




# Efficacy and safety of once-daily single-inhaler triple therapy for mild-to-moderate chronic obstructive pulmonary disease: a study protocol for a randomised and interventional study

Koichiro Takahashi <sup>1</sup>, Tomotaka Kawayama,<sup>2</sup> Ayako Takamori,<sup>3</sup> Hiroki Tashiro,<sup>1</sup> Takashi Kinoshita,<sup>2</sup> Koichi Takagi,<sup>4</sup> Kei Yamasaki,<sup>5</sup> Kentaro Machida,<sup>4</sup> Atsushi Kawaguchi,<sup>6</sup> Kazuhiro Yatera <sup>5</sup>, Hiromasa Inoue <sup>4</sup>, TRACK (Triple therapy for Japanese with mild to moderate COPD in Kyushu) study investigator group

**To cite:** Takahashi K, Kawayama T, Takamori A, et al. Efficacy and safety of once-daily single-inhaler triple therapy for mild-to-moderate chronic obstructive pulmonary disease: a study protocol for a randomised and interventional study. *BMJ Open Res* 2023;10:e001607. doi:10.1136/bmjresp-2022-001607

Received 30 December 2022  
Accepted 20 April 2023



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

## Correspondence to

Dr Koichiro Takahashi; takahak@cc.saga-u.ac.jp

## ABSTRACT

**Introduction** Bronchodilators, including long-acting muscarinic antagonists (LAMA) and long-acting beta 2 agonists (LABA), are the main treatments for chronic obstructive pulmonary disease (COPD). The efficacy of triple therapy (inhaled corticosteroids/LAMA/LABA) has also been reported. However, the effect of triple therapy on patients with mild-to-moderate COPD has not yet been clarified. This study aims to investigate the safety and efficacy of triple therapy, compared with LAMA/LABA combination therapy, for lung function and health-related quality of life in patients with mild-to-moderate COPD and identify baseline characteristics and biomarkers to predict responders and non-responders to triple therapy.

**Methods and analysis** This is a multicentre, prospective, open-label, randomised, parallel-group study. Mild-to-moderate patients with COPD will be randomised to receive fluticasone furoate/umeclidinium/vilanterol or umeclidinium/vilanterol for 24 weeks. A total of 668 patients will be enrolled from March 2022 to September 2023 from 38 sites in Japan. The primary endpoint is the change in the trough forced expiration volume in 1 s after 12 weeks of treatment. Secondary endpoints are responder rates based on the COPD assessment test score and the St. George's Respiratory Questionnaire total score after 24 weeks of treatment. The safety endpoint is the occurrence of any adverse events. We will also investigate safety in terms of changes in microbial colonisation in sputum and antimycobacterium avium complex antibodies.

**Ethics and dissemination** The study protocol and informed consent documents were approved by the Saga University Clinical Research Review Board (approval number: CRB7180010). Written informed consent will be obtained from all patients. Recruitment of the patients began in March 2022. The results will be disseminated through scientific peer-reviewed publications and domestic and international medical conferences.  
**Trial registration numbers** UMIN000046812 and jRCTs031190008.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by progressive

airflow limitation which results in dyspnoea, decreased quality of life (QOL) and decreased exercise capacity.<sup>1</sup> In 2015, COPD ranked third for a global age-standardised cause of death, accounting for approximately 3 million deaths.<sup>2</sup> One worldwide study reported that the prevalence of COPD is around 10% in people over 40 years of age.<sup>3</sup>

A Japanese epidemiological study demonstrated that 10.9% of people presented with airway limitation, and the severity of obstruction according to the Global Initiative for COPD (GOLD) criteria was mild, 56%; moderate, 38%; severe, 5% and very severe, 1%.<sup>4</sup> Among people with airway limitation, 78.9% (estimate 5.3 million people (8.6% of population aged >40 years)) and 21.1% (estimate 1.4 million people (2.3% of people aged >40 years)) were diagnosed with COPD and COPD with asthmatic symptoms (asthma-COPD overlap (ACO)). The previous Japanese epidemiological survey estimated that over 5.3 million people had COPD and the number would be increasing now.<sup>4</sup> However, the Ministry of Health, Labour and Welfare of Japan reported only 220 000 patients with COPD regularly attend medical institutes. In addition, the annual mortality was 18 000 and over patients with COPD in 2017 (Statistical Classification of Illnesses, Injuries and Causes of Death 2017. Ministry of Health, Labour and Welfare, in Japan. Available URL: <https://www.mhlw.go.jp/english/> (in Japanese)).

The undertreatment and underdiagnosis of COPD may contribute to high mortality rates in Japan. In addition, recent Japanese studies have suggested that 4.2%–66.0% of patients



with COPD are diagnosed with ACO.<sup>5–9</sup> The proportion of patients with COPD who respond to additional inhaled corticosteroid (ICS) treatment remains unclear,<sup>10–12</sup> and it has been reported that Japanese physicians use ICS for 20%–30% of patients with COPD, including those with ACO.<sup>13,14</sup>

Compared with a single-inhaler dual combination therapy (SIDT) of long-acting muscarinic antagonist (LAMA)/long-acting beta 2-agonist (LABA) or ICS/LABA, a single-inhaler triple combination therapy (SITT) comprising ICS, LAMA and LABA may improve QOL, reduce symptoms, improve lung function, and reduce annual exacerbation rates in patients with poorly controlled COPD.<sup>15–18</sup> In real-world setting, the efficacy of SITT for COPD has also been reported.<sup>19,20</sup> The efficacy of SITT cannot be generalised to patients with milder COPD or treatment-naïve patients yet because the efficacy is limited to patients with COPD with strong symptoms, severe airflow limitation, and repeated moderate and/or severe exacerbations in the previous year. Data on mild-to-moderate COPD are urgently needed to determine if the benefits observed in the previous studies in patients with symptomatic moderate-to-severe COPD and a history of exacerbations are also relevant to this population.<sup>14</sup>

Therefore, we plan to conduct a multicentre, randomised, open-label, active-control, parallel-group study to test the hypothesis that once-daily SITT of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) could improve lung function and health-related QOL for patients with mild-to-moderate COPD without moderate exacerbations in the previous year more effectively than once-daily SIDT of UMEC/VI (Efficacy and safety of once-daily single-Inhaler TRiple therapy for Japanese with mild-to-moderate COPD in Kyushu).

## METHODS AND ANALYSIS

### Study design

This is a multicentre, open-label, randomised, parallel-group study. Patients who meet the eligibility criteria and complete the interval period will be randomised (1:1) to receive one of the following target drugs: Trelegy100 (FF/UMEC/VI 100 µg/62.5 µg/25 µg) QD via ellipta dry powder inhaler (DPI) or Anoro (UMEC/VI 62.5 µg/25 µg) QD via ellipta DPI. The drugs will be administered for 24 weeks. We have established a study group in Japan which currently includes a total of 38 specialist asthma and COPD hospital-affiliated clinics. The enrolment period will be 18 months. We expect to enrol a total of 668 patients by the end of September 2023. This will be a 24-week study which will be completed by the end of March 2024.

### Patients and recruitment

#### Study population

In total, 668 patients with COPD will be recruited at clinical trial sites, specialty departments of hospitals, and clinics between March 2022 and September 2023. The potentially eligible study population will include

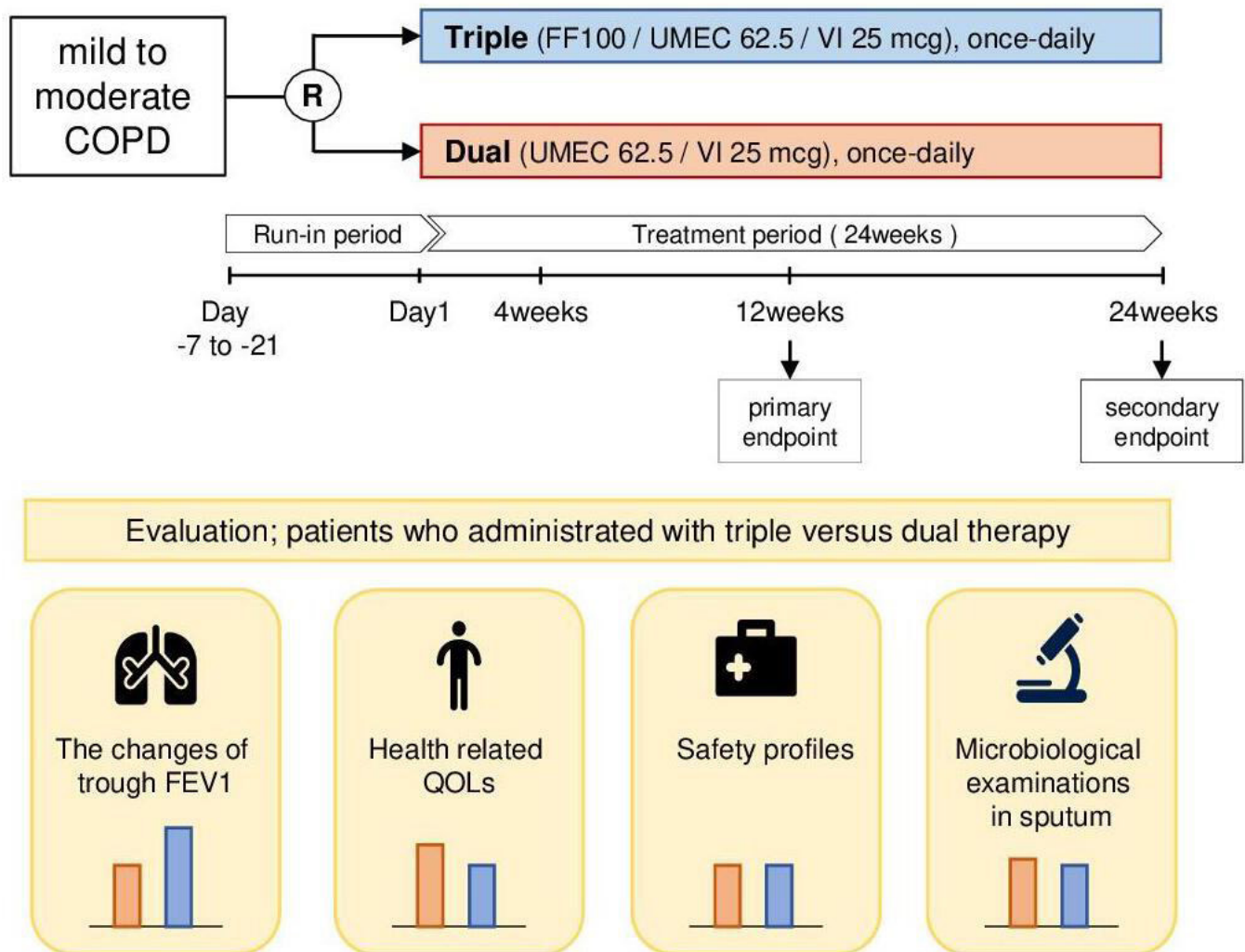
mild-to-moderate patients with COPD who meet the inclusion and exclusion criteria listed below. The institutions participating in this study have CT, pulmonary function testing equipment including pulmonary diffusing capacity, and fraction of nitric oxide, and are staffed by specialists of the Japanese Respiratory Society (JRS). In addition, all physicians participating in the study were trained in the introduction of clinical research training course.

### Inclusion criteria

1. Age over 40 years.
2. Mild-to-moderate COPD: forced expiratory volume in 1s/forced vital capacity (FEV<sub>1</sub>/FVC) ratio <0.7 and %FEV<sub>1</sub> predicted >50% assessed by the JRS criteria<sup>21</sup> after administration of short-acting beta 2 agonist (SABA).
3. Impairment of QOL (≥7 points of total COPD Assessment Test (CAT) score).<sup>22–24</sup>
4. No history of severe exacerbations in the last 12 months.
5. Prescription of LAMA or LABA monotherapy or treatment-naïve.
6. Any smoking status.

### Exclusion criteria

1. Women of childbearing potential (this includes women who are pregnant or lactating or are planning on becoming pregnant during the study).
2. A current diagnosis of asthma (however, those patients with a prior history of asthma will be eligible if they have a current diagnosis of COPD, and patients with ACO-like features, namely those whose condition partially meets the conditions defined for ACO in the JRS guidelines may be included).
3. Inability to perform lung function tests.
4. Acute respiratory tract infection or moderate or severe COPD exacerbation within 4 weeks of the screening.
5. Other comorbid diseases that are severe or unstable.
6. Active respiratory infections or malignancies.
7. Other chronic respiratory diseases including bronchiectasis, interstitial pneumonias and pneumoconiosis.
8. Inability to use any inhalation devices.
9. History of severe adverse effects or history of allergy/hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, β<sub>2</sub>-agonist, lactose/milk protein or magnesium stearate or a medical condition such as narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that poses a contraindication to participation in the study based on the opinion of the investigator.
10. Reception of investigational drug treatment within 30 days before visit 1 or within five half-lives (t<sub>1/2</sub>) of the prior investigational study (whichever is the longer of the two).



**Figure 1** Visual summary of the TRACK study. Mild-to-moderate patients with COPD are randomised to receive once-daily triple therapy (FF 100 µg/UMEC 62.5 µg/VI 25 µg) or once-daily dual therapy (UMEC 62.5 µg/VI 25 µg) for 24 weeks. COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FF, fluticasone furoate; QOL, quality of life; TRACK, Triple therApy for Japanese with mild-to-moderate COPD in Kyushu; UMEC, umeclidinium; VI, vilanterol.

11. Judgement by the physicians to be inappropriate for the study (eg, individuals with current and past histories of central nerve system disorders such as dementia, degenerative disease and cerebral vascular disease, psychological and mood disorders such as schizophrenia, depression and mania, and/or poor understanding).

### Data collection and management

The study will contain a 24-week treatment period with five separate visits (visit 1 (day -7 to -21, informed consent), visit 2 (day 1, baseline), visit 3 (4 weeks after), visit 4 (12 weeks after) and visit 5 (24 weeks after)) (figure 1). The LAMA or LABA will be washed-out for 14 ( $\pm 7$ ) days after informed consent, when regular use of LAMA or LABA is found to be prescribed as a monotherapy at visit 1. For enrolment and randomisation, each patient will be required to complete a self-reporting CAT questionnaire,

blood tests for peripheral eosinophil count and spirometry for %FEV1 predicted and FEV1/FVC ratio postbronchodilation as screening tests. The randomisation will be determined by electric systems randomisation on the next visit after enrolment (visit 2). The patients will be randomised by age, peripheral eosinophil count, %FEV1 and prescriptions (naïve or LAMA or LABA).

After education on the inhalation technique, the patients will start FF/UMEC/VI or UMEC/VI once daily in a randomised open-label manner in the morning for 24 weeks between visits 2 and 5. The adherence and technique of the inhaled medicines will be checked 4 and 12 weeks after the start of treatment at visits 3 and 4, respectively. At visit 5, the patients will be required to provide further medical information and undergo further examinations.

Table 1 shows a schedule for the study. After obtaining informed consent, baseline characteristics, including age,

**Table 1** Schedule of the study

Visit	1	2	3	4	5
Periods	Days -7 to -21	Day 1	4 weeks	12 weeks	24 weeks
Informed consents	●				
Confirmation of inclusion and exclusion criteria	●				
Randomisation	●				
Patient-related outcomes					
CAT	●	●	●	●	●
mMRC, ACT, ACQ-5, SGRQ,		●	●	●	●
Lung function tests					
Spirometry (vital capacity and flow volume curve) pre-SABA		●	●	●	●
FRC and DLco pre-SABA		●			●
Respiratory resistance (FOT/MostGraph) pre-SABA		○			○
Flow volume curve post-SABA	●	●			●
Blood tests					
WBC and eosinophil counts		●	●	●	●
Total IgE, C reactive protein		●			●
Biomarker (CCL-18, periostin, DPP-4, YKL-40)		●			●
FeNO		●	●	●	●
Sputum tests					
Smear tests, and culture for bacteria and acid-fast bacilli		●			●
Total cells counts and cell differentiation		○			○
6 min walk test		○			○
Chest high-resolution CT		Δ	Δ	Δ	Δ
Adverse events		←—————→			
Education of inhaled techniques		●	●	●	●
Collect devices and confirm adherence to inhaled medicines			●	●	●

●: mandatory, ○: if possible, Δ: Tests are accepted at any time during the study period or 24 weeks prior to visit 1.

ACQ-5, Asthma Control Questionnaire-5; ACT, Asthma control test; CAT, COPD assessment test; CCL-18, Chemokine CC Motif Ligand 18; COPD, chronic obstructive pulmonary disease; DLco, diffusing capacity of lung for carbon monoxide; DPP-4, dipeptidyl peptidase-4; FeNO, fractional exhaled nitric oxide; FOT, forced oscillation technique; FRC, Functional residual capacity; IgE, Immunoglobulin E; mMRC, modified medical research council; SABA, short-acting beta agonists; SGRQ, St. George's Respiratory Questionnaire; YKL-40, Chitinase-3 like 1 protein.

sex, height, weight, smoking status, history of chronic respiratory, allergic and other comorbid diseases, and medications will be collected from each patient by interview manners at the first visit. We will collect information on respiratory symptoms via the CAT for each patient at visit 1.

Each patient will be required not to take any medication for COPD, except for rescue medication (SABA) between visit 1 and visit 2. At visit 2, the patients will be required to complete the self-reporting questionnaires (asthma control test (ACT), Asthma Control Questionnaire (ACQ)-5, CAT, St. George's Respiratory Questionnaire (SGRQ) and modified Medical Research Council (mMRC) scale) and undergo spirometry preadministration and post-administration of SABA, measurements of functional residual capacity and diffusing capacity of the lung for carbon monoxide, blood tests and measurements

of fractional exhaled nitric oxide (FeNO) as baseline measurements. The remaining serum will be kept at  $-30^{\circ}$  between visits 2 and 5. Chest CT will be performed to classify emphysema or non-emphysema types and to detect other chronic respiratory conditions such as bronchiectasis and interstitial abnormalities. Forced oscillometry techniques or MostGraph, induced sputum tests and 6 min walk distance test will be performed as optional tests.

At visit 3, each patient will be required to complete self-reporting questionnaires, trough FEV1 measurements, blood tests for eosinophil count and measurements of FeNO. We will check for adverse events, adherence to inhaled medicines by counters of ellipta and inhalation technique, and collect the ellipta in visits 3, 4 and 5. However, the ellipta will not be kept in the clinic.

At visit 4, each patient will be required to complete self-reporting questionnaires, spirometry preadministration and postadministration of SABA, blood tests for eosinophil count, and measurements of FeNO.

At visit 5, each patient will be required to complete self-reporting questionnaires (ACT, ACQ-5, CAT, SGRQ and mMRC scale), spirometry preadministration and postadministration of SABA, and measurements of functional residual capacity and diffusing capacity of the lung for carbon monoxide, blood tests (same at second visit) and measurements of FeNO.

### Primary endpoint

The primary endpoint will be the mean change in the trough FEV1 12 weeks from baseline.

### Secondary endpoints

The secondary endpoints will be the responder rates based on the CAT score (a decrease in minimal clinically important difference (MCID)  $\geq 2$  points as a responder) and the SGRQ total score (a decrease in MICD  $\geq 4$  points as a responder) 24 weeks from baseline.

### Exploratory and other endpoints

1. Mean values and mean change from baseline for the modified MRC scale, ACT score, ACQ-5 score, CAT score at 4 weeks, 12 weeks and 24 weeks between triple therapy and LAMA/LABA combination therapy.
2. For trough FEV1, the features of responders and non-responders to triple or combination therapy at 4 weeks, 12 weeks and 24 weeks between triple therapy and LAMA/LABA combination therapy. Responders will be defined as an improvement  $\geq 300$  mL for treatment naïve and  $\geq 200$  mL for LAMA or LABA monotherapy.
3. Mean change from baseline in the reversibility of FEV1 at 12 weeks between triple therapy and LAMA/LABA combination therapy. However, the data values for patients receiving SABA for rescue use on-demand within 8 hours before spirometry will not be used in the analysis.
4. Mean change from baseline in the patient-related outcome (PRO) on the self-reporting questionnaires (ACT score, ACQ-5 score, CAT score and SGRQ score) and the features of responders and non-responders to triple or combination therapy at 4 weeks and 12 weeks between triple therapy and LAMA/LABA combination therapy. The responders will be defined as above for each questionnaire of MCID (ACT  $\geq 3$  points as a responder, ACQ-5  $\geq 0.5$  points as a responder).
5. Frequency of exacerbations and time to first moderate and severe exacerbation and also the number of rescue drugs such as SABA, systemic corticosteroids and antibiotics at 24 weeks between triple and LAMA/LABA combination therapy. The time to first

moderate and severe exacerbation (requiring hospitalisation) will be compared between treatment groups.

6. Predictors for the triple therapy response will be identified using the baseline characteristics and biomarkers (CCL-18, periostin, DPP-4, YKL-40, etc).
7. Changes in microbial colonisation in sputum and antimycobacterium avium complex (MAC) (glycopeptidolipid core IgA) antibody in serum from baseline to 24 weeks between triple and LAMA/LABA combination therapy.
8. To clarify whether emphysema or non-emphysema on chest CT scan<sup>25</sup> at the baseline is a predictor of FF/UMEC/VI efficacy.
9. The number and proportion of subjects with any adverse events during treatment.
10. To clarify the efficacy of triple therapy for patients with pure COPD based on GOLD (Global Initiative for Chronic Obstructive Lung Disease) categories A and C<sup>1</sup> and ACO based on GOLD/GINA<sup>26</sup> and JRS criteria (The JRS. The JRS guidelines for the management of ACO 2018. Tokyo: Medical Review; 2017); the definition of the ACO-like feature group follows the diagnosis of ACO by the JRS guidelines.
11. The kinetics of blood and sputum eosinophil counts (or differentiations) will be compared between triple and LAMA/LABA combination therapy.

### Statistical analysis

#### Sample size calculation

The sample size is based on the primary efficacy endpoints of the changes in trough FEV1 from baseline to 12 weeks after the start of treatment. Based on GSK internal Japanese data for the results of the IMPACT (Informing the Pathway of COPD Treatment) study,<sup>14</sup> the 20082 study,<sup>27</sup> the data for the HZC112207 study<sup>28</sup> and the KRONOS study,<sup>13</sup> it was expected that the mean treatment difference between the ICS/LABA/LAMA combination when compared with LAMA/LABA for FEV1 at 12 weeks would be approximately 45 mL. Based on these data, the required sample size is 534 when the mean difference in FEV1 at 12 weeks after baseline between ICS/LAMA/LABA and LABA/LAMA is 45 mL, the SD is 185 mL, the power is 80% and the two-sided significance level is 0.05. Assuming a 20% drop-out rate after randomisation, the final target number of subjects is set at 668 (334 in each treatment group).

#### Analyses of primary and secondary endpoints

All efficacy data will be summarised using means, SD or SEs, medians and ranges for continuous variables and frequencies and percentages for categorical variables. The changes from baseline trough FEV1 on treatment at 12 weeks as the primary efficacy endpoint will be analysed using the mixed-effects model for repeated measures. Then, the treatment group will be fitted as the explanatory variable taking into consideration the baseline age,



peripheral blood eosinophil count, prescription bronchodilators, %FEV1 predicted, smoking status and so on as covariates. The 4-week, 12-week and 24-week visits will be fitted as categorical variables and interactions between baseline measurements and measurements at each visit will be analysed to estimate treatment effects. The variance–covariance matrix will be assumed to be unstructured (UN). If the model does not converge with UN, compound symmetry (CS) will be used. For the estimated treatment differences comparing the triple therapy group with the LAMA/LABA combination therapy group, a 95% CI and p value will be calculated. All p values less than 0.05 will be considered statistically significant. The secondary endpoints of responder rates based on the CAT score and the SGRQ total score at 24 weeks from baseline will be compared between triple and LAMA/LABA combination therapy groups by multiple logistic regression analyses adjusting for predefined covariates.

## DISCUSSION

To the best of our knowledge, this study is the first randomised controlled trial (RCT) to clarify the efficacy and safety of once-daily SITT compared with once-daily SIDT in patients with mild-to-moderate COPD without moderate-to-severe exacerbations in the previous year. This subgroup includes a large number of patients, and COPD management can be markedly improved in this subgroup who experience a substantial disease burden. An exacerbation is well known as a life-threatening event and a key tenet for management in patients with COPD. Previous clinical trials of COPD were often necessary for the assessment of the frequency and severity of the exacerbations before and after treatment. However, many patients still suffer from chronic respiratory symptoms and impaired QOL every day even if they have never experienced an exacerbation in the past, defined as category A and B according to the GOLD classification. Help in the form of optimal management of respiratory symptoms and QOL improvement is still awaited.

In our study, the primary endpoint focuses on improvements in the trough FEV1 with once-daily SITT over once-daily SIDT in patients with mild-to-moderate COPD. We will conduct our study under the assumption that maximal bronchodilation would lead to improved symptoms and QOL even if we enrol mild-to-moderate patients with COPD who have a low risk of exacerbation.<sup>29</sup> In addition, Japanese patients still have respiratory symptoms and impaired QOL, although only a small proportion experiences previous exacerbations and also have few annual exacerbation rates individually.<sup>30</sup> Therefore, the secondary endpoints will be assessed to certify QOL improvement with SITT by comparing changes in CAT and SGRQ scores between SITT and SIDT. Although most studies use a cut-off CAT score of  $\geq 10$  points to demonstrate symptomatic COPD, the inclusion criteria in this study used a cut-off of  $\geq 7$  points. This was done because the CAT score of Japanese patients with COPD

is lower than that of global patients with COPD.<sup>31–32</sup> We also plan to clarify the characteristics suitable for SITT, including clinical and demographic characteristics and biomarkers. Our study allows the enrollment of non-smoking patients with COPD and ICS-naïve patients with COPD with history of asthma with airflow limitations, such as those with ACO. Our study will assess the values of FeNO at every visit because FeNO levels may be useful for detecting coexisting asthmatic factors<sup>33</sup> and predicting the addition of ICS in patients with COPD.<sup>34</sup> Previous systematic reviews<sup>35–36</sup> have demonstrated that the addition of ICS to bronchodilators, as SITT, is recommended for patients with frequent exacerbations and more than 300 cells per mL blood eosinophil counts. However, the efficacy of ICS is still unclear in patients with high blood eosinophil count without previous exacerbations. We will assess blood eosinophil counts at every visit to determine whether it is a potential biomarker to guide the addition of CS in patients with COPD without previous exacerbations.

Our study protocol has some limitations. First, our study will be conducted as an open-labelled trial. Investigators and patients may have biased beliefs regarding open-labelled drugs, and this may affect our results. Second, the sample size may not be appropriate because the size was defined based on previous randomised double-blind trials. Third, in this open-labelled trial, both investigators and patients will be aware of all data of the blood and sputum tests, FeNO measurements, and lung function tests at each visit. This may affect adherence to medicine and the results of self-reporting PRO and the subsequent tests. Fourth, our study is a multicentre trial. Each institute will assess the data of lung function and chest CT findings using different inspection equipment.

This study analyses not only the effects of triple therapy for mild-to-moderate COPD but also the adverse events. Triple therapy has been reported to be associated with a higher incidence of bacterial pneumonia than LAMA/LABA.<sup>37</sup> It is possible that Japanese patients with COPD may be at a higher risk of developing pneumonia with SITT than patients in other countries.<sup>36</sup> Older age, lower body mass index and predominance of emphysema phenotypes may result in higher risks of developing pneumonia in Japanese patients with COPD.<sup>38</sup> Moreover, we will also investigate the occurrence of bacterial pneumonia, sputum mycobacteria, and titre of anti-MAC antibodies before and after triple therapy. In addition, we plan to investigate airway organisms including tuberculosis and non-tuberculosis mycobacteria before and after treatment as some studies have shown an increased risk of these mycobacterial infections.<sup>39</sup>

The results of this study can build real-world evidence for clinical practice and reveal the usefulness of triple therapy for mild-to-moderate COPD. It will be able to clarify the safety and efficiency of triple therapy in patients with mild-to-moderate COPD.

In conclusion, this investigator-initiated RCT will be the first to compare once-daily SITT compared with

once-daily SIDT in patients with mild-to-moderate COPD, providing data on lung function, symptoms, QOL, exacerbation and steroid-related side effects.

#### Author affiliations

<sup>1</sup>Division of Hematology, Respiratory Medicine and Oncology, Department of Internal Medicine, Faculty of Medicine, Saga University, Saga, Japan

<sup>2</sup>Division of Respiriology, Neurology, and Rheumatology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan

<sup>3</sup>Clinical Research Center, Saga University Hospital, Faculty of Medicine, Saga University, Saga, Japan

<sup>4</sup>Division of Pulmonary Medicine, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan

<sup>5</sup>Department of Respiratory Medicine, University of Occupational and Environmental Health, Fukuoka, Japan

<sup>6</sup>Education and Research Center for Community Medicine, Faculty of Medicine, Saga University, Saga, Japan

**Acknowledgements** The authors would like to thank GSK for their advice to development of the TRACK study protocol.

**Collaborators** TRACK (Triple therapy for Japanese with mild to moderate COPD in Kyushu) study investigator group: Koichiro Takahashi, Tomotaka Kawayama, Kentaro Machida, Kazuhiro Yatera and Hiromasa Inoue.

**Contributors** HI and TK initiated the study. KT, KM and KY conceptualised the study. AT and AK developed the statistical analysis. All authors contributed to protocol refinement and have read and approved the final version.

**Funding** This study was funded by GSK (JRCTs031190008).

**Competing interests** KT received lecture fees from GlaxoSmithKline, AstraZeneca, Nippon Boehringer Ingelheim and Sanofi. TK received grants from Healios co., and lecture fees from AstraZeneca, GlaxoSmithKline, Nippon Boehringer Ingelheim, Novartis Pharma, Sanofi, and Kyorin Pharmaceutical. KM received lecture fees from GlaxoSmithKline. KY received grants from GlaxoSmithKline, lecture fees from GlaxoSmithKline, AstraZeneca, Nippon Boehringer Ingelheim, Sanofi, Kyorin Pharmaceutical, Novartis Pharma, Shionogi co., Teijin Home healthcare Limited., Taiho Pharma co., MSD, Astellas Pharma, Takeda Pharma co., Insmad, Thermo Fisher Scientific, Asahi Kasei Pharma co., Chugai Pharma co., Eli Lilly, Nippon Shinyaku co., Fujifilm Toyama Chemical co., Kracie Pharma, Bristol-Myers Squibb, Kyowa Kirin Co., Ono Pharma co., Taisho Pharma co., Actelion Pharma, Pfizer, Daiichi Sankyo co. and Nippon Chemipharm co. HI received grants from Nippon Boehringer Ingelheim and Kyorin Pharmaceutical, and lecture fees from AstraZeneca, GlaxoSmithKline, Nippon Boehringer Ingelheim, Novartis Pharma, Sanofi, and Kyorin Pharmaceutical. AT, HT, TK, KT, KY and AK have no competing interests.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Consent obtained directly from patient(s).

**Ethics approval** This study will be performed in accordance with the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects. The study protocol and informed consent documents were approved by the certified institutional review board at Saga University Hospital. Written informed consent will be obtained from all patients. The results will be disseminated through scientific peer-reviewed publications.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iDs

Koichiro Takahashi <http://orcid.org/0000-0003-0461-5072>

Kazuhiro Yatera <http://orcid.org/0000-0002-2955-4432>

Hiromasa Inoue <http://orcid.org/0000-0001-8080-3812>

#### REFERENCES

- Singh D, Agusti A, Anzueto A, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the gold science Committee report 2019. *Eur Respir J* 2019;53:1900164.
- Rabe KF, Watz H. Chronic obstructive pulmonary disease. *Lancet* 2017;389:1931–40.
- Buist AS, McBurnie MA, Vollmer WM, *et al*. International variation in the prevalence of COPD (the BOLD study): a population-based prevalence study. *Lancet* 2007;370:741–50.
- Fukuchi Y, Nishimura M, Ichinose M, *et al*. Copd in Japan: the nippon COPD epidemiology study. *Respirology* 2004;9:458–65.
- Tamada T, Sugiura H, Takahashi T, *et al*. Biomarker-Based detection of asthma-COPD overlap syndrome in COPD populations. *Int J Chron Obstruct Pulmon Dis* 2015;10:2169–76.
- Kobayashi S, Hanagama M, Yamada S, *et al*. Inflammatory biomarkers in asthma-COPD overlap syndrome. *Int J Chron Obstruct Pulmon Dis* 2016;11:2117–23.
- Suzuki M, Makita H, Konno S, *et al*. Asthma-Like features and clinical course of chronic obstructive pulmonary disease. An analysis from the Hokkaido COPD cohort study. *Am J Respir Crit Care Med* 2016;194:1358–65.
- Inoue H, Nagase T, Morita S, *et al*. Prevalence and characteristics of asthma-COPD overlap syndrome identified by a stepwise approach. *Int J Chron Obstruct Pulmon Dis* 2017;12:1803–10.
- Uchida A, Sakae K, Inoue H. Epidemiology of asthma-chronic obstructive pulmonary disease overlap (ACO). *Allergol Int* 2018;67:165–71.
- Hanania NA, Miravittles M. Pharmacologic management strategies of asthma-chronic obstructive pulmonary disease overlap. *Immunol Allergy Clin North Am* 2022;42:657–69.
- Mart MF, Peebles RS. Asthma-chronic obstructive pulmonary disease overlap syndrome. *Curr Opin Immunol* 2020;66:161–6.
- Jenkins C, FitzGerald JM, Martinez FJ, *et al*. Diagnosis and management of asthma, COPD and asthma-COPD overlap among primary care physicians and respiratory/allergy specialists: a global survey. *Clin Respir J* 2019;13:355–67.
- Ferguson GT, Rabe KF, Martinez FJ, *et al*. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. *Lancet Respir Med* 2018;6:747–58.
- 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;378:1671–80.
- 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;196:438–46.
- Tabberer M, Jones CE, Kilbride S, *et al*. Single-inhaler triple therapy and health-related quality of life in COPD: the impact study. *Adv Ther* 2020;37:3775–90.
- Halpin DMG, Criner GJ, Dransfield MT, *et al*. Triple versus dual combination therapy in chronic obstructive pulmonary disease in Asian countries: analysis of the impact trial. *Pulm Ther* 2021;7:101–18.
- Koara A, Yamada M, Ichikawa T, *et al*. Triple versus lama/laba combination therapy for patients with COPD: a systematic review and meta-analysis. *Respir Res* 2021;22:183.
- Pelaia C, Procopio G, Deodato MR, *et al*. Real-Life clinical and functional effects of fluticasone furoate/umeclidinium/vilanterol-combined triple therapy in patients with chronic obstructive pulmonary disease. *Respiration* 2021;100:127–34.
- Pelaia C, Procopio G, Rotundo FL, *et al*. Real-Life therapeutic effects of beclomethasone dipropionate/formoterol fumarate/glycopyrronium combined triple therapy in patients with chronic obstructive pulmonary disease. *Ther Adv Respir Dis* 2023;17:17534666231155778.
- Kubota M, Kobayashi H, Quanjer PH, *et al*. Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous values. *Respir Investig* 2014;52:242–50.
- Jones PW, Harding G, Berry P, *et al*. Development and first validation of the COPD assessment test. *Eur Respir J* 2009;34:648–54.
- Tsuda T, Suematsu R, Kamohara K, *et al*. Development of the Japanese version of the COPD assessment test. *Respir Investig* 2012;50:34–9.
- Suetomo M, Kawayama T, Kinoshita T, *et al*. COPD assessment tests scores are associated with exacerbated chronic obstructive pulmonary disease in Japanese patients. *Respir Investig* 2014;52:288–95.
- Goddard PR, Nicholson EM, Laszlo G, *et al*. Computed tomography in pulmonary emphysema. *Clin Radiol* 1982;33:379–87.



- 26 Reddel HK, Bacharier LB, Bateman ED, *et al.* Global initiative for asthma strategy 2021: Executive summary and rationale for key changes. *Eur Respir J* 2022;59:2102730.
- 27 Siler TM, Nagai A, Scott-Wilson CA, *et al.* A randomised, phase III trial of once-daily fluticasone furoate/vilanterol 100/25 µg versus once-daily vilanterol 25 µg to evaluate the contribution on lung function of fluticasone furoate in the combination in patients with COPD. *Respir Med* 2017;123:8–17.
- 28 Martinez FJ, Boscia J, Feldman G, *et al.* Fluticasone furoate/vilanterol (100/25; 200/25 µg) improves lung function in COPD: A randomised trial. *Respiratory Medicine* 2013;107:550–9.
- 29 Singh D, D'Urzo AD, Donohue JF, *et al.* Weighing the evidence for pharmacological treatment interventions in mild COPD; a narrative perspective. *Respir Res* 2019;20:141.
- 30 Nishimura M, Makita H, Nagai K, *et al.* Annual change in pulmonary function and clinical phenotype in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012;185:44–52.
- 31 Nishimura K, Oga T, Nakayasu K, *et al.* How different are COPD-specific patient reported outcomes, health status, dyspnoea and respiratory symptoms? an observational study in a working population. *BMJ Open* 2019;9:e025132.
- 32 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;14:2849–61.
- 33 Takayama Y, Ohnishi H, Ogasawara F, *et al.* Clinical utility of fractional exhaled nitric oxide and blood eosinophils counts in the diagnosis of asthma-COPD overlap. *Int J Chron Obstruct Pulmon Dis* 2018;13:2525–32.
- 34 Yamaji Y, Oishi K, Hamada K, *et al.* Detection of type2 biomarkers for response in COPD. *J Breath Res* 2020;14:026007.
- 35 Cazzola M, Rogliani P, Calzetta L, *et al.* Triple therapy versus single and dual long-acting bronchodilator therapy in COPD: a systematic review and meta-analysis. *Eur Respir J* 2018;52:1801586.
- 36 Koarai A, Yamada M, Ichikawa T, *et al.* Triple versus LAMA/LABA combination therapy for Japanese patients with COPD: a systematic review and meta-analysis. *Respir Investig* 2022;60:90–8.
- 37 Dransfield MT, Crim C, Criner GJ, *et al.* Risk of exacerbation and pneumonia with single-inhaler triple versus dual therapy in impact. *Ann Am Thorac Soc* 2021;18:788–98.
- 38 Takahashi S, Betsuyaku T. The chronic obstructive pulmonary disease comorbidity spectrum in Japan differs from that in Western countries. *Respir Investig* 2015;53:259–70.
- 39 Andr jak C, Nielsen R, Thomsen Vibeke  , Thomsen VO, *et al.* Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. *Thorax* 2013;68:256–62.