

# BMJ Open Clinical benefit of two-times-per-day acclidinium bromide compared with once-a-day tiotropium bromide hydrate in COPD: a multicentre, open-label, randomised study

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## ABSTRACT

**Objective** Chronic obstructive pulmonary disease (COPD) is mainly treated pharmaceutically with bronchodilators. The purpose of this study was to evaluate the clinical benefits of two-times-per-day acclidinium bromide (Acli-BID) compared with once-a-day tiotropium bromide hydrate (Tio-QD) in patients with COPD.

**Design** This study was a multicentre, open-label, randomised study.

**Setting** Four centres in Kagawa prefecture, Japan.

**Participant** Patients who were diagnosed to have COPD Grade 2–3 according to the Global Initiative for Chronic Obstructive Lung Disease 2015 criteria were enrolled.

**Interventions** Patients were randomly assigned to receive Acli-BID or Tio-QD at a 1:1 ratio, and followed for 8 weeks. Acli-BID was administered in the morning and night, and Tio-QD was administered in the night.

**Primary and secondary outcome measures** Primary outcome was forced expiratory volume in one second area under the curve (FEV<sub>1</sub>AUC<sub>0–3</sub>), and secondary outcomes were pulmonary function, physical activity, St George's Respiratory Questionnaire (SGRQ), modified Medical Research Council (mMRC), the 8-item Short-Form Health Survey (SF-8) and COPD exacerbations. Adverse events were evaluated during the study.

**Results** 44 patients were included in this study. FEV<sub>1</sub>AUC<sub>0–3</sub> at week 8 was 4.62±1.43 L·hour in Acli-BID and 4.73±1.60 L·hour in Tio-QD (mean difference (MD) –0.11 L·hour; 95% CI, –1.04 to 0.83). Significant improvement was observed in activity-related subscales of SGRQ (MD –7.78; 95% CI –14.61 to –0.94) and SF-8 (MD 4.01; 95% CI 0.37 to 7.65), mMRC (MD –0.66; 95% CI –1.19 to –0.13) and rate ratio (0.52, 95% CI 0.27 to 0.99) of exacerbations in the Acli-BID compared with the Tio-QD. Acli-BID and Tio-QD significantly improved sedentary behaviour (MD –35.20 min; 95% CI –67.41 to –2.94 and MD –55.40 min; 95% CI –98.15 to –12.77) within each group, but there was no significant difference between the two groups.

**Conclusion** Acli-BID as with Tio-QD could be one of the therapeutic options for patients with COPD to improve pulmonary function. Also, our results suggest that intervention with bronchodilators enhanced physical activity in patients with COPD.

## Strengths and limitations of this study

- This was the first study to evaluate the clinical benefit of two-times-per-day acclidinium bromide compared with once-a-day tiotropium bromide hydrate, assessed through evaluation of pulmonary function and physical activity.
- Physical activity was evaluated objectively using the triaxial accelerometer as well as subjectively using self-reported questionnaires.
- Because we conducted this study in a real-life setting, the inclusion and exclusion criteria were not very stringent.
- This was an exploratory study, and as such, it is a small open-label study with a short period of follow-up and without placebo.

**Trial registration number** UMIN 000020020.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major chronic respiratory disease. It is a progressive and irreversible pathological condition and is among the leading causes of death worldwide. To improve the quality of life (QoL) of patients with COPD, particularly in ageing societies such as Japan, Europe and the USA, inhibiting disease progression by early therapeutic intervention with bronchodilators is considered to be increasingly important.<sup>1</sup> The recommendation of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) was changed in the 2017 report to select treatment plans for individual patients considering the severity based on pulmonary function and the evaluation of subjective symptoms, including COPD assessment test, and the frequency of acute exacerbation, reflecting the increasing importance

of achieving symptomatic control and increasing QoL in patients with COPD.<sup>2</sup> GOLD 2017 also recommends increasing the level of physical activity, because reduced physical activity is a strong predictor of fatality.<sup>3</sup>

Inhalation therapy, including long-acting  $\beta_2$  agonists (LABA) and long-acting muscarinic antagonists (LAMA), is one of the main treatment options for COPD. Aclidinium, a novel, long-acting, inhaled muscarinic agent, for which a Genuair inhaler is used as an inhalation device, has been approved as a COPD treatment drug for two-times-per-day administration in Japan, Europe and the USA. Aclidinium demonstrated equal efficacy to tiotropium for pulmonary function after 6 weeks of inhalation in phase IIIb study comparing acclidinium and tiotropium (LAMA).<sup>4</sup> Post hoc analysis of this study reported that acclidinium improved COPD symptoms in the early morning and at night.<sup>5</sup>

Our speculation was that providing two peaks of forced expiratory volume in one second ( $FEV_1$ ) with two-times-per-day administration might be more beneficial compared with one peak of  $FEV_1$  with once-a-day administration for the improvement of morning symptoms and daytime physical activity. Although once a day is the preferred frequency of inhalation from the point of view of treatment adherence, it is also important to consider administering inhalation therapy when it is needed the most (ie, during time of day when the COPD symptoms are worse and when physically most active). However, it has not yet been clarified whether there is a difference in the therapeutic effect of LAMAs on early morning symptoms and physical activity, depending on the difference in the number of doses per day.

## OBJECTIVE

Given this background, we compared once-a-day inhalation therapy of tiotropium bromide hydrate and two-times-per-day inhalation therapy of acclidinium bromide in terms of pulmonary function, health-related QoL (HRQoL), and dyspnoea, and also studied their effects on physical activity measured by a validated GT3X-BT (ActiGraph) triaxial accelerometer, as recommended in the European Respiratory Society statement.<sup>6</sup>

## METHODS

### Study design

This study was a multicentre, open-label, randomised, parallel-group, controlled study, named 'Command Study'.

### Setting

This study was conducted across four centres in Kagawa prefecture, Japan.

### Participants

Eligible patients were outpatients over the age of 40, with disease severity of Grade 2–3 defined by GOLD

2015. Patients were eligible if they had had spirometry performed in the previous year and had predicted  $FEV_1$  ( $\geq 30\%$  and  $< 80\%$ ) and  $FEV_1$ /forced vital capacity  $< 70\%$ . Patients were also only eligible if they had a smoking history of at least 10 pack-years and had been controlled by medicines other than LAMA for at least 4 weeks before enrolment. Patients were excluded if they had inhaled corticosteroid (ICS); if their ICS/LABA treatment was changed in the previous 4 weeks; had concurrent bronchial asthma; if they were clearly diagnosed as having pulmonary fibrosis by CT or high-resolution (HR) CT; had contracted upper or lower airway infection in the previous 4 weeks; had been hospitalised due to exacerbation of COPD in the previous 3 months; or if they were judged ineligible by the investigator or subinvestigators. Other eligibility criteria, including treatment transition criteria, are shown in the study protocol (see online supplementary study protocol).

Participants were recruited from four study centres in Kagawa prefecture between December 2015 and March 2016. The study was conducted in compliance with the Declaration of Helsinki (revised in October 2013), Ethical Principles for Medical Research Involving Human Subjects. Ethical principles, selection of study sites, storing of documents, monitoring and audit were conducted based on the International Conference on Harmonization-Good Clinical Practice.

## Intervention

At visit 1 (week -4), informed consent was obtained. Enrolment and randomisation were conducted at visit 2 (week 0), and the investigator enrolled patients who fulfilled the criteria. The patients were randomly assigned either to an acclidinium group (Acli-BID) or a tiotropium group (Tio-QD) using block randomisation, comprising four patients per block using a 1:1 allocation scheme. The block randomisation was conducted with the support of a clinical research organisation, Mebix. A third-party blinding committee was commissioned by the study organisation. The patients were sequentially assigned from visit 2, with stratification according to the centre from which they were recruited. For 8 weeks, acclidinium bromide 400  $\mu$ g was administered two times per day (in the morning between 9:00 and 11:00 hours and in the night between 21:00 and 23:00 hours), and tiotropium bromide hydrate 5  $\mu$ g was administered once-a-day (in the night between 20:00 and 22:00 hours). Aclidinium was inhaled using a Genuair, and tiotropium was inhaled using a Respimat inhaler. A clinical research organisation (Mebix) conducted data collection, statistical analysis and data centre operations. The investigators enrolled patients who visited the centres for the treatment of their respiratory symptoms if they met the inclusion and exclusion criteria at visit 1. At visit 1, baseline characteristics assessment, clinical examinations and respiratory function test were conducted by investigators in each centre. Also, the investigators provided the subjects with GT3X-BT and explained how to use it. The compliance to treatment was checked by investigators in each centre at visits 3 (week 4)

and 4 (week 8) based on the study protocol. The endpoints and evaluation schedule were shown in the online supplementary table 1.

### Primary and secondary outcome measures

The area under the curve (AUC) of FEV<sub>1</sub> in the continuous respiratory function test (FEV<sub>1</sub>AUC<sub>0-3</sub>, L·hour), the primary outcome, was evaluated at week 8. The participants were asked to visit their respective study centres between 9:00 and 11:00 hours. In the Acli-BID group, continuous respiratory function tests were performed before inhaling the study drug and 1, 2 and 3 hours after inhalation, while in the Tio-QD group, continuous respiratory function tests were performed at the time of the patients' arrival and 1, 2 and 3 hours later. The secondary endpoints, which were the patient-reported HRQoL based on St George's Respiratory Questionnaire (SGRQ), which was a disease-specific quality of life questionnaire, the 8-item Short-Form Health Survey (SF-8), which was general health questionnaire and modified Medical Research Council (mMRC) questionnaire, which was a scale of dyspnoea in daily living, were assessed at visit 2, 3 and 4. COPD exacerbations were confirmed by investigators according to the Guidelines for the Diagnosis and Treatment of COPD (fourth edition) issued by the Japanese respiratory society. The degree of exacerbation was evaluated at the investigator's interviews at visits 2, 3 and 4 and calculated the rate ratio of exacerbation (person-years). The radiologists and pulmonologists made the diagnosis of emphysema using HRCT. The compliance to treatment was checked by investigators in each centre at visit 3 and 4 based on study protocol. Also, the adverse events were evaluated through the investigator's interviews at visit 2, 3 and 4.

### Physical activity assessment with accelerometer

Patients wore a validated triaxial accelerometer GT3X-BT (ActiGraph), which is a physiological sensor that provides an indicator of activities. Physical activity was categorised based on the amount of counts per minute (cpm), recorded by the GT3X-BT device during the study period. The physical activity was categorised into an intensity-related indicator depending on the measured cpm as 'sedentary' (<100 cpm) or 'light' (100–1951 cpm). To determine the activity indicator values at visit 2, 3 and 4, the mean score over the previous 7 consecutive days before each visit (days -7 to -1) was used. The average duration of each intensity-related indicator during the morning (6:00–12:00 hours), afternoon (12:00–22:00 hours) and over the day (6:00–22:00 hours) were calculated and expressed in minutes.<sup>7</sup> The data from GT3X-BT was downloaded to a personal computer and was calculated using the ActiLife 6 Data Analysis Software. The data was independently checked by the two of the authors.

### Statistical analyses

To calculate the number of patients needed to evaluate the difference between once-a-day administration and

two-times-per-day administration of the inhaled muscarinic agents, we estimated FEV<sub>1</sub>AUC of Acli-BID to be 186 mL·hour and that of Tio-QD to be 93 mL·hour (SD was 80% for both) based on a paper by Beier *et al.*<sup>4</sup> With  $\alpha=0.05$  and for a power of 80%, 52 patients were needed to have statistically significant differences on both sides. With the dropout rate set at 10%, 30 patients in each group, a total of 60 patients were needed. But, it was calculated at the first enrolment of up to 15 patients that the SD value of AUC<sub>0-3</sub> would be smaller than 80%. SD was predicted to be 30%. Given this was the first study comparing acclidinium bromide and tiotropium bromide hydrate in Japan, we recalculated the sample size as follows; When FEV<sub>1</sub>AUC was 186±56 in Acli-BID, 93±28 mL·hour in Tio-QD with  $\alpha=0.05$  and a power of 80%, 40 patients were needed to have statistically significant differences with effect size, allocation ratio and dropout rate are 1, 1 and 10%, respectively. Data were expressed as mean±SD deviation, mean difference (MD) and 95% CI. Statistical significance was defined as  $p<0.05$  in all analyses. FEV<sub>1</sub>AUC in the continuous respiratory function test was calculated using the trapezoidal method to obtain FEV<sub>1</sub>AUC<sub>0-3</sub>. Analysis of covariance was used to estimate the difference in FEV<sub>1</sub>AUC<sub>0-3</sub> adjusting for baseline measures. Paired t-test was used for intragroup comparison of outcomes between different evaluation time points, and Student's t-test was used for intergroup comparison. For data of outcomes that followed a non-normal distribution, the Wilcoxon signed rank test or Wilcoxon rank sum test was performed. Poisson analysis of the number of COPD exacerbations during the study period was performed to compare the frequency in terms of person-years. The linear correlation between physical activities indicators was evaluated using the Pearson product-moment correlation coefficient. The factors affecting the physical activities from baseline were investigated by a simple linear regression and stepwise multiple linear regression with covariates using backward elimination. All analyses were conducted with SAS V.9.4 and JMP V.13 (SAS Institute).

### Patient and public involvement

In this randomised study, patients attending the clinics of either of the four participating centres were recruited. The burden of participating in the study was explained to the patients when informed consent was sought from all patients. The results of the study were registered in the University hospital Medical Information Network Center, which is accessible to patients. Patients were not involved in the development of the research question, study aim and design of this study.

## RESULTS

### Participants

Of the 47 participants enrolled, three participants dropped out before administration of the study drug; two patients were found to be ineligible (no smoking history, spirometry results did not meet the selection criteria), and

one patient was hospitalised with exacerbation of COPD. Participants were registered at four centres in Kagawa prefecture. The remaining 44 patients were randomised to Acli-BID or Tio-QD. One patient requested to discontinue during the study period because of difficulties in using the device to self-administer tiotropium. This patient discontinued treatment at visit 3 and was not included in the calculations for the primary and secondary outcomes (visit 4). Forty-three patients completed the study (figure 1). Characteristics of the patients at baseline were similar between the Acli-BID group and the Tio-QD group (table 1). The patients enrolled in this study had never experienced the use of tiotropium. The compliance to treatment was >80% in all patients. The baseline patient characteristics for each study centre are shown in the online supplementary table 2.

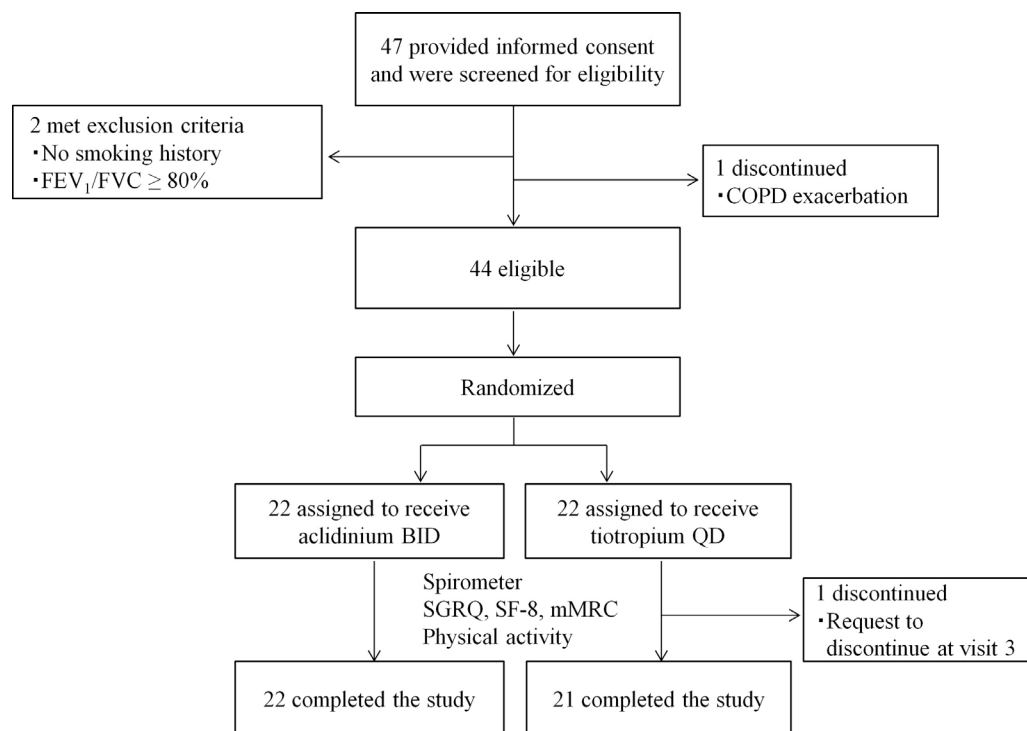
### Primary and secondary outcomes

$FEV_1AUC_{0-3}$  (L·hour) of primary outcome was  $4.62\pm 1.43$  L·hour in the Acli-BID group and  $4.73\pm 1.60$  L·hour in the Tio-QD group, showing no statistically significant difference between the two groups (MD  $-0.11$  L·hour; 95% CI  $-1.04$  to  $0.83$ ) (figure 2).  $FEV_1$  in Acli-BID and Tio-QD were determined at 0 hour, 1 hour, 2 hours and 3 hours. Although 0 hour for the Acli-BID group was preinhalation, 0 hour for the Tio-QD group was about 12 hours after night inhalation.  $FEV_1$  values after 0 hour, 1 hour, 2 hours and 3 hours at week 8 were  $1.48\pm 0.42$ ,  $1.55\pm 0.43$ ,  $1.56\pm 0.46$  and  $1.56\pm 0.44$  L in the Acli-BID group and  $1.59\pm 0.57$ ,  $1.60\pm 0.55$ ,  $1.62\pm 0.55$  and  $1.62\pm 0.56$  L in the Tio-QD group, respectively. Each value

of  $FEV_1$  AUC was shown in the figure 2. Change in the SGRQ activity score from week 0 to week eight significantly improved in the Acli-BID group ( $-4.11\pm 11.77$ ) compared with the Tio-QD group ( $3.67\pm 10.33$ ) (MD  $-7.78$ ; 95% CI  $-14.61$  to  $-0.94$ ), and the change reached a minimal clinically important difference, which was defined as an improvement of 4 points. Although the difference in improvement in physical functioning was not significant between the two groups, there was a significant improvement in the role physical domain of SF-8 at weeks 4 and 8 in the Acli-BID group ( $3.91\pm 6.32$ ,  $2.41\pm 6.33$ ) compared with the Tio-QD group ( $-2.11\pm 5.54$ ,  $-1.60\pm 5.43$ ) (MD  $6.01$ ; 95% CI  $2.40$  to  $9.63$ , MD  $4.01$ ; 95% CI  $0.37$  to  $7.65$ , respectively). The mMRC score also demonstrated significant improvement at week 8 in the Acli-BID group ( $-0.18\pm 0.85$ ) compared with the Tio-QD group ( $0.48\pm 0.87$ ) (MD  $-0.66$ ; 95% CI  $-1.19$  to  $-0.13$ ) (table 2). The scores at week 0, week 4 and week 8 are detailed in the online supplementary table 3. Interpretation and range of questionnaires are detailed in the online supplementary table 4.

During the study period, the total number of COPD exacerbation was two in the Acli-BID group and four in the Tio-QD group. Frequency of exacerbation was 0.64/person-year in the Acli-QD group and 1.23/person-year in the Tio-QD group. Rate ratio of exacerbation was 0.52 (95% CI 0.27 to 0.99) with Acli-BID relative to Tio-QD.

Objectively measured physical activity showed no significant differences in sedentary behaviour (MD 15.81 min; 95% CI  $-32.05$  to  $63.68$ ) or in light behaviour (MD 10.58 min; 95% CI  $-23.65$  to  $44.81$ ) between the



**Figure 1** Study flow. COPD, chronic obstructive pulmonary disease; BID, two times per day;  $FEV_1$ , forced expiratory volume in one second; FVC, forced vital capacity; mMRC, Medical Research Council; QD, once a day; SF-8, 8-item Short-Form Health Survey; SGRQ, St George's Respiratory Questionnaire.

**Table 1** Patient characteristics at baseline

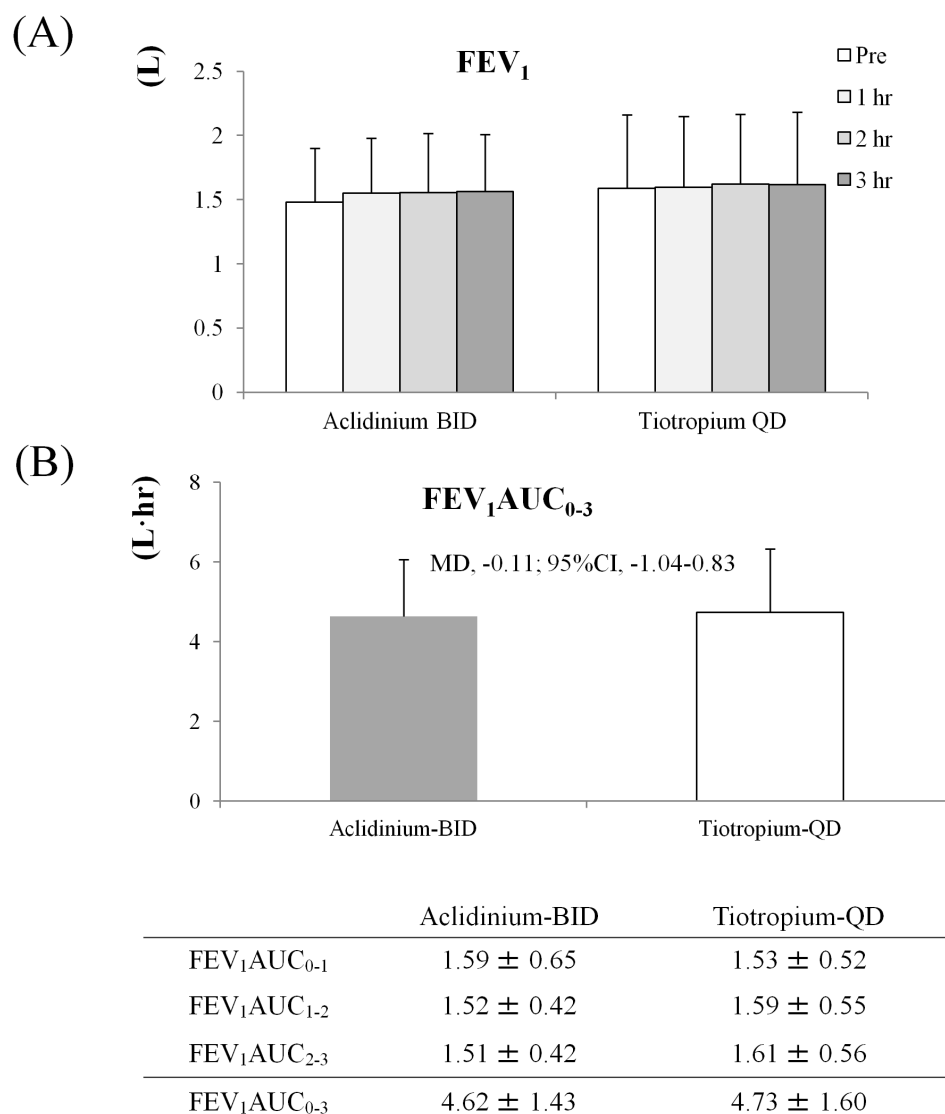
Characteristics		Acclidinium BID (n=22)	Tiotropium QD (n=22)
Gender (male), n (%)		20 (90.9)	20 (90.9)
Age (years), mean (SD)		72.3 (6.7)	70.9 (7.4)
BMI (kg/m <sup>2</sup> ), mean (SD)		22.8 (2.9)	22.5 (3.4)
Duration of smoking (years), mean (SD)		41.9 (10.5)	40.5 (12.9)
Current smoker, n (%)		6 (27.3)	6 (27.3)
COPD duration (years), mean (SD)		7.2 (6.0)	5.3 (3.3)
COPD severity, n (%)			
Moderate		15 (68.2)	13 (59.1)
Severe		7 (31.8)	9 (40.9)
Emphysema type, n (%)		21 (95.5)	22 (100)
Pulmonary fibrosis by HRCT, n (%)		0 (0)	1 (0.5)
Previous exacerbation, n (%)		7 (31.8)	10 (45.5)
Exacerbation (n/year), mean (SD)		0.4 (0.7)	0.6 (0.7)
Previous medicine, n (%)			
Long-acting $\beta_2$ agonists	Indacaterol	12 (54.5)	14 (63.6)
	Formoterol	—	1 (4.5)
	Tulobuterol	—	1 (4.5)
Inhaled corticosteroid /long-acting $\beta_2$ agonists	Fluticasone/Salmeterol	2 (9.1)	3 (13.6)
Working, n (%)		7 (31.8)	6 (27.3)
Working time (hours), mean (SD)		9.9 (1.2)	6 (3.5)
Working days, mean (SD)		4.9 (0.9)	5.7 (1.2)
SGRQ total score, mean (SD)		28.9 (10.9)	35.0 (12.4)
SGRQ symptom, mean (SD)		51.6 (14.8)	54.6 (10.8)
SGRQ activity, mean (SD)		35.1 (21.4)	44.6 (17.8)
SGRQ impact, mean (SD)		19.0 (8.9)	23.6 (13.1)
mMRC, mean (SD)		1.0 (1.0)	1.1 (1.1)
SF-8 physical component summary, mean (SD)		46.7 (8.2)	45.7 (4.7)
SF-8 mental component summary, mean (SD)		50.2 (4.8)	48.6 (8.3)
SF-8 physical functioning		45.1 (8.8)	44.7 (7.1)
SF-8 role physical, mean (SD)		46.8 (8.1)	45.0 (8.5)
FEV <sub>1</sub> (L), mean (SD)		1.6 (0.4)	1.5 (0.5)
%FEV <sub>1</sub> predicted (%), mean (SD)		60.1 (14.6)	57.6 (15.5)
FEV <sub>1</sub> /FVC (%), mean (SD)		56.3 (8.6)	56.8 (8.9)
IC (L), mean (SD)		2.2 (0.6)	2.0 (0.7)

\*COPD severity defined by Global Initiative for Chronic Obstructive Lung Disease.

BID, two times per day; BMI, body mass index; COPD, Chronic Obstructive Pulmonary Disease; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; HRCT, high-resolution CT; IC, inhaled corticosteroid; mMRC, modified medical research council; QD, once a day; SF-8, 8-item Short-Form Health Survey; SGRQ, St George's Respiratory Questionnaire.

two groups. Significant difference over the treatment period was observed within each group in sedentary behaviour in Acli-BID (MD  $-35.18$  min; 95% CI  $-67.41$  to  $-2.94$ ) and Tio-QD (MD  $-55.46$  min; 95% CI  $-98.15$  to  $-12.77$ ) (figure 3A) but not observed with regards to light behaviour between the two groups (figure 3B). Duration of sedentary behaviour in the morning hours significantly

reduced in the Acli-BID group (MD  $-19.35$ ; 95% CI  $-34.56$  to  $-4.14$ ) (figure 3C), while that in the afternoon hours significantly reduced in the Tio-QD group (MD  $-32.00$ ; 95% CI  $-61.27$  to  $-2.74$ ) (figure 3D). A strong negative correlation (Acli-BID;  $r=-0.75$ , Tio-QD;  $r=-0.85$ ,  $p<0.0001$ ) was found between the mean changes in the duration of sedentary behaviour and light behaviour (see



**Figure 2** (A) FEV<sub>1</sub> measured at week 8. (B) FEV<sub>1</sub>AUC<sub>0-3</sub> at week 8. The values of FEV<sub>1</sub> were shown as mean±SD, and FEV<sub>1</sub>AUC were shown as mean±SD, MD and 95% CI. FEV<sub>1</sub>AUC<sub>0-3</sub> was calculated as follows; FEV<sub>1</sub>AUC<sub>0-1</sub>=(FEV<sub>1</sub> (0 hour)+FEV<sub>1</sub> (1 hour))×(measurement time (1 hour)– measurement time (0 hour))÷2, and FEV<sub>1</sub>AUC<sub>1-2</sub>, and FEV<sub>1</sub>AUC<sub>2-3</sub> were calculated as well. Finally, FEV<sub>1</sub>AUC<sub>0-3</sub>=FEV<sub>1</sub>AUC<sub>0-1</sub>+FEV<sub>1</sub>AUC<sub>1-2</sub>+FEV<sub>1</sub>AUC<sub>2-3</sub>. ANCOVA was used for intergroup comparison of FEV<sub>1</sub>AUC<sub>0-3</sub>. Statistical significance, p<0.05. ANCOVA, analysis of covariance;AUC, area under the curve; BID, two times per day; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in one second; QD, once a day.

online supplementary figure 1A,B, respectively). In fact, 88% of patients showing the increase in light behaviour showed the decrease of sedentary behaviour. The factors influencing the sedentary behaviour were age, duration of smoking, comorbidities and %FEV<sub>1</sub> (see online supplementary table 5).

In the Acli-BID group, nine adverse events occurred, and in the Tio-QD group, seven adverse events occurred. There were no serious adverse events. Adverse events were as follows: in the Acli-BID group, there were two events of skin rash and one event each of dizziness, pollinosis, bronchitis, dry mouth, pneumonia, vertigo, and senile dementia; in the Tio-QD group, there were two events of bronchitis and one event each of upper airway

inflammation, cramp, herpes zoster, acute exacerbation of COPD and allergic rhinitis.

## DISCUSSION

We evaluated the clinical benefit of two-times-per-day therapy of acclidinium bromide (at morning and night-time administration) comparing with once-a-day therapy of tiotropium (at night-time administration) in patients with moderate-to-severe COPD. There was no significant difference between Acli-BID and Tio-QD in terms of FEV<sub>1</sub>AUC<sub>0-3</sub>, the primary outcome. These results could lead to conclusion that the bronchodilating effect of Acli-BID and Tio-QD was similar from the viewpoint

**Table 2** Mean change of SGRQ, HRQoL (SF-8) and mMRC scores from week 0

N	Change in score Week 4 week 0			Change in score Week 8 week 0		
	Acclidinium- BID Mean (SD)	Tiotropium-QD Mean (SD)	Mean differences (95% CI)	Acclidinium-BID Mean (SD)	Tiotropium-QD Mean (SD)	Mean differences (95% CI)
22	22			22	21	
<b>SGRQ</b>						
Total score	0.92 (6.33)	2.94 (6.20)	-2.01 (-5.83 to 1.80)	0.09 (8.37)	2.69 (5.26)	-2.59 (-6.92 to 1.73)
Symptom	0.09 (9.18)	4.07 (15.56)	-3.98 (-11.75 to 3.79)	0.00 (16.74)	2.80 (10.47)	-2.80 (-11.45 to 5.85)
Activity	1.54 (10.52)	0.26 (9.48)	1.28 (-4.82 to 7.37)	-4.11 (11.77)	3.67 (10.33)	-7.78 (-14.61 to 0.94)
Impact	0.77 (8.28)	4.15 (8.93)	-3.39 (-8.63 to 1.85)	2.59 (8.62)	2.26 (6.17)	0.33 (-4.30 to 4.97)
<b>SF-8</b>						
Physical component summary	1.97 (5.70)	-1.53 (4.53)	3.50 (0.36 to 6.63)	1.59 (7.12)	-1.49 (4.03)	3.09 (-0.50 to 6.67)
Mental component Summary	1.52 (5.37)	0.80 (8.25)	0.71 (-3.52 to 4.95)	1.16 (5.38)	0.32 (7.96)	0.84 (-3.33 to 5.01)
General health	0.77 (6.32)	-0.25 (5.72)	1.02 (-2.65 to 4.69)	1.64 (4.84)	0.42 (7.85)	1.21 (-2.78 to 5.21)
Physical functioning	1.65 (6.31)	-0.23 (4.67)	1.88 (-1.50 to 5.26)	1.31 (7.52)	-1.78 (5.56)	3.09 (-1.00 to 7.18)
Role physical	3.91 (6.32)	-2.11 (5.54)	6.01 (2.40 to 9.63)	2.41 (6.33)	-1.60 (5.43)	4.01 (0.37 to 7.65)
Bodily pain	1.62 (6.04)	0.09 (8.51)	1.53 (-2.96 to 6.02)	2.34 (8.04)	-1.11 (7.95)	3.45 (-1.47 to 8.38)
Vitality	0.69 (4.47)	-3.07 (6.08)	3.76 (0.51 to 7.01)	0.12 (5.73)	-1.17 (7.57)	1.29 (-2.83 to 5.41)
Social functioning	1.98 (6.03)	0.80 (10.65)	1.18 (-4.08 to 6.45)	0.07 (7.89)	0.96 (10.38)	-0.89 (-6.55 to 4.78)
Mental health	2.03 (5.63)	1.07 (6.26)	0.96 (-2.66 to 4.58)	2.57 (5.36)	-0.30 (6.14)	2.87 (-0.68 to 6.41)
Role emotional	2.20 (5.43)	0.22 (8.31)	1.98 (-2.29 to 6.25)	1.65 (6.19)	-0.86 (8.51)	2.51 (-2.06 to 7.07)
mMRC	-0.14 (0.71)	0.36 (0.85)	-0.50 (-0.98 to 0.02)	-0.18 (0.85)	0.48 (0.87)	-0.66 (-1.19 to 0.13)

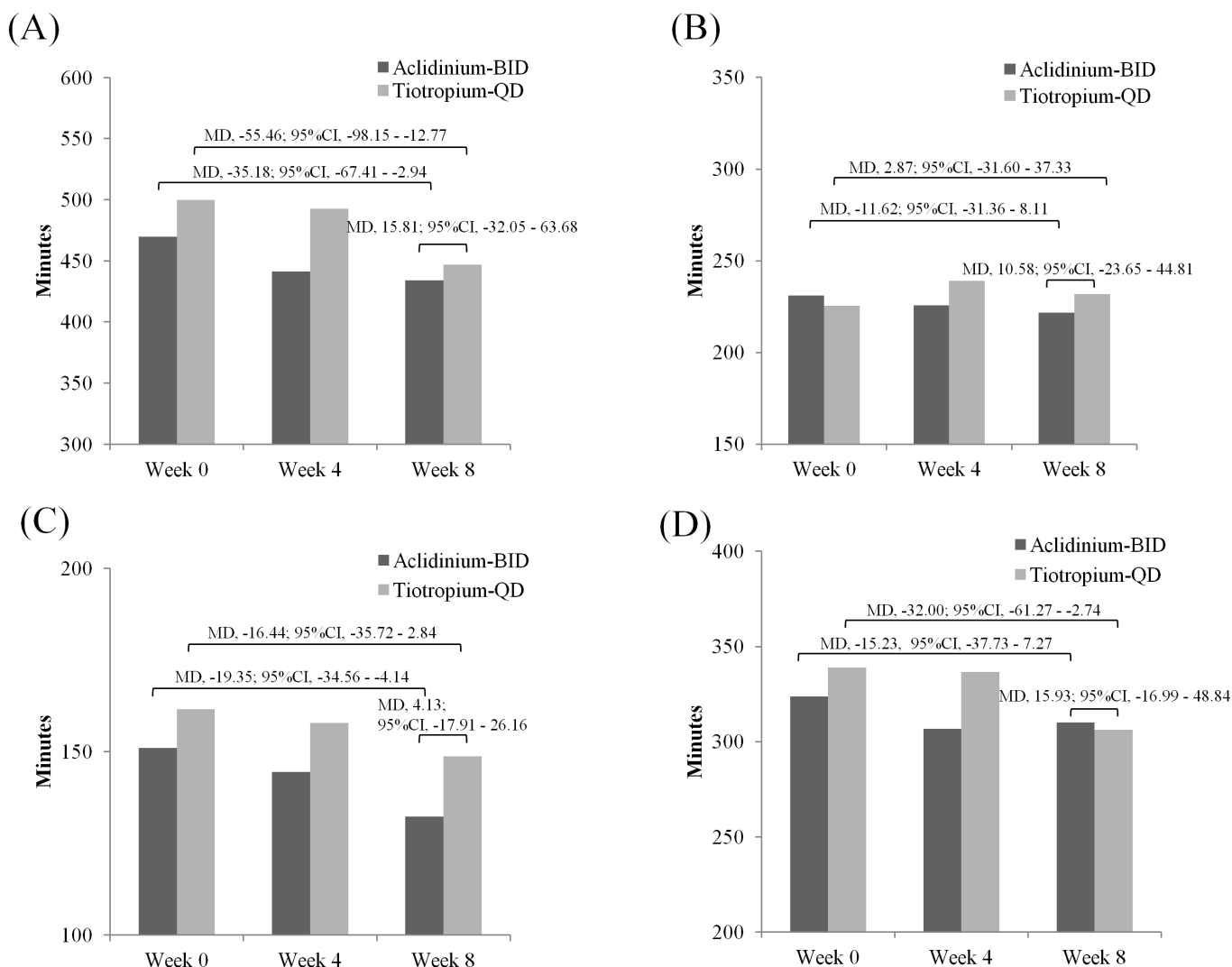
Data within-treatment change from week 0 presented as mean (SD) and between-treatment difference in change presented as mean (95% CI).

BID, two times per day; HRQoL, health-related quality of life; mMRC, modified medical research council dyspnoea scale; QD, once a day; SF-8, 8-item Short-Form Health Survey; SGRQ, St George's Respiratory Questionnaire.

of improving  $FEV_1AUC_{0-3}$ . We chose  $FEV_1AUC_{0-3}$  as the primary outcome instead of  $\Delta FEV_1AUC_{0-3}$ , given the different timing of administration between the two treatment groups. As the pre  $FEV_1$  value (0 hour) at visit 4 in the Accli-BID group was a trough value, it was lower in comparison with that in the Tio-QD group, in which the drug was administered at the previous night between 20:00 and 22:00. Thus,  $\Delta FEV_1AUC_{0-3}$  (mL/hour) in the Accli-BID group could be more favourable compared with that in the Tio-QD group.

Both Accli-BID and Tio-QD reduced objectively measured sedentary behaviour, with neither treatment demonstrating superiority over the other. However, Accli-BID improved physical activity-related subscales of self-administered questionnaires such as the SGRQ and SF-8 when compared with Tio-QD. Thus, even though Accli-BID demonstrated equivalence to Tio-QD in terms of improving the objective parameters, it was considered superior to Tio-QD in terms of the subjective but

pertinent measures of activity in patients with COPD. This study is the first to show the decrease of sedentary behaviour in COPD patients with the use of LAMAs. Decreasing sedentary behaviour in COPD patients is an important issue, given that it is an independent factor related to fatality.<sup>8</sup> Moreover, sedentary behaviour is more common in patients with COPD, as was demonstrated in a large-scale health survey conducted in the USA, which demonstrated that the proportion of sedentary behaviour was higher in patients with COPD.<sup>9</sup> Most importantly, decreasing the sedentary behaviour and increasing the light behaviour are thought to be more feasible than increasing the moderate or more intense behaviour in patients with COPD, thereby hopefully improving the prognosis of patients.<sup>10</sup> A recent study showed that sedentary behaviour was reduced by comprehensive pulmonary rehabilitation, and strong correlation between sedentary behaviour and light behaviour was also found in patients with COPD by using a triaxial accelerometer.<sup>11</sup> Likewise,



**Figure 3** Objectively measured physical activity parameters. (A) Mean duration (in minutes) of sedentary behaviour at day 1. (B) Mean duration (in minutes) of light behaviour at day 1. (C) Mean duration (in minutes) of sedentary behaviour in the morning hours. (D) Mean duration (in minutes) of sedentary behaviour in the afternoon hours. The values were shown as MD and 95% CI. Paired t-test was used for intragroup comparison. Student's t-test was used for intergroup comparison (assessed as change from week 0). Statistical significance,  $p < 0.05$ . BID, two times per day; MD, mean difference; QD, once a day.

we were also able to demonstrate a correlation between sedentary behaviour and light behaviour through the administration of LAMs in patients with COPD.

COPD symptoms frequently occurred in the morning, resulting in limitations of morning activities.<sup>12</sup> In another study, an association between morning symptoms and physical activity was demonstrated.<sup>13</sup> Morning symptoms of COPD are related to deterioration of QoL and impaired activity.<sup>14 15</sup> Although we anticipated that the night-time administration of tiotropium would improve the morning symptoms, there was no improvement in HRQoL. Meanwhile, the sedentary behaviour in the morning hours significantly reduced and HRQoL improved in the Accli-BID group.

The VESUTO study<sup>16</sup> (Efficacy of tiotropium/olodaterol on lung volume, exercise capacity, and physical activity) set up certain criteria when measuring exercise

tolerance and physical activity. That study, as well as ours, will provide important information for evaluating physical activity in patients with COPD in the future.

Some of the limitations of this study include the fact that we did not set up the study to have stringent inclusion/exclusion criteria. As such, the baseline activity levels and the lifestyles of the participants were heterogeneous and may have been reflected in the wide variation of objective activity levels measured by the accelerometer.

Although we did not determine the FEV<sub>1</sub> over a 24-hour period, we inferred from previous reports that an important change in FEV<sub>1</sub> occurred 12–15 hours after Tio-QD inhalation.<sup>4 17</sup> It was reported that FEV<sub>1</sub> was not significantly different when Tio-QD was inhaled in the morning or evening, and FEV<sub>1</sub> in Accli-BID compared with Tio-QD, which was inhaled in the evening, was not significantly different.<sup>18</sup> In the present study, acclidinium



was administered two times per day at 9:00–11:00 hours and 21:00–23:00 hours, while tiotropium was administered at 20:00–22:00 hours, intending to improve all morning COPD symptoms. Tiotropium was administered at night, with the intention of improving the morning COPD symptoms, given that the drug needs time to exert its therapeutic effects.

This was an exploratory study in a small-scale conducted in a single prefecture in Japan with a short follow-up duration, being open labelled and without a placebo control. Although the participants were randomly assigned to the treatment arms, the patients might have assumed that, for example, two-times-a-day administration would be better than once-a-day administration, and through such placebo effect, improvement might have been achieved in some of the results for Acli-BID. Finally, because we did not determine FEV<sub>1</sub> AUC<sub>0-3</sub> at visit 2, the difference between visit 2 and visit 4 could not be compared between the inhalants. These limitations might have made the study insufficient in evaluation of clinical benefit such as pulmonary function, exacerbation and physical activity.

## CONCLUSIONS

Acli-BID as with Tio-QD could be one of the therapeutic options for patients with COPD to improve pulmonary function, HRQoL and physical activity. In particular, this study suggests that intervention with bronchodilators may enhance physical activity by decreasing sedentary behaviour and increasing light behaviour.

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