)
or prior therapy with a single drug (LAMA)</td><td>I
It cannot to be said that additional benefit is indicated.
CMA</td><td>J
With additional benefit.
CEA</td><td>LAMA/LABA</td></tr>
<tr><td>Single drug</td><td>LAMA</td><td>K
With additional benefit.
CEA</td><td>L
With additional benefit.
CEA</td><td>ICS/LABA</td></tr>
<tr><td>Other</td><td></td><td colspan="2">Not included in analysis</td><td></td></tr>
</table>

The additional benefit of FF/UMEC/VI when the eosinophil count cutoff was set at 150/μL was not reported by the manufacturer. On the other hand, the relative risk (RR) of moderate and severe exacerbations was reported as a

parameter of treatment effect for conducting a cost-effectiveness evaluation when the cutoff for eosinophil count was set at 150/μL (Table 2-16). When compared with the data on the rate ratio of exacerbations when the cutoff for eosinophil count was set at 100/μL (Table 2-17), the trends in the estimates of treatment effect were generally consistent. Therefore, the evaluation of additional benefit when the cutoff for eosinophil count was set at 150/μL was treated in the same way as when the cutoff for eosinophil count was set at 100/μL.

Table 2-16 Relative risk of exacerbation with eosinophil count of 150/uL as cutoff

Prior therapy	Details of the prior therapy	Eosinophil count		Comparator
		< 150/μL	≥ 150/μL	
Triple-drug therapy	MITT (Triple-drug therapy with inhalation of 2 drug products)	A	B	MITT (Triple-drug therapy with inhalation of 2 drug products)
		C Moderate:RR=0.78, SE=0.06, p=0.001 Severe:RR=0.92, SE=0.15, p=0.591	D Moderate:RR=0.92, SE=0.06, p=0.224 Severe:RR=0.71, SE=0.10, p=0.017	ICS/LABA
		E Moderate:RR=0.78, SE=0.07, p=0.006 Severe:RR=1.01, SE=0.21, p=0.961	F Moderate:RR=0.66, SE=0.05, p<0.001 Severe:RR=0.50, SE=0.08, p<0.001	LAMA/LABA
Dual-drug therapy	ICS/LABA	G Moderate:RR=0.74, SE=0.08, p=0.003 Severe:RR=1.17, SE=0.26, p=0.462	H Moderate:RR=0.81, SE=0.07, p=0.022 Severe:RR=0.77, SE=0.15, p=0.173	ICS/LABA
Prior therapy: Dual-drug therapy (LAMA/LABA) or prior therapy with a single drug (LAMA)		I Moderate:RR=1.08, SE=0.20, p=0.687 Severe:RR=1.05, SE=0.48, p=0.909	J Moderate:RR=0.84, SE=0.12, p=0.229 Severe:RR=0.54, SE=0.16, p=0.032	LAMA/LABA
Single drug	LAMA	K Moderate:RR=0.73, SE=0.16, p=0.145 Severe:RR=0.66, SE=0.36, p=0.387	L Moderate:RR=0.81, SE=0.16, p=0.276 Severe*:RR=0.81, SE=0.16, p=0.276	ICS/LABA
Other		Non target for the analysis		

Prepared from values reported by the manufacturer

RR: Relative risk

*The RR of severe exacerbation of L was difficult to estimate, so the manufacturer substituted a moderate RR.

Table 2-17 Rate ratio of exacerbations with eosinophil count of 100/uL as cutoff

Prior therapy	Details of the prior therapy	Eosinophil count		Comparator
		< 100/μL	≥ 100/μL	
Triple-drug therapy	MITT (Triple-drug therapy with inhalation of 2 drug products)	A	B	MITT (Triple-drug therapy with inhalation of 2 drug products)
		C 0.83 [0.69, 0.99] p=0.044	D 0.86 [0.77, 0.95] p=0.003	ICS/LABA
		E 0.78 [0.63, 0.97] p=0.023	F 0.67 [0.59, 0.76] p<0.001	LAMA/LABA
Dual-drug therapy	ICS/LABA	G 0.78 [0.61, 1.00] p=0.050	H 0.82 [0.71, 0.95] p=0.008	ICS/LABA
Prior therapy: Dual-drug therapy (LAMA/LABA) or prior therapy with a single drug (LAMA)		I 1.37 [0.83, 2.24] p=0.217	J 0.81 [0.65, 1.01] p=0.065	LAMA/LABA
Single drug	LAMA	K 0.67 [0.41, 1.09] p=0.104	L 0.87 [0.64, 1.19] p=0.392	ICS/LABA
Other		Non target for the analysis		

Prepared from values reported by the manufacturer
Rate ratio

3. Evaluation of cost-effectiveness

3.1 Summary of manufacturer's results and review by academic group

<Summary of CMA for populations A and B>

The manufacturer conducted a cost-minimization analysis assuming equivalence of effects between treatments for populations A and B. In the cost-minimization analysis, the consumption of medical resources other than the cost of drug therapy was assumed to be equal, and the cost of drug therapy for one year in the combined population of A and B was compared. As a result, the total annual cost of FF/UMEC/VI and the comparator [MITT] (lowest cost ICS/LABA + lowest cost LAMA) were estimated to be JPY107,721 and JPY125,910, respectively, indicating that the cost of FF/UMEC/VI was JPY18,189 lower than that of MITT.

<Summary of CEA for populations C to L>

A cost-effectiveness analysis was conducted in the target population C-L, assuming that FF/UMEC/VI had an additional benefit over the comparator. The Galaxy COPD model was used to estimate the ICERs of FF/UMEC/VI by extrapolating the difference in the CFB of FEV_1 between FF/UMEC/VI and the comparator. The model incorporated a risk estimation equation based on prospective studies from overseas, which predicted COPD symptoms (FEV_1, percentage of dyspnea symptoms, percentage of cough and sputum symptoms), occurrence of exacerbations, and exercise capacity (6-minute walk distance) for the next cycle based on the difference in FEV_1 CFB and baseline background factors. From these predicted values of COPD pathology, medical costs, quality of life (SGRQ, utilities), and survival rates in the same cycle were estimated. Using these predicted COPD pathophysiological values and background factors, the predicted pathophysiological values for the next cycle were further calculated, and by repeating the same process thereafter, the long-term costs and QALYs for each treatment group and the ICERs for FF/UMEC/VI were estimated (Table 3-1).

Table 3-1 Results of the base case analysis by the manufacturer

Population	Description	Treatment	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY/QALY)
A+B (CMA#)	Prior therapy: MITT	FF/UMEC/VI	-	-	107,721	-18,189	Cost saving
		MITT	-	-	125,910	-	-
C (CEA)	Prior therapy: MITT	FF/UMEC/VI	4.902	0.133	4,139,444	-5,460	Dominant
	EOS < 100/μL	FF/VI	4.769	-	4,144,904	-	-
D (CEA)	Prior therapy: MITT	FF/UMEC/VI	4.910	0.140	4,112,646	-32,258	Dominant
	EOS ≥ 100/μL	FF/VI	4.769	-	4,144,904	-	-
E (CEA)	Prior therapy: MITT	FF/UMEC/VI	4.845	0.075	4,297,127	58,632	779,044
	EOS < 100/μL	UMEC/VI	4.769	-	4,238,495	-	-
F (CEA)	Prior therapy: MITT	FF/UMEC/VI	4.905	0.136	3,874,014	-364,480	Dominant
	EOS ≥ 100/μL	UMEC/VI	4.769	-	4,238,495	-	-
G (CEA)	Prior therapy: ICS+LABA	FF/UMEC/VI	4.879	0.110	4,297,829	152,925	1,396,294
	EOS < 100/μL	FF/VI	4.769	-	4,144,904	-	-
H (CEA)	Prior therapy: ICS+LABA	FF/UMEC/VI	4.920	0.151	4,222,901	77,997	517,736
	EOS ≥ 100/μL	FF/VI	4.769	-	4,144,904	-	-
I (CEA)	Prior therapy: LAMA/LABA or LAMA	FF/UMEC/VI	4.880	0.111	4,651,551	413,056	3,726,572
	EOS < 100/μL	UMEC/VI	4.769	-	4,238,495	-	-
J (CEA)	Prior therapy: LAMA/LABA or LAMA	FF/UMEC/VI	4.920	0.150	3,843,478	-395,017	Dominant
	EOS ≥ 100/μL	UMEC/VI	4.769	-	4,238,495	-	-
K (CEA)	Prior therapy: LAMA	FF/UMEC/VI	5.023	0.254	3,948,004	-196,900	Dominant
	EOS < 100/μL	FF/VI	4.769	-	4,144,904	-	-
L (CEA)	Prior therapy: LAMA	FF/UMEC/VI	4.981	0.212	4,286,733	141,829	669,299
	EOS ≥ 100/μL	FF/VI	4.769	-	4,144,904	-	-

Annual drug costs was compared in CMA

<Critique on the setting of drug costs in CMA>
The manufacturer used the cheapest drug price in the cost-minimization analysis for population A and B, assuming that the dosage form of MITT is ICS/LABA + LAMA. Since there is no single ICS drug that is covered by insurance for COPD in Japan, the manufacturer's setting is reasonable.

<Critique on the model used in CEA>
The Galaxy COPD model used in the cost-effectiveness analysis is elaborate and complex, and has recently been published as original articles but the following points need to be kept in mind when using it for decision making in this system.

- Improvement in FEV_1, rather than avoidance of exacerbations as determined in the analytical framework, is used as an input parameter to the model to estimate various treatment effects, which is not necessarily consistent with the discussion in the assessment of additional benefit, and should be interpreted with caution.
- The model is designed to predict various events and estimate outcomes using the difference in CFB of FEV_1. However, when the predicted values of exacerbation RR and SGRQ by the model deviate from the observed values in clinical trials, these values have to be calibrated manipulatively, which limits the predictive performance of the model relying only on FEV_1.
- There is a tendency for the model to overestimate the incidence of exacerbations and underestimate the mortality rate compared to the observed values of the prospective studies on which the risk estimation equation is based[6].

On the other hand, it is possible to consider a re-analysis by academic group based on the structure of the Galaxy COPD model for the following reasons.

- Based on the results of the manufacturer’s report and additional literature review, the Galaxy COPD model has some validity in representing the pathogenesis and prognosis of COPD.
- Even if the extrapolation method using FEV_1 is used, if (1) the treatment effect of avoiding exacerbations is recognized in the additional benefit assessment and (2) the treatment effect of avoiding exacerbations (rate ratio of exacerbations) confirmed in clinical trials is appropriately reflected in the model, a certain degree of validity is ensured, and therefore, it is possible to discuss cost-effectiveness in accordance with the analytical framework.
- There is not necessarily sufficient consensus on the optimal model structure to be used for health economic evaluation in the field of COPD, and it is difficult to determine the superiority or inferiority among multiple models [6].

<Critique on the parameter settings in the CEA model>

- The manufacturer used the data from ITT population of the IMPACT trial to set parameters for background factors that are assumed to affect the outcome in the Galaxy COPD model. On the other hand, according to the post-hoc analysis of the IMPACT study, the distribution of patient background factors such as age and gender differed between the ITT population and the Japanese population[7]. Therefore, in order to estimate the ICER of FF/UMEC/VI to be evaluated that better matches the real world settings in Japan, it is necessary to change the settings of the background factors of the patient population entered into the model to match the Japanese population.
- The manufacturer uses the risk estimation equation in the Galaxy COPD model (which predicts survival based on the predicted values of COPD pathology, including FEV_1) to estimate ICERs with different survival rates between treatment groups based on the difference in CFB of FEV_1, but such a setting is not necessarily valid. In other words, if there is a difference in FEV_1, there will be a difference in mortality in the model, but the results of the post-hoc analysis of the IMPACT trial, for example, suggest that there is no difference in life expectancy between treatments in some of the analyzed populations [8]. Therefore, in order to more accurately estimate the ICERs of FF/UMEC/VI, it is necessary to consider a setting in which there is no difference in survival between treatments in the relevant analytic population.
- The manufacturer estimates the ICER of FF/UMEC/VI using the risk estimation equation in the Galaxy COPD model (which predicts the SGRQ based on the predicted values of COPD pathology including FEV_1) and the mapping algorithm (which predicts the utilities based on the SGRQ). However, there are some challenges in doing so. That is, the IMPACT study showed a statistically significant difference between FF/UMEC/VI and comparator in the CFB of SGRQ, and the percentage of patients who achieved the minimum clinically significant difference (MCID) of 4 units was reported to be 42% in the FF/UMEC/VI group and 34% in the control group. Therefore, FF/UMEC/VI has a certain improvement effect on health-related quality of life[9, 10]. On the other hand, there is no empirical report showing that FF/UMEC/VI is superior to the comparator in utility weights such as EQ-5D. Therefore, from the perspective of providing reference information that contributes to decision-making, it is necessary to consider a setting in which utility weights do not differ between treatments as a scenario analysis.

3.2 Summary of revisions by academic group

Following the results of a review on the cost-effectiveness evaluation by the manufacturer and the additional benefit assessment by academic group, a revised analysis of the cost-effectiveness evaluation is necessary to be conducted as follows.

<Revised base case analysis>

(1) For populations A and B, no revised analysis was conducted because the analytical methods submitted by the manufacturer were appropriate.
(2) For populations C and D, no revised analysis of the cost-effectiveness assessment was conducted because of the difficulty in assessing additional benefit.
(3) For populations E, F, and I, a cost-minimization analysis assuming equivalence of efficacy among treatments were conducted because the additional benefit of FF/UMEC/VI over the comparator was not demonstrated.
(4) For populations G, H, J, K, and L, a revised cost-effectiveness analysis was performed changing the parameter settings of the background factors of the Galaxy COPD model to the statistics of the Japanese population, because it is suggested that the background factors of patients differ between the ITT population of the IMPACT study and the Japanese population.
(5) For populations G, H, J, K, and L, a revised cost-effectiveness analysis was performed assuming that the survival rates of FF/UMEC/VI and comparator in the Galaxy COPD model were the same value (the mean of both), because the post-hoc analysis of the IMPACT trial suggest that there is no difference in prognosis between the treatments in these populations.

<Revised scenario analysis>

(1) For populations G, H, J, K, and L, scenario analysis was performed assuming that the utility weights of FF/UMEC/VI and comparator in the Galaxy COPD model were the same value (the mean of both), because superiority of FF/UMEC/VI to comparator has not been indicated in utility weights.

3.3 Methods of the revised base case analysis

3.3.1 Cost-effectiveness in population C and D

Table 3-2 Corresponding part of report by manufacturer

In the reports, submitted by the manufacturer		
Section	Number of pages	Start line number (or figure/table number)
5.1.1	P94	Table 5-2 Summary of the result of CUA 1

<Description of report>

A report by the manufacturer, excerpted/summarized from Table 5-2

Population	Description	Treatment	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY /QALY)
C	Prior therapy: MITT EOS < 100/μL	FF/UMEC/VI	4.902	0.133	4,139,444	-5,460	Dominant
		FF/VI	4.769	-	4,144,904	-	-
D	Prior therapy: MITT EOS ≥ 100/μL	FF/UMEC/VI	4.910	0.140	4,112,646	-32,258	Dominant
		FF/VI	4.769	-	4,144,904	-	-

< Details of academic analysis (revision)>

- The cost-effectiveness assessment for populations C and D were treated as unanalyzable based on the results of the additional benefit assessment.

3.3.2 Cost-minimization analysis in population E, F, and I

Table 3-3 Corresponding part of report by manufacturer

In the reports, etc. submitted by the manufacturer		
Section	Number of pages	Start line number (or figure/table number)
5.1.1	P94	Table 5-2 Summary of the result of CUA 1

<Description of report>

A report by the manufacturer, excerpted/summarized from Table 5-2

Population	Description	Treatment	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER (JPY /QALY)
E	Prior therapy: MITT EOS < 100/μL	FF/UMEC/VI	4.845	0.075	4,297,127	58,632	779,044
		UMEC/VI	4.769	-	4,238,495	-	-
F	Prior therapy: MITT EOS ≥ 100/μL	FF/UMEC/VI	4.905	0.136	3,874,014	-364,480	Dominant
		UMEC/VI	4.769	-	4,238,495	-	-
I	Prior therapy: LAMA/LABA or LAMA EOS < 100/μL	FF/UMEC/VI	4.880	0.111	4,651,551	413,056	¥3,726,572
		UMEC/VI	4.769	-	4,238,495	-	-

< Details of academic analysis (revision)>

- For populations E, F, and I, a cost-minimization analysis was performed assuming that the effects of FF/UMEC/VI were equivalent to those of the comparator, as no additional benefit of FF/UMEC/VI over the comparator was shown.
- Assuming that the consumption of medical resources other than the drug costs was equivalent, annual drug costs in the FF/UMEC/VI group and the comparator (LAMA/LABA) group were estimated and compared.
- Similar to the manufacturer's method, the annual drug costs (= [unit drug price] × [number of inhalations per day] / [number of inhalations per kit] × 365) for the FF/UMEC/VI and LAMA/LABA groups were estimated and compared.
- The drug price of FF/UMEC/VI was set to be JPY 8,853.80 (JPY 295.13 per day).
- The least expensive LAMA/LABA should be Ultibro inhalation capsules (JPY

245.5 per day [drug price standard as of October 2019]).

3.3.3 Cost-effectiveness analysis in population G, H, J, K, and L (Settings of background factors)

Table 3-4 Corresponding part of report by manufacturer

In the reports, etc. submitted by the manufacturer		
Section	Number of pages	Start line number (or figure/table number)
Response to an inquiry on the report submitted by the manufacturer (August 17, 2020)	P8	Table 2 Comparison of integrated ITT population and Japanese specific baseline characteristics

<Description of report>

Table 2 Comparison of ITT population and Japanese specific baseline characteristics

Parameter	ITT		Japanese specific	
(1) Female (%)	34.00%		7.14%	
(2) Age (years old), mean	65.3	SE=0.08	70.54	SE=0.37
(3) BMI: Low (<21, %)	17.0%		38.62%	
(3) BMI: Middle (21 to 30, %)	58.0%		59.53%	
(3) BMI: High (>30, %)	25.0%		1.85%	
(4) Every comorbidity of CVD (%)	44.0%		33.60%	
(5) Ever other comorbidity (%)	57.0%		55.03%	
(6) Previous history of exacerbation ≥1 (%)	99.9%		100.00%	
(7) mMRC score ≥2 (%)	37.0%		22.28%	
(8) Current smoker (%)	35.0%		24.07%	
(9) Height (cm), mean	167.5	SE=0.09	163.99	SE=0.36
(10) Number of exacerbations in the year before (moderate or severe), mean per person	1.71	SE=0.01	1.72	SE=0.06
(11) Moderate exacerbation	1.41		1.36	
(12) Severe exacerbation	0.30		0.37	
(13) Total score of SGRQ at the time of start	50.70	SE=0.2	40.34	SE=0.79
(14) %FEV_1 at the time of start	45.5%	SE=0.1%	50.19%	SE=0.81%
FEV_1 of results (based on entered predictive values [%] and baseline characteristics)*	1215.3		1248.3	
(15) 6-minute walk distance (m)*	365.8	SE=2.74	387.91	SE=2.74

* The value is calculated with the model.

< Details of academic analysis (revision)>

- In the manufacturer's submission, the parameters of background factors

that were assumed to affect the outcome were commonly used for the ITT population settings. Based on the results of the post-hoc analysis of the IMPACT trial, it was assumed that the Japanese population tended to have (1) older age, (2) lower BMI, (3) current smoker/low, (4) higher %FEV_1, (5) lower SGRQ, and (6) lower eosinophil count, and relatively lower COPD symptoms and risk compared to the ITT population[7]. Therefore, it was necessary to change the background factors of patients to those of the Japanese population in order to more accurately estimate the ICERs of FF/UMEC/VI.

- The revised analysis was performed based on the information on the background factors of the Japanese population provided by the manufacturer in the response to the inquiry on the report submitted by the manufacturer (August 17, 2020) (Table A-3). In addition, a comparison was made with the results using the background factors of the Japanese population presented by the manufacturer in the response to the inquiry.

3.3.4 Cost-effectiveness analysis in population G, H, J, K, and L (Settings of survival probability)

Table 3-5 Corresponding part of report by manufacturer

In the reports, etc. submitted by the manufacturer		
Section	Number of pages	Start line number (or figure/table number)
Attachment data C. Risk equation parameters	P237~P240	Table C-9 Final outcome equation 2, coefficient for Weibull survival model

<Description of report>

There is no detailed description on making a distinction in a survival rate between treatment groups

< Details of academic analysis (revision)>

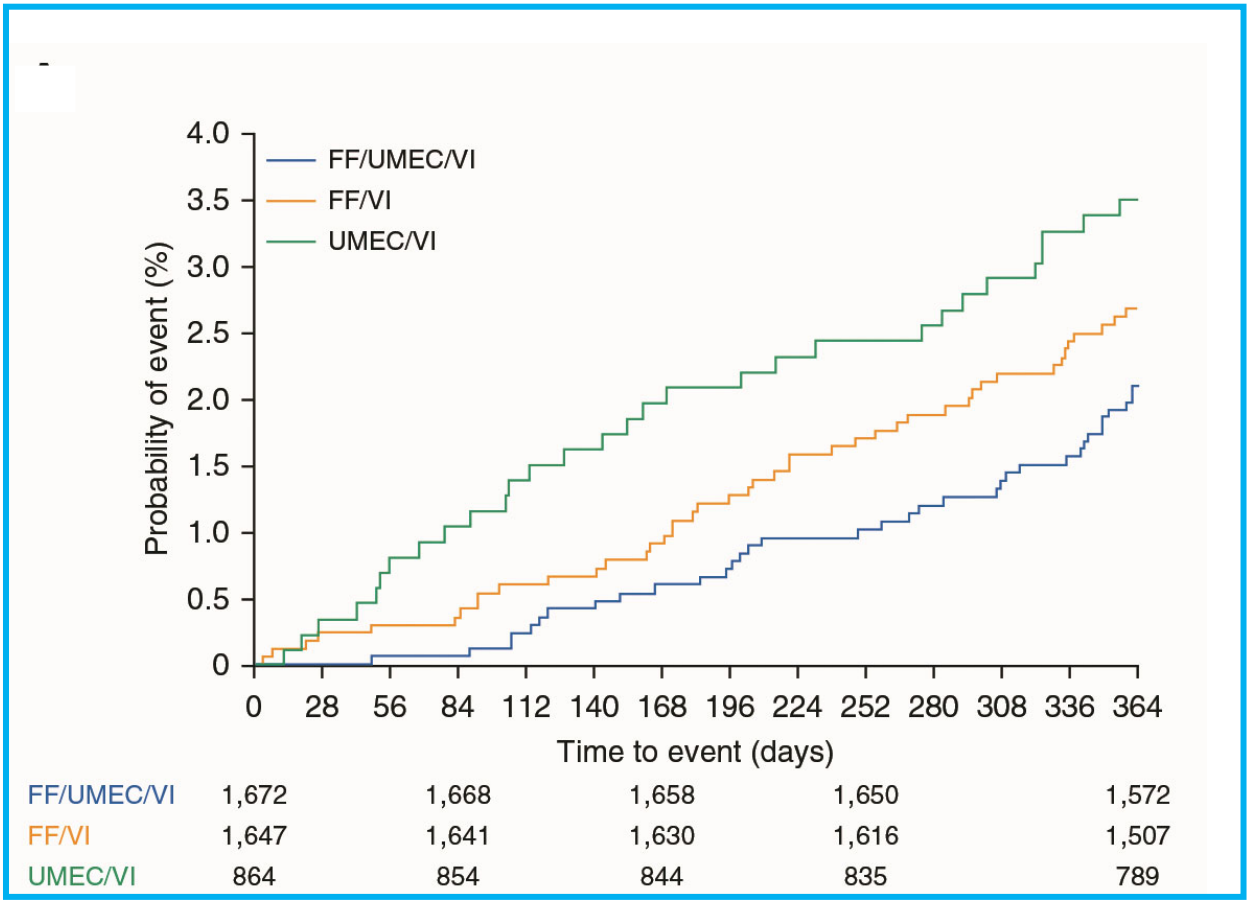
- In the manufacturer's submission, the CEA was performed assuming a difference in survival between treatment groups based on an indirect estimate using a risk estimation formula, which is not necessarily appropriate.
- Post-hoc analysis of the IMPACT trial suggested that (1) there was no difference in all-cause mortality between FF/UMEC/VI and ICS/LABA in populations with pretreatment other than MITT (ICS/LABA, LAMA/LABA or LAMA), and (2) there was no difference in all-cause mortality between FF/UMEC/VI and ICS/LABA in populations with pretreatment including ICS (MITT or ICS/LABA), and (3) there was no difference in all-cause mortality between FF/UMEC/VI, ICS/LABA, and LAMA/LABA in populations without ICS as pretreatment (LAMA/LABA or LAMA) (Figure 3-1)[8].
- Therefore, in the revised CEA for populations G, H, J, K, and L, it was necessary to consider settings that do not differ in survival rates between treatment groups.
- The manufacturer's model uses different survival rates estimated from FEV_1 under different conditions for the FF/UMEC/VI and comparator arms. However, after discontinuation of treatment in both groups, the survival rates estimated for the comparator group were used.
- In the revised analysis, the survival rates estimated under each condition for the FF/UMEC/VI and comparator were averaged and used as the survival rates during and after treatment for each group (Table A-4).

Figure 3-1 A relationship between the result of the post hoc analysis on prognosis of IMPACT study and the analytical framework [8]

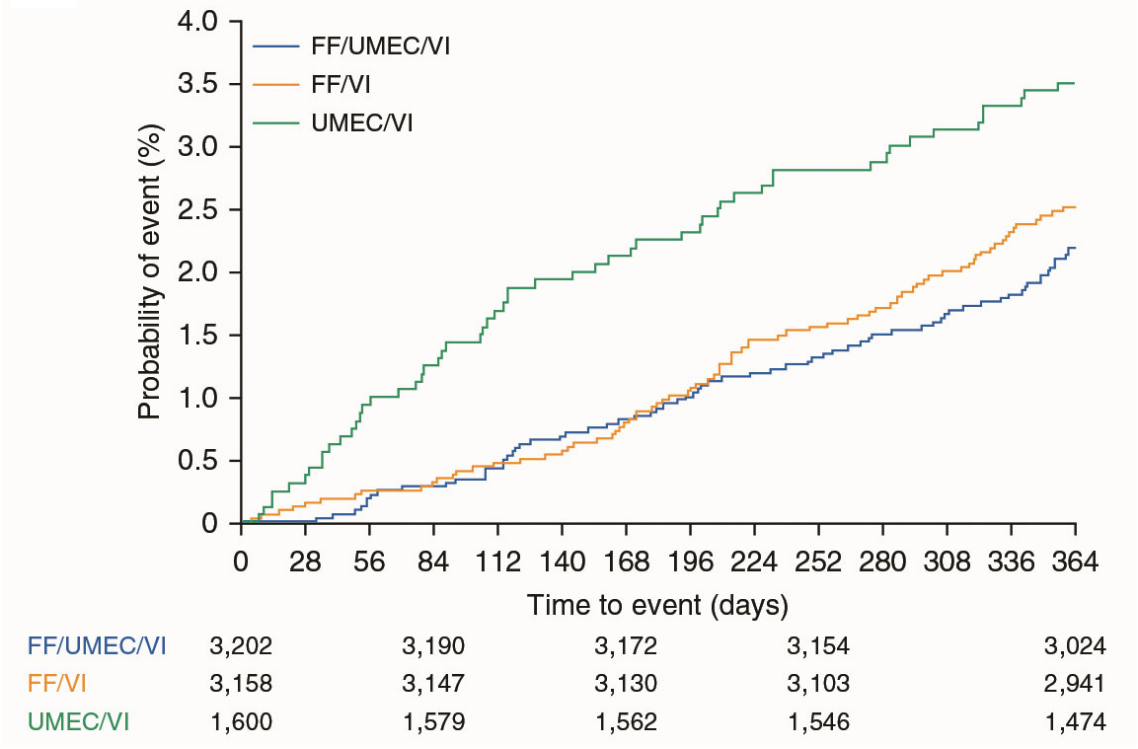
(a) A correspondence between subgroups of the post hoc analysis and the analytical framework

Prior therapy	Details of the prior therapy	Eosinophil count		Comparator
		< 100/μL	≥ 100/μL	
Triple-drug therapy	MITT (Triple-drug therapy with inhalation of 2 drug products)	A	B	MITT (Triple-drug therapy with inhalation of 2 drug products)
		C	D	ICS/LABA
		E	F	LAMA/LABA
Dual-drug therapy	ICS/LABA	G	H	ICS/LABA
Prior therapy: Dual-drug therapy (LAMA/LABA) or prior therapy with a single drug (LAMA)		I	J	LAMA/LABA
Single drug	LAMA	K	L	ICS/LABA
Other		Not included in analysis		

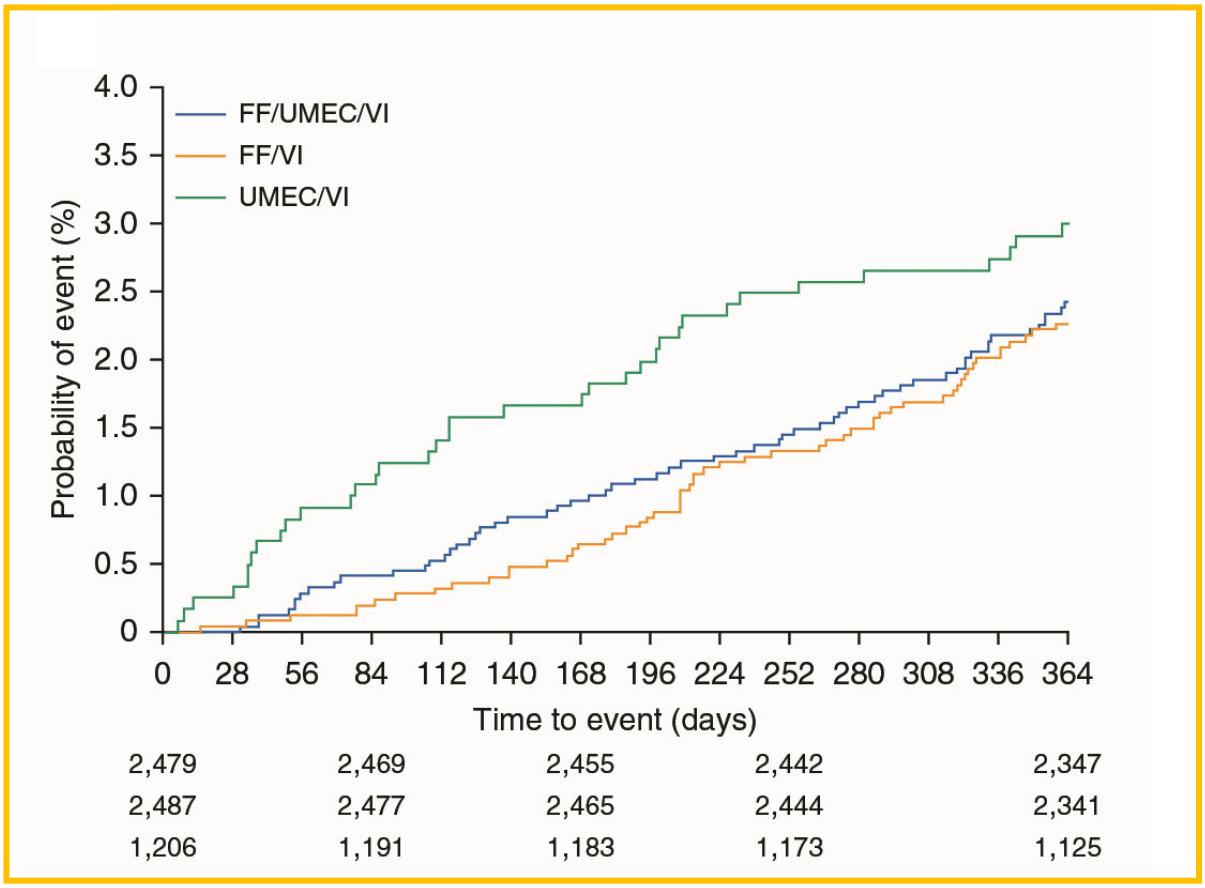
(b) Group 1 (blue, populations A to F)



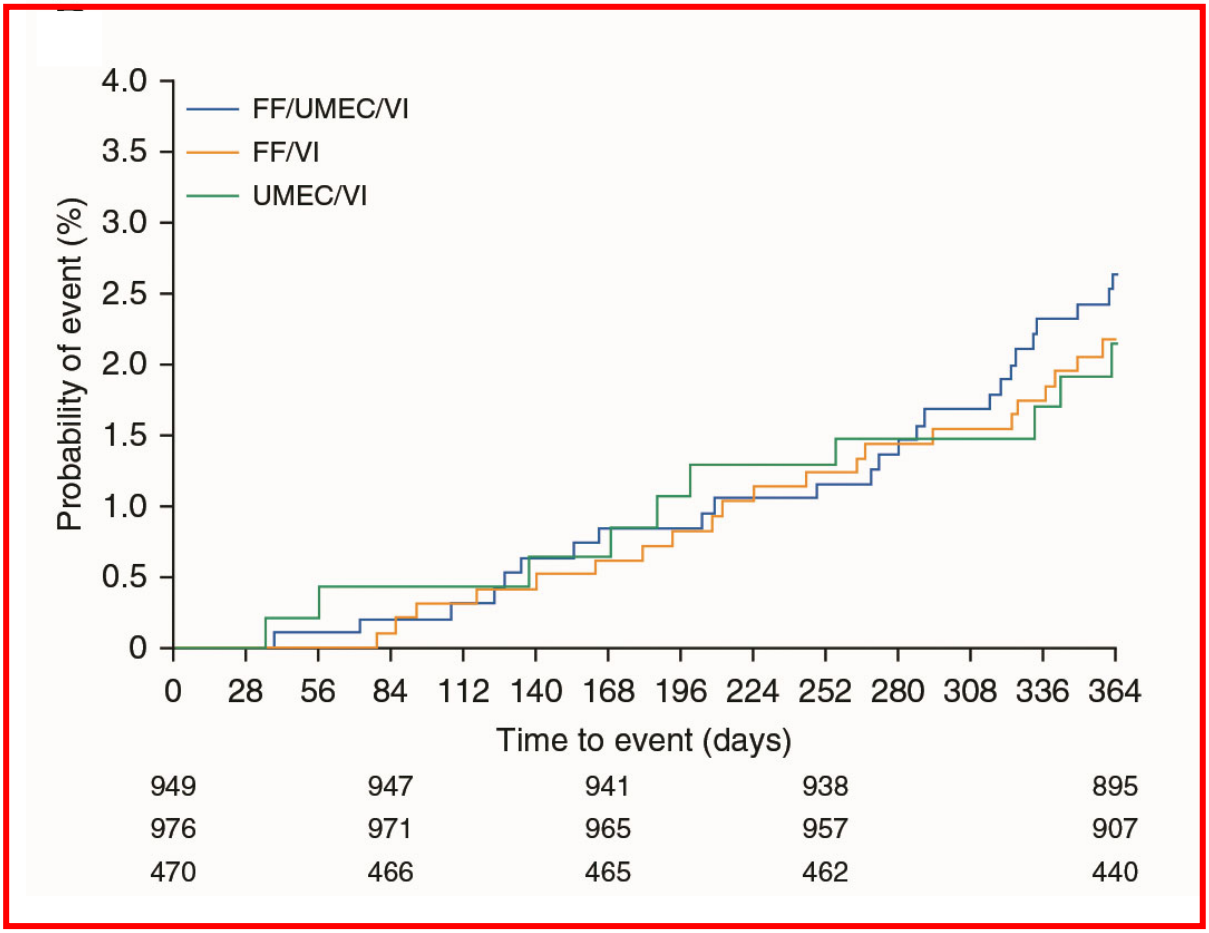
(c) Group 2 (green, populations A to H)



(d) Group 3 (yellow, populations G to L)



(e) Group 4 (red, populations I to L)



3.4 Methods of the revised scenario analysis

3.4.1 Cost-effectiveness analysis in population G, H, J, K, and L (Settings in Utilities)

Table 3-6 Corresponding part of report by manufacturer

In the reports, etc. submitted by the manufacturer		
Section	Number of pages	Start line number (or figure/table number)
4.2.2 Details of QOL values	P84~85	Line 32

<Description of report>
Utilities were estimated from predicted SGRQ in each model cycle, based on the following process:

1. The model predicted SGRQ-C in each model cycle (see equation in Appendix C)

2. SGRQ-C was converted to SGRQ using equation 1: (29)
Equation 1: SGRQ = SGRQ-C*0.9 + 3.1

3. SGRQ was then transformed to an EuroQOL-5 Dimension (EQ-5D) utility estimate using the algorithm developed by Starkie et al., presented in equation 2: (30)

Equation 2: EQ-5D = 0.9617 - 0.0013*SGRQ total - 0.0001*SGRQ total2+ 0.0231*%male

Utilities in subsequent cycles were calculated from the model-predicted SGRQ scores using the same approach. With a baseline SGRQ of 50.7, the resulting starting utility is 0.676. The model applies half-cycle correction to the QALY estimates for each cycle.

< Details of academic analysis (revision)>
- The manufacturer's model used a multi-step estimation method using a risk estimation equation and a mapping algorithm to differentiate utility weights between treatment groups, but the appropriateness of this method was controversial.
- Although the IMPACT trial showed a statistically significant improvement in SGRQ in the FF/UMEC/VI group, there was no report showing the superiority of FF/UMEC/VI for utilities directly measured by EQ-5D.

- Therefore, it was necessary to examine the setting in which there was no difference in utility weights between treatments.
- In the manufacturer's model, different utility weights estimated under different conditions were used for the FF/UMEC/VI and the comparator groups. However, after discontinuation of treatment in both groups, the utilities estimated for the comparator were used.
- In the revised analysis, the utilities estimated under each condition in the FF/UMEC/VI and comparator groups were averaged and used as the utilities during and after treatment for each group (Table A-5).

4. Results of cost-effectiveness assessment

4.1 Summary

The results of the revised base case analysis were summarized in Table 4-1. In the revised analysis, populations C and D were deemed unanalyzable based on the results of additional benefit assessment. For populations E, F, and I, a cost minimization analysis was performed. For groups G, H, J, K, and L, a revised cost-effectiveness analysis was conducted in which the background factors were changed to those of the Japanese population and the parameter for survival rate was changed to the same value (mean value of both) between the treatment groups. The results of the cost-effectiveness evaluation by the manufacturer were shown in the rightmost column of Table 4-1. There was no change in the base case analysis for groups A and B, and FF/UMEC/VI became "cost saving" compared to MITT, as did the results of the manufacturer. For populations C and D, according to the manufacturer's results, FF/UMEC/VI was Dominant compared to ICS/LABA, but the revised analysis judged this population to be unanalyzable, and ICERs were not estimated. According to the manufacturer's submission, the results of the ICER in the populations E, F, and I were JPY 779,044/QALY, Dominant, and JPY 3,726,572/QALY, respectively. However, the revised analysis showed that FF/UMEC/VI became "cost increasing" compared to LAMA/LABA in this population. The results of the revised analysis for populations G, H, and L showed that the ICER of FF/UMEC/VI was less than JPY 5 million/QALY, similar to the results for the manufacturer. The results of the revised analysis of the populations J and K showed that FF/UMEC/VI was dominant compared to the comparator, as did the results of the manufacturer. The results of additional CEA were summarized in Table A-6, assuming that the additional benefit assessment was the same when the eosinophil count cutoff was set at 150/μL as when it was set at 100/μL.

Table 4-1 Results of the revised basic analysis

Population	Description	Treatment	Effectiveness(QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER by the academic group (JPY/QALY)	ICER by the manufacturer (JPY/QALY)
A,B (CMA)	Prior therapy: MITT	FF/UMEC/VI	-	-	107,721	-18,189	Cost saving	Cost saving
		MITT	-	-	125,910	-	-	-
C (Unable to be analyzed)	Prior therapy: MITT	FF/UMEC/VI	-	-	-	-	Unable to be analyzed	Dominant (Dominant)
	EOS < 100/μL	FF/VI	-	-	-	-	-	-
D (Unable to be analyzed)	Prior therapy: MITT	FF/UMEC/VI	-	-	-	-	Unable to be analyzed	Dominant
	EOS ≥ 100/μL	FF/VI	-	-	-	-	-	-
E (CMA)	Prior therapy: MITT	FF/UMEC/VI	-	-	107,721	18,114	Cost increasing	779,044
	EOS < 100/μL	UMEC/VI	-	-	89,608	-	-	-
F (CMA)	Prior therapy: MITT	FF/UMEC/VI	-	-	107,721	18,114	Cost increasing	Dominant
	EOS ≥ 100/μL	UMEC/VI	-	-	89,608	-	-	-
G (CEA)	Prior therapy: ICS+LABA	FF/UMEC/VI	5.498	0.055	3,242,120	100,408	1,833,684	1,396,294
	EOS < 100/μL	FF/VI	5.443	-	3,141,711	-	-	-
H (CEA)	Prior therapy: ICS+LABA	FF/UMEC/VI	5.564	0.070	3,209,063	22,941	328,585	517,736
	EOS ≥ 100/μL	FF/VI	5.494	-	3,186,122	-	-	-
I	Prior therapy:	FF/UMEC/VI	-	-	107,721	18,114	Cost increase	3,726,572

(CMA)	LAMA/LABA or LAMA							
	EOS < 100/µL	UMEC/VI	-	-	89,608	-	-	-
J (CEA)	Prior therapy: LAMA/LABA or LAMA	FF/UMEC/VI	5.568	0.066	2,940,676	-345,791	Dominant	Dominant
	EOS ≥ 100/µL	UMEC/VI	5.503	-	3,286,467	-	-	-
K (CEA)	Prior therapy: LAMA	FF/UMEC/VI	5.652	0.139	3,016,838	-185,338	Dominant	Dominant
	EOS < 100/µL	FF/VI	5.513	-	3,202,176	-	-	-
L (CEA)	Prior therapy: LAMA	FF/UMEC/VI	5.662	0.093	3,293,670	44,982	483,056	669,299
	EOS ≥ 100/µL	FF/VI	5.569	-	3,248,688	-	-	-

4.2 Revised base case analysis

For the populations A and B, the analyses submitted by the manufacturer were reasonable and therefore accepted. For the other populations, the results were as follows.

4.2.1 Cost-effectiveness in population C and D

Since these populations were judged as "unable to analyze", ICERs were not estimated (Table 4-1).

4.2.2 Cost-minimization analysis in population E, F, and I

Results of the CMA of FF/UMEC/VI compared to LAMA/LABA were as follows.

- Annual drug cost of FF/UMEC/VI = [a unit price of the drug] x [number of daily inhalation]/[number of inhalations per kit] × 365=8,853.80 × 1/30 × 365=JPY 107,721.2
- Annual drug cost of LAMA/LABA = [a unit price of the drug] x [number of daily inhalation]/[number of inhalations per kit] ×365) =245.5 × 1/1 × 365 = JPY 89,607.5
- Incremental cost of FF/UMEC/VI compared to LAMA/LABA = JPY 107,721.2 – JPY 89,607.5 yen = JPY 18,113.7 (cost increasing)

4.2.3 Cost-effectiveness analysis in population G, H, J, K, and L (Settings of background factors)

Table 4-2 shows the results of the revised CEA in which the background factor was changed to the Japanese population setting for populations G, H, J, K, and L (Table 4-1 shows the results when the changes in 4.2.3 and 4.2.4 were made simultaneously.). When the results of this analysis were compared with the results by the manufacturer at the time of the response to the inquiry (August 17, 2020), it was confirmed that there was no deviation.

Table 4-2 The results of revised analysis in populations G, H, J, K, and L (Settings of background factors)

Population	Description	Treatment	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER by academic group (JPY /QALY)
G	Prior therapy: ICS+LABA	FF/UMEC/VI	5.474	0.104	3,217,944	134,692	1,289,873
	EOS < 100/μL	FF/VI	5.370		3,083,252		
H	Prior therapy: ICS+LABA	FF/UMEC/VI	5.520	0.150	3,160,970	77,719	516,577
	EOS ≥ 100/μL	FF/VI	5.370		3,083,252		
J	Prior therapy: LAMA/LABA or LAMA	FF/UMEC/VI	5.519	0.149	2,882,462	-292,130	Dominant
	EOS ≥ 100/μL	UMEC/VI	5.370		3,174,592		
K	Prior therapy: LAMA	FF/UMEC/VI	5.601	0.231	2,956,890	-126,361	Dominant
	EOS < 100/μL	FF/VI	5.370		3,083,252		
L	Prior therapy: LAMA	FF/UMEC/VI	5.590	0.220	3,214,998	131,746	597,743
	EOS ≥ 100/μL	FF/VI	5.370		3,083,252		

4.2.4 Cost-effectiveness analysis in population G, H, J, K, and L (Settings of survival rate)

Table 4-3 shows the results of revised analysis in which the survival rate was changed to the same value across treatment groups in populations G, H, J, K, and L (Table 4-1 describes the results when the changes in 4.2.3 and 4.2.4 were made simultaneously.).

Table 4-3 The results of revised analysis in populations G, H, J, K, and L (Settings of survival rate)

Population	Description	Treatment	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER by academic group (JPY /QALY)
G	Prior therapy: ICS+LABA	FF/UMEC/VI	4.902	0.069	4,341,524	109,054	1,580,733
	EOS < 100/μL	FF/VI	4.833		4,232,470		
H	Prior therapy: ICS+LABA	FF/UMEC/VI	4.958	0.088	4,295,572	11,167	127,044
	EOS ≥ 100/μL	FF/VI	4.870		4,284,405		
J	Prior therapy: LAMA/LABA or LAMA	FF/UMEC/VI	4.965	0.084	3,935,451	-462,679	Dominant
	EOS ≥ 100/μL	UMEC/VI	4.882		4,398,130		
K	Prior therapy: LAMA	FF/UMEC/VI	5.070	0.177	4,044,813	-273,509	Dominant
	EOS < 100/μL	FF/VI	4.893		4,318,322		
L	Prior therapy: LAMA	FF/UMEC/VI	5.040	0.117	4,398,684	40,224	344,499
	EOS ≥ 100/μL	FF/VI	4.923		4,358,460		

4.3 Revised sensitivity analysis

One-way sensitivity analyses were conducted for the populations G, H, J, K, and L, excluding populations A, B, E, F, and I, which were subject to cost minimization analysis, and population C and D, which were unable to analyze (Table 4-4 to Table 4-8). The range of variation of the parameters were in accordance with the manufacturer's submission. In the population G, the rate ratio of severe exacerbations and the setting of SGRQ-C suggested that the conclusion of cost-effectiveness evaluation of FF/UMEC/VI might change (Table 4-4). The results also showed that the ICER of FF/UMEC/VI was significantly affected by the setting of the rate ratio of severe exacerbations in the population L (Table 4-8).

Table 4-4 The results of the sensitivity analysis in population G (Prior therapy: ICS+LABA +EOS < 100/μL)

Results of the basic analysis: ICER=JPY1,833,684/QALY				
Scenario	Lower limit	Upper limit	Results of the lower limit (JPY/QALY)	Results of the upper limit (JPY/QALY)
Rate ratio of severe exacerbation	0.61	1.67	Dominant	11,525,432
Change in SGRQ-C	-4.89	0.67	813,993	Dominated (Nondominant)
Rate ratio of moderate exacerbation	0.56	0.95	1,523,232	2,235,982
Health care cost of moderate exacerbation	50%	200%	2,062,810	1,375,431
Change in FEV_1 (mL)	-4	80	2,095,005	1,709,860
Annual disease management cost	50%	200%	1,936,225	1,628,601
Time frame of the analysis (year)	5	10	2,113,222	1,884,209
Health care cost of severe exacerbation	50%	200%	1,801,644	1,897,763
Discount rate	0%	4%	1,794,340	1,870,705

Table 4-5 Results of the sensitivity analysis in population H (Prior therapy: ICS+LABA + EOS ≥ 100/μL)

Results of the basic analysis：ICER=JPY328,585/QALY				
Scenario	Lower limit	Upper limit	Results of the lower limit (JPY/QALY)	Results of the upper limit (JPY/QALY)
Rate ratio of severe exacerbation	0.65	1.27	Dominant	4,324,593
Health care cost of severe exacerbation	50%	200%	859,207	Dominant
Change in SGRQ-C	-4.33	-1.00	206,408	845,106
Health care cost of moderate exacerbation	50%	200%	463,290	59,175
Rate ratio of moderate exacerbation	0.69	0.94	171,083	568,085
Annual disease management cost	50%	200%	455,555	74,644
Time frame of the analysis (year)	5	10	592,792	386,232
Change in FEV_1 (mL)	58	110	442,817	277,488
Discount rate	0%	4%	291,156	363,312

Table 4-6 Results of the sensitivity analysis in population J (Prior therapy: LAMA/LABA or LAMA + EOS ≥ 100/μL)

Results of the basic analysis: Dominant				
Scenario	Lower limit	Upper limit	Results of the lower limit (JPY/QALY)	Results of the upper limit (JPY/QALY)
Change in SGRQ-C	-4.78	-0.22	Dominant	Dominant
Health care cost of severe exacerbation	50%	200%	Dominant	Dominant
Rate ratio of severe exacerbation	0.31	0.88	Dominant	Dominant
Rate ratio of moderate exacerbation	0.69	1.12	Dominant	Dominant
Annual disease management cost	50%	200%	Dominant	Dominant
Health care cost of moderate exacerbation	50%	200%	Dominant	Dominant
Time frame of the analysis (year)	5	10	Dominant	Dominant
Change in FEV_1 (mL)	37	123	Dominant	Dominant
Discount rate	0%	4%	Dominant	Dominant

Table 4-7 Results of the sensitivity analysis in population K (Prior therapy: LAMA + EOS < 100/μL)

Results of the basic analysis: Dominant				
Scenario	Lower limit	Upper limit	Results of the lower limit (JPY/QALY)	Results of the upper limit (JPY/QALY)
Change in SGRQ-C	-10.33	-0.56	Dominant	Dominant
Rate ratio of severe exacerbation	0.4	1.08	Dominant	1,020,839
Health care cost of severe exacerbation	50%	200%	Dominant	Dominant
Rate ratio of moderate exacerbation	0.4	1.08	Dominant	Dominant
Health care cost of moderate exacerbation	50%	200%	Dominant	Dominant
Change in FEV_1 (mL)	-26	169	Dominant	Dominant
Annual disease management cost	50%	200%	Dominant	Dominant
Time frame of the analysis (year)	5	10	Dominant	Dominant
Discount rate	0%	4%	Dominant	Dominant

Table 4-8 Results of the sensitivity analysis in population L (Prior therapy: LAMA + EOS ≥ 100/μL)

Results of the basic analysis: ICER=JPY483,056/QALY				
Scenario	Lower limit	Upper limit	Results of the lower limit (JPY/QALY)	Results of the upper limit (JPY/QALY)
Rate ratio of severe exacerbation	0.46	1.94	Dominant	9,048,398
Change in SGRQ-C	-6.44	-0.67	275,779	2,359,729
Health care cost of severe exacerbation	50%	200%	778,956	Dominant
Rate ratio of moderate exacerbation	0.63	1.21	213,249	839,825
Annual disease management cost	50%	200%	603,027	243,116
Time frame of the analysis (year)	5	10	719,698	529,790
Health care cost of moderate exacerbation	50%	200%	545,692	357,786
Change in FEV_1 (mL)	104	215	569,991	430,622
Discount rate	0%	4%	450,206	513,720

4.4 Revised scenario analysis

4.4.1 Cost-effectiveness analysis in population G, H, J, K, and L (Settings of utility)

Table 4-9 shows the results of the scenario analysis in which the utility was changed to the same value among the treatment groups in the cost-effectiveness analysis for the populations G, H, J, K, and L.

Table 4-9 The scenario analysis assuming that the utility was equivalent

Population	Description	Treatment	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER by academic group (JPY/QALY)
G	Prior therapy: ICS+LABA	FF/UMEC/VI	4.897	0.042	4,297,829	152,925	3,676,921
	EOS < 100/μL	FF/VI	4.855	-	4,144,904	-	-
H	Prior therapy: ICS+LABA	FF/UMEC/VI	4.944	0.064	4,222,901	77,997	1,214,796
	EOS ≥ 100/μL	FF/VI	4.879	-	4,144,904	-	-
J	Prior therapy: LAMA/LABA or LAMA	FF/UMEC/VI	4.945	0.068	3,843,478	-395,017	Dominant
	EOS ≥ 100/μL	UMEC/VI	4.876	-	4,238,495	-	-
K	Prior therapy: LAMA	FF/UMEC/VI	5.071	0.079	3,948,004	-196,900	Dominant
	EOS < 100/μL	FF/VI	4.992	-	4,144,904	-	-
L	Prior therapy: LAMA	FF/UMEC/VI	5.012	0.097	4,286,733	141,829	1,456,611
	EOS ≥ 100/μL	FF/VI	4.914	-	4,144,904	-	-

4.5 Interpretation of results

Table 4-10 to Table 4-21 show the interpretation of the results by academic group for population A~L.

Table 4-10 Interpretation of the results in population A

Population	Population A (Patients receiving triple therapy with two inhaled drugs, eosinophil count less than 100/μL)
Comparator technology	MITT (Triple-drug therapy with inhalation of 2 drug products)
Reference value for ICER	■ Regular product □ Product requiring special consideration
Intervals where ICER is most likely to belong	■ Cost reduction or dominant □ 5 million yen or less (7.5 million yen or less) □ More than 5 million yen (more than 7.5 million yen) and not more than 7.5 million yen (not more than 11.25 million yen) □ More than 7.5 million yen (more than 11.25 million yen) and not more than 10 million yen (not more than 15 million yen) □ More than 10 million yen (more than 15 million yen) □ Efficacy equivalent (or inferior) and expensive
Reason for such judgment	The results of base case analysis showed that it was cost saving compared to the comparator.

Table 4-11 Interpretation of the results in population B

Population	Population B (Patients receiving triple therapy with two inhaled drugs, eosinophil count more than 100/μL)
Comparator technology	MITT (Triple-drug therapy with inhalation of 2 drug products)
Reference value for ICER	■ Regular product □ Product requiring special consideration
Intervals where ICER is most likely to belong	■ Cost reduction or dominant □ 5 million yen or less (7.5 million yen or less) □ More than 5 million yen (more than 7.5 million yen) and not more than 7.5 million yen (not more than 11.25 million yen) □ More than 7.5 million yen (more than 11.25 million yen) and not more than 10 million yen (not more than 15 million yen) □ More than 10 million yen (more than 15 million yen) □ Efficacy equivalent (or inferior) and expensive
Reason for such judgment	The results of base case analysis showed that it was cost saving compared to the comparator.

Table 4-12 Interpretation of the results in population C

Population	Population C (Patients receiving triple therapy with two inhaled drugs, appropriate for step-down withdrawal from LAMA, and eosinophil count less than 100/μL)
Comparator technology	ICS/LABA
Reference value for ICER	■ Regular product □ Product requiring special consideration
Intervals where ICER is most likely to belong	☐ Cost reduction or dominant ☐ 5 million yen or less (7.5 million yen or less) ☐ More than 5 million yen (more than 7.5 million yen) and not more than 7.5 million yen (not more than 11.25 million yen) ☐ More than 7.5 million yen (more than 11.25 million yen) and not more than 10 million yen (not more than 15 million yen) ☐ More than 10 million yen (more than 15 million yen) ☐ Efficacy equivalent (or inferior) and expensive
Reason for such judgment	It was judged as "unable to analyze" because there was no clinical data.

Table 4-13 Interpretation of the results in population D

Population	Population D (Patients receiving triple therapy in inhaled formulations, for whom a step-down procedure to wean off LAMA is appropriate, and have an eosinophil count of 100/μL or higher)
Comparator technology	ICS/LABA
Reference value for ICER	■ Regular product □ Product requiring special consideration
Intervals where ICER is most likely to belong	☐ Cost reduction or dominant ☐ 5 million yen or less (7.5 million yen or less) ☐ More than 5 million yen (more than 7.5 million yen) and not more than 7.5 million yen (not more than 11.25 million yen) ☐ More than 7.5 million yen (more than 11.25 million yen) and not more than 10 million yen (not more than 15 million yen) ☐ More than 10 million yen (more than 15 million yen) ☐ Efficacy equivalent (or inferior) and expensive
Reason for such judgment	It was judged as "unable to analyze" because there was no clinical data.

Table 4-14 Interpretation of the results in population E

Population	Population E (Patients receiving triple therapy with two inhalation formulations, for whom a step-down from ICS is appropriate, and whose eosinophil count is less than 100/μL)
Comparator technology	LAMA/LABA
Reference value for ICER	■ Regular product □ Product requiring special consideration
Intervals where ICER is most likely to belong	☐ Cost reduction or dominant ☐ 5 million yen or less (7.5 million yen or less) ☐ More than 5 million yen (more than 7.5 million yen) and not more than 7.5 million yen (not more than 11.25 million yen) ☐ More than 7.5 million yen (more than 11.25 million yen) and not more than 10 million yen (not more than 15 million yen) ☐ More than 10 million yen (more than 15 million yen) ■ Efficacy equivalent (or inferior) and expensive
Reason for such judgment	It has not been shown to have additional benefit for populations where a step-down from ICS is clinically appropriate. "Cost increasing"

Table 4-15 Interpretation of the results in population F

Population	Population F (Patients receiving triple therapy with two inhalers, appropriate for step-down withdrawal from ICS, and eosinophil count ≥100/μL)
Comparator technology	LAMA/LABA
Reference value for ICER	■ Regular product □Product requiring special consideration
Intervals where ICER is most likely to belong	□ Cost reduction or dominant □ 5 million yen or less (7.5 million yen or less) □ More than 5 million yen (more than 7.5 million yen) and not more than 7.5 million yen (not more than 11.25 million yen) □ More than 7.5 million yen (more than 11.25 million yen) and not more than 10 million yen (not more than 15 million yen) □ More than 10 million yen (more than 15 million yen) ■ Efficacy equivalent (or inferior) and expensive
Reason for such judgment	It has not been shown to have additional benefit for populations where a step-down from ICS is clinically appropriate. "Cost increasing"

Table 4-16 Interpretation of the results in population G

Population	Population G (Patients receiving ICS/LABA combination therapy and eosinophil count less than 100/μL)
Comparator technology	ICS/LABA
Reference value for ICER	■ Regular product □ Product requiring special consideration
Intervals where ICER is most likely to belong	☐ Cost reduction or dominant ■ 5 million yen or less (7.5 million yen or less) ☐ More than 5 million yen (more than 7.5 million yen) and not more than 7.5 million yen (not more than 11.25 million yen) ☐ More than 7.5 million yen (more than 11.25 million yen) and not more than 10 million yen (not more than 15 million yen) ☐ More than 10 million yen (more than 15 million yen) ☐ Efficacy equivalent (or inferior) and expensive
Reason for such judgment	The results of base case analysis showed the ICER of JPY 1,833,684 /QALY. Although the one-way sensitivity analysis indicated that the ICER was below JPY 5 million/QALY in the main analysis, although the results suggested that the judgment on the cost-effectiveness of FF/UMEC/VI varied in some settings. Based on the above, the ICERs in this analysis population are most likely to belong to the interval below JPY 5 million/QALY.

Table 4-17 Interpretation of the results in population H

Population	Population H (Patients receiving ICS/LABA combination therapy and eosinophil count ≥100/μL)
Comparator technology	ICS/LABA
Reference value for ICER	■ Regular product □ Product requiring special consideration
Intervals where ICER is most likely to belong	□ Cost reduction or dominant ■ 5 million yen or less (7.5 million yen or less) □ More than 5 million yen (more than 7.5 million yen) and not more than 7.5 million yen (not more than 11.25 million yen) □ More than 7.5 million yen (more than 11.25 million yen) and not more than 10 million yen (not more than 15 million yen) □ More than 10 million yen (more than 15 million yen) □ Efficacy equivalent (or inferior) and expensive
Reason for such judgment	The results of base case analysis showed the ICER of JPY 328,585 /QALY. Also, the one-way sensitivity analysis and the scenario analysis both showed that it was under JPY 5 million/QALY. Based on the above, the ICERs in this analysis population are most likely to belong to the interval below JPY 5 million/QALY.

Table 4-18 Interpretation of the results in population I

Population	Population I (Patients who are receiving only LAMA or a combination therapy with LAMA/LABA in addition to their eosinophil count of < 100/μL)
Comparator technology	LAMA/LABA
Reference value for ICER	■ Regular product □ Product requiring special consideration
Intervals where ICER is most likely to belong	□ Cost reduction or dominant □ 5 million yen or less (7.5 million yen or less) □ More than 5 million yen (more than 7.5 million yen) and not more than 7.5 million yen (not more than 11.25 million yen) □ More than 7.5 million yen (more than 11.25 million yen) and not more than 10 million yen (not more than 15 million yen) □ More than 10 million yen (more than 15 million yen) ■ Efficacy equivalent (or inferior) and expensive
Reason for such judgment	No additional benefit has been shown. "Cost increasing"

Table 4-19 Interpretation of the results in population J

Population	Population J (Patients receiving LAMA monotherapy or LAMA/LABA combination therapy with eosinophil count ≥100/μL)
Comparator technology	LAMA/LABA
Reference value for ICER	■ Regular product □ Product requiring special consideration
Intervals where ICER is most likely to belong	■ Cost reduction or dominant □ 5 million yen or less (7.5 million yen or less) □ More than 5 million yen (more than 7.5 million yen) and not more than 7.5 million yen (not more than 11.25 million yen) □ More than 7.5 million yen (more than 11.25 million yen) and not more than 10 million yen (not more than 15 million yen) □ More than 10 million yen (more than 15 million yen) □ Efficacy equivalent (or inferior) and expensive
Reason for such judgment	The results of base case analysis showed that FF/UMEC/VI became dominant. Also, the one-way sensitivity analysis and the scenario analysis both showed that it would be cost saving or dominant. Based on the above, the ICER in the target population is most likely to be cost-saving or dominant.

Table 4-20 Interpretation of the results in population K

Population	Population K (Patients receiving LAMA monotherapy and eosinophil count less than 100/μL)
Comparator technology	ICS/LABA
Reference value for ICER	■ Regular product □ Product requiring special consideration
Intervals where ICER is most likely to belong	■ Cost reduction or dominant □ 5 million yen or less (7.5 million yen or less) □ More than 5 million yen (more than 7.5 million yen) and not more than 7.5 million yen (not more than 11.25 million yen) □ More than 7.5 million yen (more than 11.25 million yen) and not more than 10 million yen (not more than 15 million yen) □ More than 10 million yen (more than 15 million yen) □ Efficacy equivalent (or inferior) and expensive
Reason for such judgment	The results of base case analysis showed that FF/UMEC/VI became dominant. Also, the one-way sensitivity analysis and the scenario analysis both showed that it would be cost saving or dominant. Based on the above, the ICER in the target population is most likely to be cost-saving or dominant.

Table 4-21 Interpretation of the results in population L

Population	Population L (Patients receiving LAMA monotherapy and eosinophil count ≥100/μ)
Comparator technology	ICS/LABA
Reference value for ICER	■ Regular product □ Product requiring special consideration
Intervals where ICER is most likely to belong	□ Cost reduction or dominant ■ 5 million yen or less (7.5 million yen or less) □ More than 5 million yen (more than 7.5 million yen) and not more than 7.5 million yen (not more than 11.25 million yen) □ More than 7.5 million yen (more than 11.25 million yen) and not more than 10 million yen (not more than 15 million yen) □ More than 10 million yen (more than 15 million yen) □ Efficacy equivalent (or inferior) and expensive
Reason for such judgment	The results of base case analysis showed the ICER of JPY 483,056/QALY. Although the one-way sensitivity analysis indicated that the ICER was below JPY 5 million/QALY in the main analysis, although the results suggested that the judgment on the cost-effectiveness of FF/UMEC/VI varied in some settings. Based on the above, the ICERs in this analysis population are most likely to belong to the interval below JPY 5 million/QALY.

4.6 Proportion of patients in the analyzed population

4.6.1 Methods and results of estimating the proportion of patients

The manufacturer sets the proportion of the patients based on the target population in IMPACT study. Since the IMPACT study is an RCT, it may not reflect the actual proportion of patients in clinical practice in Japan. The proportion of patients in the analyzed population was estimated using the anonymous receipt information and anonymous specific health checkup information database.
In December 2019, the target population was patients with COPD and a combination of three components (ICS/LABA/LAMA) or two components (ICS/LABA or LABA/LAMA) of the target drugs shown in Table 4-22 were recorded as the same prescription in medical outpatient or dispensing receipts. The target population was those with three components (ICS/LABA/LAMA) or two components (ICS/LABA or LABA/LAMA) recorded as the same prescription. However, if there were multiple prescriptions in December 2019, the most recent prescription was included. The combinations of 1 to 3 components of the target drug that occurred in the prescriptions prior to the prescriptions identified above and were consistent with the previous treatment of the target population were counted. If the previous prescription did not occur before January 2019, the patient was excluded. To divide the target population by eosinophil count, we used the proportion of patients based on the IMPACT study as described in the manufacturer report (Table 4-23), because this database does not contain eosinophil count data. As a result, the total number of eligible patients was 456,635, of which 424,339 met the pretreatment criteria for the analysis population. The percentage of patients is shown in Table 4-24.
The proportion of patients in the analysis group C and D is 0%, because clinicians believe that patients receiving triple therapy are unlikely to be stepped down to LAMA only.

Table 4-22 Target medicines

Claims computerized processing system code	Product name
621929601	Asmanex Twisthaler 100 µg 60 doses, 6 mg 100 µg
622014501	Asmanex Twisthaler 200 µg 60 doses, 12mg
620004885	Adoair 100 Diskus, 28 blisters
620007565	Adoair 100 Diskus, 60 blisters
621781401	Adoair 100 Diskus 28 puffs, 28 blisters
621829501	Adoair 100 Diskus 60 puffs, 60 blisters
621981201	Adoair 125 Aerosol 120 puffs, 12.0 g
621981301	Adoair 250 Aerosol 120 puffs, 12.0 g
620004886	Adoair 250 Diskus 28 blisters
620007566	Adoair 250 Diskus 60 blisters
621781501	Adoair 250 Diskus 28 puffs, 28 blisters
621829601	Adoair 250 Diskus 60 puffs, 60 blisters
620004887	Adoair 500 Diskus 28 blisters
620007567	Adoair 500 Diskus 60 blisters
621781601	Adoair 500 Diskus 28 puffs, 28 blisters
621829701	Adoair 500 Diskus 60 puffs, 60 blisters
620009104	Adoair 50 Air 120 puffs, 12.0 g
621895501	Adoair 50 Aerosol 120 puffs, 12.0 g
622552201	Arnuity 100 µg Ellipta 30 doses
622552301	Arnuity 200 µg Ellipta 30 doses
622426401	Anoro Ellipta 30 doses
622363901	Anoro Ellipta 7 doses
622287701	Ultibro inhalation capsules
622414701	Eklira 400 µg Genuair 30 doses
622414801	Eklira 400 µg Genuair 60 doses
622415901	Encruse 62.5 µg Ellipta 30 puffs
622415801	Encruse 62.5 µg Ellipta 7 puffs
622180901	Oxis 9 µg Turbuhaler 28 doses, 252 µg (9 µg)
622277401	Oxis 9 µg Turbuhaler 60 doses, 540 µg (9 µg)
620004889	Alvesco 100 µg Inhaler 112 puffs, 11.2 mg 6.6 g
622057501	Alvesco 100 µg Inhaler 56 puffs, 5.6 mg 3.3 g
620004890	Alvesco 200 µg Inhaler 56 puffs, 11.2 mg 3.3 g
620004888	Alvesco 50 µg Inhaler 112 puffs, 5.6 mg 6.6 g
622096401	Onbrez inhalation capsules 150 µg

660462002	Qvar 100 Aerosol 15 mg 8.7 g
660462001	Qvar 50 Aerosol 7 mg 8.7 g
622210401	Seebri inhalation capsules 50 µg
621950701	Symbicort Turbuhaler 30 doses
621950801	Symbicort Turbuhaler 60 doses
622450101	Spiolto Respimat 28 puffs
622450201	Spiolto Respimat 60 puffs
622507801	Spiriva 1.25 µg Respimat 60 puffs, 75 µg
621984201	Spiriva 2.5 µg Respimat 60 puffs, 150 µg
620002421	Spiriva inhalation capsules 18 µg
660462003	Serevent 25 Rotadisk 25 µg
620001944	Serevent 50 Diskus, 50 µg 60 blisters
660462004	Serevent 50 Rotadisk, 50 µg
622678801	Trelegy 100 Ellipta 14 doses
622678901	Trelegy 100 Ellipta 30 doses
620005290	Pulmicort 100 µg Turbuhaler 112 doses, 11.2 mg
620005292	Pulmicort 200 µg Turbuhaler 112 doses, 22.4 mg
620005291	Pulmicort 200 µg Turbuhaler 56 doses, 11.2 mg
620004366	Pulmicort Respules 0.25 mg, 2 mL
620004367	Pulmicort Respules 0.5 mg, 2 mL
622687001	Breztri Aerosphere 56 inhalations
622700201	BudeForu Drypowder inhaler 30 doses “JG”
622702601	BudeForu Drypowder inhaler 30 doses “MYL”
622816601	BudeForu Drypowder inhaler 30 doses “Nipro”
622700301	BudeForu Drypowder inhaler 60 doses “JG”
622702701	BudeForu Drypowder inhaler 60 doses “MYL”
622816701	BudeForu Drypowder inhaler 60 doses “Nipro”
621572201	Flutide 100 µg Aerosol 60 puffs, 11.67 mg 7.0 g
620000453	Flutide 100 Air 12.25 mg 7.0 g
660451013	Flutide 100 Diskus 100 µg 60 blisters
660421113	Flutide 100 Rotadisk 100 µg
660451016	Flutide 200 Diskus 200 µg 60 blisters
660421114	Flutide 200 Rotadisk 200 µg
621512601	Flutide 50 µg Aerosol 120 puffs, 8.83 mg 10.6 g
660462011	Flutide 50 Air 9.72 mg 10.6 g
660451012	Flutide 50 Diskus 50 µg 60 blisters
660421112	Flutide 50 Rotadisk 50 µg

622278201	Flutiform 125 Aerosol 120 puffs
622278001	Flutiform 125 Aerosol 56 puffs
622278101	Flutiform 50 Aerosol 120 puffs
622277901	Flutiform 50 Aerosol 56 puffs
622279201	Relvar 100 Ellipta 14 doses
622375501	Relvar 100 Ellipta 30 doses
622279301	Relvar 200 Ellipta 14 doses
622375601	Relvar 200 Ellipta 30 doses

Table 4-23 Proportion of patients by eosinophil count based on IMPACT study

	Eosinophil count < 100		Eosinophil count ≥ 100		
Population	n	%	Population	n	%
A,C,E	961	24%	B,D,F	3,004	76%
G	768	26%	H	2,202	74%
I,K	411	25%	J,L	1,243	75%

Prepared from values reported by the manufacturer

Table 4-24 Proportion of patients

A prescription before A		A: A combination of prescriptions in December 2019	Population			Proportion of patients					
				n	%		n	%		n	%
Triple-drug therapy	ICS/LABA/LAMA	ICS/LABA/LAMA	A+B	78,138	18.4%	A	18,938	4.5%	B	59,200	14.0%
		LAMA/LABA	E+F	1,244	0.3%	E	302	0.1%	F	942	0.2%
Dual-drug therapy	ICS/LABA	ICS/LABA/LAMA	G+H	230,099	54.2%	G	59,500	14.0%	H	170,599	40.2%
		ICS/LABA									
	LAMA/LABA	ICS/LABA/LAMA	I+J	111,025	26.2%	I	27,588	6.5%	J	83,437	19.7%
		LAMA/LABA									
Single drug	LAMA	LAMA/LABA									
		ICS/LABA/LAMA	K+L	3,833	0.9%	K	952	0.2%	L	2,881	0.7%
		ICS/LABA									
		Total		424,339	100.0%		107,281	25.3%		317,058	74.7%

As to the populations C and D, the proportion of the patient number is treated as 0%.

Table 4-25 Summary of the results

Population	Proportion of patients	Additional benefit	ICER
A	4.5%	Not shown	Cost saving
B	14.0%	Not shown	Cost saving
C	0%	"Unable to analyze"	
D	0%	"Unable to analyze"	
E	0.1%	Not shown	Cost increasing
F	0.2%	Not shown	Cost increasing
G	14.0%	Yes	< JPY 5 million/QALY
H	40.2%	Yes	< JPY 5 million/QALY
I	6.5%	Not shown	Cost increasing
J	19.7%	Yes	Dominant
K	0.2%	Yes	Dominant
L	0.7%	Yes	< JPY 5 million/QALY

5. References

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6. Supplementary material

Table A-1 Summary of subgroup analysis studies

Study name	FULFIL Subgroup analysis	FULFIL Subgroup analysis	FULFIL Subgroup analysis	IMPACT Subgroup analysis
Title of article	Preventing clinically important deterioration with single-inhaler triple therapy in COPD	Single-inhaler triple therapy in symptomatic COPD patients: FULFIL subgroup analyses	The Efficacy and Safety of Once-daily Fluticasone Furoate/Umeclidinium/Vilanterol Versus Twice-daily Budesonide/Formoterol in a Subgroup of Patients from China with Symptomatic COPD at Risk of Exacerbations (FULFIL Trial)	The IMPACT Study – Single Inhaler Triple Therapy (FF/UMEC/VI) Versus FF/VI And UMEC/VI In Patients With COPD: Efficacy And Safety In A Japanese Population
Author name	Naya I, et al.	Halpin DMG, et al.	Zheng J, et al.	M Kato et al.
Bibliographic information	ERJ Open Res. 2018;4: 00047-2018.	COPD. 2018;15(4):334-340.	ERJ Open Res. 2018;4(2). pii: 00119-2017.	Int J Chron Obstruct Pulmon Dis. 2019;14:2849–2861.
Test location	Multicenter (16 countries)	Multicenter (16 countries)	Multicenter (16 countries)	Multicenter (37 countries)
Study enrollment period	From January 2015 to April 2016	From January 2015 to April 2016	From January 2015 to April 2016	From June 2014 to July 2017
Target population	≥ 40 years old, diagnosed as COPD, CAT ≥ 10, receiving a maintenance therapy, has a history of exacerbation within	≥ 40 years old, diagnosed as COPD, CAT ≥ 10, receiving a maintenance therapy, has a history of exacerbation within	≥ 40 years old, diagnosed as COPD, CAT ≥ 10, receiving a maintenance therapy, has a history of exacerbation within	≥ 40 years old, diagnosed as COPD, has a history of smoking, CAT ≥ 10, $FEV_1/FVC < 0.7$, receiving a maintenance therapy, has a

	previous 12 months etc. (A paper for evaluation of clinical important difference: CID)	previous 12 months etc. (A subgroup analysis by prior therapy, severity, and a history of exacerbation)	previous 12 months etc. (A subgroup analysis in China)	history of exacerbation within previous 12 months etc. (subgroup analysis in Japan)
Key exclusion criteria	A patient who has asthma at present, a patient who has unresolved pneumonia/exacerbation etc.	A patient who has asthma at present, a patient who has unresolved pneumonia/exacerbation etc.	A patient who has asthma at present, a patient who has unresolved pneumonia/exacerbation etc.	A patient who has asthma at present, a patient who has other respiratory diseases, a person who has experienced exacerbation before a study or during a run-in period etc.
Details of intervention method	Trelegy group (n = 911 24 weeks, n = 210 24 weeks): FF/UMEC/VI 100 mcg/62.5 mcg/25 mcg	Trelegy group (n=911 24 weeks, n=210 24 weeks): FF/UMEC/VI 100 mcg/62.5 mcg/25 mcg	Trelegy group (n=911 24 weeks, n=210 24 weeks): FF/UMEC/VI 100 mcg/62.5 mcg/25 mcg	Trelegy group (n=4151): FF/UMEC/VI 100 mcg/62.5 mcg/25 mcg
Details of comparator	ICS/LABA group (n=899 24 weeks, n=220 52 weeks): BUD/FOR 400mcg/12 mcg	ICS/LABA group (n=899 24 weeks, n=220 52 weeks): BUD/FOR 400mcg/12 mcg	ICS/LABA group (n=899 24 weeks, n=220 52 weeks): BUD/FOR 400mcg/12 mcg	ICS/LABA groups (n=4134): FF/VI 100 mcg/25 mcg LAMA/LABA groups (n=2070): UMEC/VI 62.5 mcg/25 mcg
Study design	Phase III, RCT	Phase III, RCT	Phase III, RCT	Phase III, RCT
Blinding method	Double-blind	Double-blind	Double-blind	Double-blind

Primary endpoint	- Change in FEV_1 (24 weeks) - Change in FEV_1 (52 weeks) - Change in SGRQ (24 weeks) - Change in SGRQ (52 weeks)	- Change in FEV_1 (24 weeks) - Change in FEV_1 (52 weeks) - Change in SGRQ (24 weeks) - Change in SGRQ (52 weeks)	- Change in FEV_1 (24 weeks) - Change in FEV_1 (52 weeks) - Change in SGRQ (24 weeks) - Change in SGRQ (52 weeks)	Incidence of moderate/severe exacerbation event (52 weeks)
Key secondary endpoints	- Incidence of moderate/severe exacerbation event (24 weeks) - Incidence of moderate/severe exacerbation event (52 weeks) etc.	- Incidence of moderate/severe exacerbation event (24 weeks) - Incidence of moderate/severe exacerbation event (52 weeks) etc.	- Incidence of moderate/severe exacerbation event (24 weeks) - Incidence of moderate/severe exacerbation event (52 weeks) etc.	- Change in FEV_1 - Change in SGRQ - Time to first incidence of moderate/severe exacerbation event - Incidence of moderate/severe exacerbation event (Population with ≥ eosinophil count 150)、 - Time to first incidence of moderate/severe exacerbation event (Population with ≥ eosinophil count 150) ・Incidence of severe exacerbation event
Statistical methods	- Amount of change is analyzed with MMRM - Incidence of exacerbation	- Amount of change is analyzed with MMRM - Incidence of exacerbation	- Amount of change is analyzed with MMRM - Incidence of exacerbation	- Incidence of exacerbation is analyzed with the generalized linear model

	is analyzed with the generalized linear model assuming a negative binomial distribution	is analyzed with the generalized linear model assuming a negative binomial distribution	is analyzed with the generalized linear model assuming a negative binomial distribution	assuming a negative binomial distribution - Amount of change is analyzed with MMRM - Time to event is analyzed with Cox proportional-hazards model

Table A-2 Bayesian interpretation of rate ratios of exacerbation

Target population	[1] Point estimate of a rate ratio	[2] Lower limit of 95% CI of a rate ratio	[3] Upper limit of 95% CI of a rate ratio	[4] Point estimate of a rate ratio (logarithm)	[5] Lower limit of 95% CI of a rate ratio (logarithm)	[6] Upper limit of 95% CI of a rate ratio (logarithm)	[7] SE of a rate ratio (logarithm)	[8] Probability of a rate ratio to be 1 or less	[9] Probability of a rate ratio to be 1 or more	[10] Probability of a rate ratio to be 0.95 or less	[11] Probability of a rate ratio to be 0.95 or more
C	0.83	0.69	0.99	-0.19	-0.37	-0.01	0.09	97.85%	2.15%	92.87%	7.13%
D	0.86	0.77	0.95	-0.15	-0.26	-0.05	0.05	99.76%	0.24%	96.84%	3.16%
E	0.78	0.63	0.97	-0.25	-0.46	-0.03	0.11	98.80%	1.20%	96.33%	3.67%
F	0.67	0.59	0.76	-0.40	-0.53	-0.27	0.06	100.00%	0.00%	100.00%	0.00%
G	0.78	0.61	1.00	-0.25	-0.49	0.00	0.13	97.56%	2.44%	94.10%	5.90%
H	0.82	0.71	0.95	-0.20	-0.34	-0.05	0.07	99.62%	0.38%	97.62%	2.38%
I	1.37	0.83	2.24	0.31	-0.19	0.81	0.25	10.69%	89.31%	7.42%	92.58%
J	0.81	0.65	1.01	-0.21	-0.43	0.01	0.11	96.95%	3.05%	92.19%	7.81%
K	0.67	0.41	1.09	-0.40	-0.89	0.09	0.25	94.58%	5.42%	91.92%	8.08%
L	0.87	0.64	1.19	-0.14	-0.45	0.17	0.16	81.06%	18.94%	71.09%	28.91%

Assuming that the distributions of rate ratio from the clinical trial were posterior distributions for treatment effect (lognormal distribution was assumed), the probability that the rate ratio of exacerbations would be less than 1 (FF/UMEC/VI is superior) and the probability that the rate ratio of exacerbations would be less than 0.95 (FF/UMEC/VI is associated with a risk reduction of 5% or more) was calculated, respectively.

Excel computational expression

[4]=LN([1]), [5]=LN([2]), [6]=LN([3]), [7]=([6]-[5])/(1.96*2), [8]=NORM.DIST(LN(1), [4], [7], TRUE), [9]=1-[8], [10]=NORM.DIST(LN(0.95), [4], [7], TRUE), [11]=1-[10]

Table A-3 Revisions of the model (Settings of background factors)
Sheet "Baseline Demographics"
Before change

Parameters	FF/VI		FF/UMEC/VI	
Gender	%		%	
Female	34%		34%	
Male	66%		66%	
	mean	SE	mean	SE
Age	65.3	0.08	65.3	0.08
BMI	%		%	
Low (<21, %)	17%		17%	
Med (21-30, %)	58%		58%	
High (>30, %)	25%		25%	
Any CVD Comorbidity (%)	44%		44%	
Without Comorbidity	56%		56%	
Any Other Comorbidity (%)	57%		57%	
Without comorbidity	43%		43%	
0 Prior Exacerbations at baseline (%)	0%		0%	
History of exacerbation, 1 or more (%)	100%		100%	
mMRC score >= 2 (%)	37%		37%	
Score of 0 or 1 (%)	63%		63%	
Current Smokers (%)	35%		35%	
Former Smokers (%)	65%		65%	
	Mean	SE	Mean	SE
Height (cm)	167.50	0.09	167.50	0.09
Fibrinogen (ug/dl)	477.46	2.37	477.46	2.37

Number of Moderate and Severe Exacerbations in Prior Year (Average per person)		1.71	0.01		1.71	0.01
Moderate Exacerbations	82%	1.41		82%	1.41	
Severe Exacerbations	18%	0.30		18%	0.30	
Starting SGRQ-C or SGRQ	SGRQ	50.70	0.25	SGRQ	50.70	0.25
Resulting HRQL		0.676			0.676	
Starting FEV_1% Predicted		45.50%	0.15%		45.50 %	0.15%
Resulting FEV_1		1215.3			1215.3	
6 Minute Walk Distance (meters)		365.79	2.74		365.79	2.74

After change

Parameters	FF/VI		FF/UMEC/VI	
Gender	%		%	
Female	7.14%		7.14%	
Male	92.86%		92.86%	
	mean	SE	mean	SE
Age	70.54	0.37	70.54	0.37
BMI	%		%	
Low (<21, %)	38.62%		38.62%	
Med (21-30, %)	59.53%		59.53%	
High (>30, %)	1.85%		1.85%	
Any CVD Comorbidity (%)	33.60%		33.60%	
Without Comorbidity	66.40%		66.40%	
Any Other Comorbidity (%)	55.03%		55.03%	
Without comorbidity	44.97%		44.97%	
0 Prior Exacerbations at baseline (%)	0.00%		0.00%	
History of exacerbation, 1 or more (%)	100.00 %		100.00 %	
mMRC score >= 2 (%)	22.28%		22.28%	
Score of 0 or 1 (%)	77.72%		77.72%	
Current Smokers (%)	24.07%		24.07%	
Former Smokers (%)	75.93%		75.93%	
	Mean	SE	Mean	SE
Height (cm)	163.99	0.36	163.99	0.36
Fibrinogen (ug/dl)	468.76	2.37	468.76	2.37

Number of Moderate and Severe Exacerbations in Prior Year (Average per person)		1.72	0.06		1.72	0.06
Moderate Exacerbations	79%	1.36		79%	1.36	
Severe Exacerbations	21%	0.37		21%	0.37	
Starting SGRQ-C or SGRQ	SGRQ	40.34	0.79	SGRQ	40.34	0.79
Resulting HRQL		0.777			0.777	
Starting FEV_1% Predicted		50.19%	0.81 %		50.19%	0.81 %
Resulting FEV_1		1248.3			1248.3	
6 Minute Walk Distance (meters)		387.91	2.74		387.91	2.74

Table A-4 Revisions of the model (Settings of survival probability)

	Before change	After change
Sheet ”RefDrug” (R44-R75)	=IF(R43<0.01,0,(EXP(-((_t*365.25*EXP(-(_I+MMULT($G44:$H44,R$6:R$7)+R$29*$J44+MMULT($L44:$O44,R$30:R$33)+_fWScale)))^(1/$R$34)))))	=AVERAGE(IF(R43<0.01,0,(EXP(-((_t*365.25*EXP(-(_I+MMULT($G44:$H44,R$6:R$7)+R$29*$J44+MMULT($L44:$O44,R$30:R$33)+_fWScale)))^(1/$R$34)))),IF(drug!R43<0.01,0,(EXP(-((_t*365.25*EXP(-(_I+MMULT(drug!$G44:drug!$H44,drug!R$6:drug!R$7)+drug!R$29*drug!$J44+MMULT(drug!$L44:drug!$O44,drug!R$30:drug!R$33)+_fWScale)))^(1/drug!$R$34))))))
Sheet ”RefDrug” (R123-R154)	=IF(R122<0.01,0,(EXP(-(($E123*365.25*EXP(-(_I+MMULT($G123:$H123,R$6:R$7)+R$29*$J123+MMULT($L123:$O123,R$30:R$33)+_fWScale)))^(1/$R$34)))))	=R44
Sheet ”drug” (R44-R75)	=IF(R43<0.01,0,(EXP(-((_t*365.25*EXP(-(_I+MMULT($G44:$H44,R$6:R$7)+R$29*$J44+MMULT($L44:$O44,R$30:R$33)+_fWScale)))^(1/$R$34)))))	=AVERAGE(IF(R43<0.01,0,(EXP(-((_t*365.25*EXP(-(_I+MMULT($G44:$H44,R$6:R$7)+R$29*$J44+MMULT($L44:$O44,R$30:R$33)+_fWScale)))^(1/$R$34)))),IF(RefDrug!R43<0.01,0,(EXP(-((_t*365.25*EXP(-(_I+MMULT(RefDrug!$G44:RefDrug!$H44,RefDrug!R$6:RefDrug!R$7)+RefDrug!R$29*RefDrug!$J44+MMULT(RefDrug!$L44:RefDrug!$O44,RefDrug!R$30:RefDrug!R$33)+_fWScale)))^(1/RefDrug!$R$34))))))
Sheet ”drug” (R123-R154)	=IF(R122<0.01,0,(EXP(-(($E123*365.25*EXP(-(_I+MMULT($G123:$H123,R$6:R$7)+R$29*$J123+MMULT($L123:$O123,R$30:R$33)+_fWScale)))^(1/$R$34)))))	=R44

Table A-5 Revisions of the model (Settings of utility)

	Before change	After change
Sheet ”RefDrug” (Q43-Q75)	=IF(R43=0,0,(IF(0.9617 - 0.0013*(P43*0.9+3.1) - 0.0001*(P43*0.9+3.1)^2 + 0.0231*(1-$Z$14)<0,0,0.9617 - 0.0013*(P43*0.9+3.1) - 0.0001*(P43*0.9+3.1)^2 + 0.0231*(1-$Z$14))))*Utility_SA	=IF(R43=0,0,AVERAGE(IF(R43=0,0,(IF(0.9617 - 0.0013*(P43*0.9+3.1) - 0.0001*(P43*0.9+3.1)^2 + 0.0231*(1-$Z$14)<0,0,0.9617 - 0.0013*(P43*0.9+3.1) - 0.0001*(P43*0.9+3.1)^2 + 0.0231*(1-$Z$14)))),IF(drug!R43=0,0,(IF(0.9617 - 0.0013*(drug!P43*0.9+3.1) - 0.0001*(drug!P43*0.9+3.1)^2 + 0.0231*(1-drug!$Z$14)<0,0,0.9617 - 0.0013*(drug!P43*0.9+3.1) - 0.0001*(drug!P43*0.9+3.1)^2 + 0.0231*(1-drug!$Z$14))))))*Utility_SA
Sheet ”RefDrug” (Q122-Q154)	=IF(R122=0,0,(IF(0.9617 - 0.0013*(P122*0.9+3.1) - 0.0001*(P122*0.9+3.1)^2 + 0.0231*(1-$Z$14)<0,0,0.9617 - 0.0013*(P122*0.9+3.1) - 0.0001*(P122*0.9+3.1)^2 + 0.0231*(1-$Z$14))))*Utility_SA	=Q43

Sheet ”drug” (Q43-Q75)	=IF(R43=0,0,(IF(0.9617 - 0.0013*(P43*0.9+3.1) - 0.0001*(P43*0.9+3.1)^2 + 0.0231*(1-$Z$14)<0,0,0.9617 - 0.0013*(P43*0.9+3.1) - 0.0001*(P43*0.9+3.1)^2 + 0.0231*(1-$Z$14))))*Utility_SA	=IF(RefDrug!R43=0,IF(R43=0,0,(IF(0.9617 - 0.0013*(P43*0.9+3.1) - 0.0001*(P43*0.9+3.1)^2 + 0.0231*(1-$Z$14)<0,0,0.9617 - 0.0013*(P43*0.9+3.1) - 0.0001*(P43*0.9+3.1)^2 + 0.0231*(1-$Z$14)))),AVERAGE(IF(R43=0,0,(IF(0.9617 - 0.0013*(P43*0.9+3.1) - 0.0001*(P43*0.9+3.1)^2 + 0.0231*(1-$Z$14)<0,0,0.9617 - 0.0013*(P43*0.9+3.1) - 0.0001*(P43*0.9+3.1)^2 + 0.0231*(1-$Z$14)))),IF(RefDrug!R43=0,0,(IF(0.9617 - 0.0013*(RefDrug!P43*0.9+3.1) - 0.0001*(RefDrug!P43*0.9+3.1)^2 + 0.0231*(1-RefDrug!$Z$14)<0,0,0.9617 - 0.0013*(RefDrug!P43*0.9+3.1) - 0.0001*(RefDrug!P43*0.9+3.1)^2 + 0.0231*(1-RefDrug!$Z$14))))))*Utility_SA
Sheet ”drug” (Q122-Q154)	=IF(R122=0,0,(IF(0.9617 - 0.0013*(P122*0.9+3.1) - 0.0001*(P122*0.9+3.1)^2 + 0.0231*(1-$Z$14)<0,0,0.9617 - 0.0013*(P122*0.9+3.1) - 0.0001*(P122*0.9+3.1)^2 + 0.0231*(1-$Z$14))))*Utility_SA	=Q43

Table A-6 Results of the cost-effectiveness evaluation using a cutoff of 150/μL for eosinophil count

Population	Description	Treatment	Effectiveness(QALY)	Incremental effectiveness (QALY)	Cost (JPY)	Incremental cost (JPY)	ICER by the academic group (JPY/QALY)	ICER by the manufacturer (JPY/QALY)
A+B (CMA)	Prior therapy: MITT	FF/UMEC/VI	-	-	107,721	-18,189	Cost saving	Cost saving
		MITT	-	-	125,910	-	-	-
C (Unable to be analyzed)	Prior therapy: MITT	FF/UMEC/VI	-	-	-	-	Unable to be analyzed	691,075
	EOS < 100/μL	FF/VI	-	-	-	-	-	-
D (Unable to be analyzed)	Prior therapy: MITT	FF/UMEC/VI	-	-	-	-	Unable to be analyzed	Dominant
	EOS ≥ 100/μL	FF/VI	-	-	-	-	-	-
E (CMA)	Prior therapy: MITT	FF/UMEC/VI	-	-	107,721	18,114	Cost increasing	580,531
	EOS < 100/μL	UMEC/VI	-	-	89,608	-	-	-
F (CMA)	Prior therapy: MITT	FF/UMEC/VI	-	-	107,721	18,114	Cost increasing	Dominant
	EOS ≥ 100/μL	UMEC/VI	-	-	89,608	-	-	-
G (CEA)	Prior therapy: ICS+LABA	FF/UMEC/VI	5.537	0.066	3,381,419	216,775	3,297,647	2,435,085
	EOS < 100/μL	FF/VI	5.471	-	3,164,643	-	-	-
H (CEA)	Prior therapy: ICS+LABA	FF/UMEC/VI	5.560	0.070	3,104,397	-78,643	Dominant	Dominant
	EOS ≥ 100/μL	FF/VI	5.490	-	3,183,040	-	-	-
I	Prior therapy:	FF/UMEC/VI	-	-	107,721	18,114	Cost increase	1,163,973

(CMA)	LAMA/LABA or LAMA							
	EOS < 100/μL	UMEC/VI	-	-	89,608	-	-	-
J (CEA)	Prior therapy: LAMA/LABA or LAMA	FF/UMEC/VI	5.556	0.066	2,935,405	-341,183	Dominant	Dominant
	EOS ≥ 100/μL	UMEC/VI	5.491	-	3,276,588	-	-	-
K (CEA)	Prior therapy: LAMA	FF/UMEC/VI	5.718	0.184	3,046,167	-174,297	Dominant	Dominant
	EOS < 100/μL	FF/VI	5.534	-	3,220,465	-	-	-
L (CEA)	Prior therapy: LAMA	FF/UMEC/VI	5.629	0.049	3,198,358	-60,494	Dominant	29,275
	EOS ≥ 100/μL	FF/VI	5.580	-	3,258,852	-	-	-

The result of additional benefit assessment was assumed to be the same as in a case setting 100/μL as a cut-off value of eosinophil count.