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ORIGINAL RESEARCH

Imidafenacin, An Orally Active Muscarinic Receptor Antagonist, Improves Pulmonary Function In Patients With Chronic Obstructive Pulmonary Disease: A Multicenter, Randomized, Double-Blind, Placebo-Controlled 3×3 Crossover Phase II Trial

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Background: Although long-acting muscarinic receptor antagonists are central to the management of chronic obstructive pulmonary disease (COPD), inhaled medicines may have technical difficulty in some patients and adherence barriers.

Methods: A multicenter, randomized, double-blind, placebo-controlled 3×3 crossover Phase II trial was performed to evaluate the efficacy and safety of oral administration of the antimuscarinic agent imidafenacin in patients with COPD. Twenty-seven male COPD patients with % forced expiratory volume in 1 s (FEV_1) ≥30% and <80% predicted were randomized to single oral dose of imidafenacin 0.1 mg, imidafenacin 0.2 mg, or placebo.

Results: Maximum change in FEV_1 with both doses of imidafenacin significantly improved from baseline to 24 hrs after administration when compared with a placebo. Area under the curve in FEV_1 during 24 hrs after administration with 0.2 mg, but not 0.1 mg dose, was significantly improved when compared with a placebo, and the improvement was significantly based on dose-dependent manners. Plasma imidafenacin level was positively correlated with change in FEV_1. All subjects with both doses of imidafenacin completed without moderate nor severe adverse events.

Conclusion: A single oral dose of imidafenacin 0.1 mg or imidafenacin 0.2 mg may contribute to the improvement of pulmonary function with excellent safety and tolerability in patients with COPD.

Trial registration: JapicCTI-121760 (Japan Pharmaceutical Information Center – Clinical Trials Information [JapicCTI]; http://www.clinicaltrials.jp/user/cteSearch_e.jsp).

Keywords: anti-cholinergic, bronchodilator, imidafenacin, lung function, COPD

Introduction

Long-acting bronchodilators play a central role in the management for patients with chronic obstructive pulmonary disease (COPD), which is characterized by persistent airflow limitation.[1] Long-acting muscarinic 3 (M_3) receptor antagonists (LAMAs) and β_2-agonists (LABA) are well known to improve lung function, quality of life (QOL), exercise tolerance, and attenuate frequency and severity of exacerbations and mortality in stable patients with COPD.[2–7] To maximize the bronchodilation via direct effects and minimize the systemic effects, every medicine of LAMAs is inhalant for management of chronic respiratory diseases.[8–11] However, some patients, especially elderly, with COPD have difficulty in mastering inhalation techniques.[12,13]

Oral bronchodilators may potentially be more convenient, particularly for less compliant patients and those who have difficulty using inhaled medicines. Imidafenacin, 4-(2-methyl-1-H-imidazol-1-yl)-2,2-diphenyl butanamide, is one of the LAMAs with high affinity for the M_3 and M_1 muscarinic receptor subtypes and low affinity for the M_2 subtype.[14] The M_3 subtype is expressed on airway smooth muscle and mediates bronchoconstriction. In contrast, prejunctional M_2 receptors are expressed in nerves innervating the heart and lungs and inhibit the release of acetylcholine, and inhibition of the M_2 subtype potentially increases the risk of bronchoconstriction and tachycardia. Therefore, we hypothesized that imidafenacin may have fewer side effects, allowing higher exposure and a favorable therapeutic margin. Doses of 0.1 mg–0.2 mg of oral imidafenacin already have established safety and tolerability in patients with overactive bladder worldwide including Japan.[15,16]

Preclinical studies demonstrated that oral administration of imidafenacin inhibited methacholine-induced bronchial constriction in a dose-dependent manner in guinea pigs (Figure S1). To verify a hypothesis based on the preclinical results that imidafenacin can improve pulmonary function, we conducted a multicenter, randomized, double-blind, placebo-controlled crossover Phase II trial with a 3×3 design, wherein the efficacy and safety of oral imidafenacin were examined in patients with COPD.

Methods
Study Design
To assess the efficacy and tolerability of two single doses of oral imidafenacin (0.1 mg and 0.2 mg) in patients with COPD, a multicenter, randomized, placebo-controlled, double-blind, three-treatment tertiary stage, crossover study was intended. The primary endpoint was the maximum change in forced expiratory volume in 1 s (FEV_1) from baseline at various times during 24 hrs after administration of oral imidafenacin 0.1 mg or 0.2 mg. The secondary endpoint was the area under the curve (AUC) of FEV_1 from baseline to 24 hrs after administration (AUC_{24h}). The forced vital capacity (FVC), peak expiratory flow (PEF), maximal mid-expiratory flow (MMF), maximal expiratory flow at 50% (50) and 25% (25) vital capacity, and 50/25 were assessed as the exploratory endpoints.

The study was conducted in accordance with the principles of the Amended Declaration of Helsinki (2008) and the Guideline for Good Clinical Practice, and was approved by the Ethics Committee of each institution. After providing written informed consents, screening, and a 4-week run-in period, eligible patients were randomized to three separated 1-day treatment periods (Figure 1). Laboratory tests, vital signs, and a 12-lead electrocardiogram (ECG) were assessed at the screening visit. The treatments comprised a single dose of oral imidafenacin 0.1 mg, imidafenacin 0.2 mg, or placebo. All doses were administered in the morning between 08:00 and 10:00. Each treatment period was separated by a 7–28-day washout period.

Subjects
Japanese male or female patients aged ≥40 years with stable COPD stages II and III (an FEV_1/FVC ratio <0.70 and 30% ≤ %FEV_1 <80% predicted at post-bronchodilator: 2 puffs of salbutamol) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) reports modified in 2010[1] and who had a smoking history of ≥10 pack-years were enrolled in the trial. Patients with a history of asthma, lung cancer, bronchiectasis, diffuse panbronchiolitis, sinobronchial syndrome, interstitial pneumonia, tuberculosis, and active malignancies were excluded. Patients with surgery of lungs, pregnant, nursing, and contraindications for imidafenacin were also excluded. Patients with long-term oxygen therapy (≥15 hrs/day) were also excluded.

Medication Restrictions
A list of contraindicating medicines and periods of nonrecognition prior to pulmonary function tests at each visit are shown below; inhaled short-acting β_2-agonists and muscarinic receptor antagonists for 8 hrs and 12 hrs, respectively, twice-daily and once-daily inhaled LABAs for 24 and 48 hrs, respectively, oral or transdermal β_2-agonists for 24 hrs, LAMAs, injected or oral muscarinic receptor antagonists, and cholinergic agonists for 7 days, and twice-daily and once-daily theophylline for 24 and 48 hrs, respectively. Contraindication medicines were prohibited until the last administration of the study medications. Systemic corticosteroids, anti-allergic or histaminic agents, and injective methylxanthines were not accepted for COPD-related exacerbations through the trial.

Efficacy Assessments
Spirometry was performed in accordance with previous recommendations.[17,18] The best value of three tests was employed. Assessments were conducted at the beginning of each period, and at 1, 2, 3, 4, 8, 12, and 24 hrs after administration of oral imidafenacin (Figure 1).
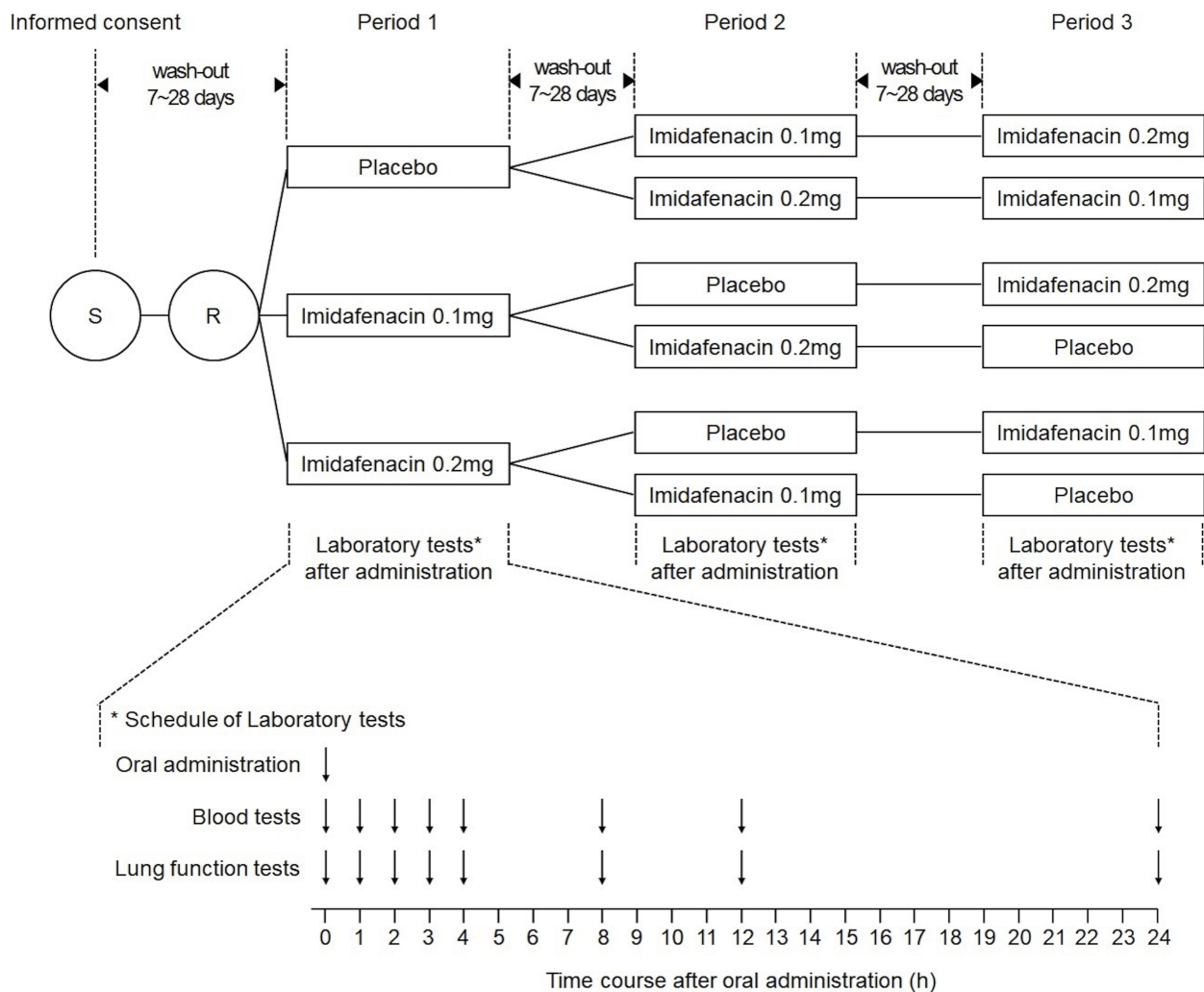
Figure 1 Study design. After screening visit (S), eligible patients were randomized (R) to three 1-day treatment periods. The treatments comprised a single oral dose of imidafenacin 0.1 mg, imidafenacin 0.2 mg, or placebo.

Pharmacokinetics

Within 15 mins before or after the pulmonary function tests, 5 mL of heparinized blood samples were collected before medication, and 1, 2, 3, 4, 8, 12, and 24 hrs after administration at each visit (Figure 1). The plasma concentration of imidafenacin was determined from blood samples by liquid chromatography–tandem mass spectrometry. A non-compartment analysis was used to determine the maximum plasma concentration of the analyte (C_{max}), time to reach C_{max} (T_{max}), AUC_{24h}, AUC from time 0 to infinity (AUC_{inf}), elimination half-life ($T_{1/2}$), and apparent clearance (CL/F).

Safety Assessments

Adverse events (AEs) were documented from screening visit to 28 days after the last study medications (period 3).

However, the AEs related to imidafenacin or AEs which may be attributed to imidafenacin were recognized as side effects.

Statistical Analysis

Four patient populations were defined: all randomized patients (RND); safety analysis set (SAF); full analysis set (FAS); and per protocol set (PPS). The SAF comprised all patients who received at least one dose of study medication. The FAS included all randomized patients who received doses of the study medication and had at least one post-medication measurement. The PPS consisted of the subset of FAS patients who completed all doses of the study medication, who complied with the medication restrictions and who had all data of the maximum FEV_1 change from baseline during 24 hrs after administration. The primary analysis

population for efficacy was the PPS. As supportive analyses, the primary efficacy analyses were performed based on the FAS. The least-square mean values of peak FEV_1 were compared between the groups by analysis of covariance (ANCOVA), which included the primary endpoint as the response variable, baseline FEV_1 data at each test period as covariates, test drug effects, group effects, and period effects as factors, and subjects as random effects. Descriptive statistics were also calculated. The values for the secondary endpoint, AUC_{24h} of FEV_1, were compared between the groups by ANCOVA. Additional secondary endpoints of the maximum change rates and maximum changes of FVC, PEF, MMF, 50, 25, and 50/25 were evaluated by the same ANCOVA as that for the primary endpoint. The sample size of 26 (planned) was calculated using a paired *t*-test, to achieve at two-sided significance level of 5%, and power of 90% prior to the study, assuming a mean peak FEV_1 and a standard deviation of between imidafenacin and placebo as 150.0 mL and 200.0 mL, respectively, based on study of tiotropium,[19] referring to a previous preliminary study of imidafenacin[20] using a crossover design, two-sided significance level of 5%, and power of 80%. For the safety analysis population, the incidence, severity, and time-course of AEs or side effects were collected by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class as well as the preferred term in each treatment group of the SAF. Pharmacokinetic parameters such as C_{max}, T_{max}, AUC_{24h}, AUC_{inf}, $T_{1/2}$, and CL/F were determined by a non-compartment analysis. An exposure/response analysis was also carried out using the FEV_1 data.

Results

Patient Characteristics

A total of 27 patients were randomized to the treatment groups (Figure 2). The baseline characteristics of the patients are summarized in Table 1. All patients were males with a mean age of 69.9 ± 5.9 years old and a mean duration of COPD for 30.3 ± 28.3 months. The mean $\%FEV_1$ predicted and a ratio of FEV_1/FVC after bronchodilators were 53.4% and 46.8%, respectively.

Efficacy Assessment

The primary analysis population for efficacy was the PPS. The results for efficacy in the FAS were similar to those in the PPS. The FEV_1 values at baseline did not differ among the groups for each treatment, and no group effect, period effect, or order effect were observed. Thus, it was judged that the crossover test was unbiased.

As shown in Table 2A, imidafenacin 0.1 mg and 0.2 mg produced a greater increase in the maximum change of FEV_1 from baseline during 24 hrs after administration, compared with placebo, with differences of 0.06 and 0.09 L, respectively. Both differences were statistically significant (*P*=0.0286 and *P*=0.0017, respectively). Regarding the secondary endpoint, AUC_{24h} of FEV_1, the differences between imidafenacin 0.1 mg and placebo and between imidafenacin 0.2 mg and placebo were 0.91 L·h (*P*=0.0729) and 1.25 L·h (*P*=0.0175), respectively (Table 2B). For the exploratory endpoints, both the imidafenacin 0.1 mg and 0.2 mg groups showed significantly higher maximum change rates of FEV_1
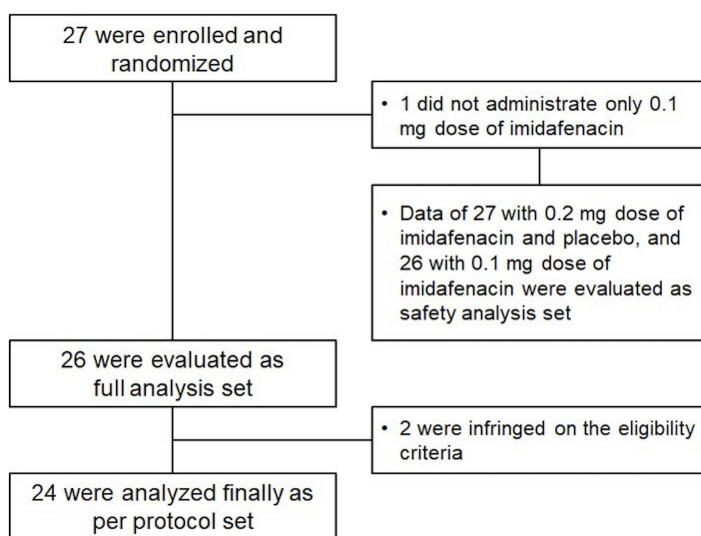

Figure 2 Analyses for the enrolled subjects.

Table 1 Baseline Characteristics Of Patients

Characteristics (RDN)	n=27
Male, n (%)	27 (100.0)
Age, years	69.9 ± 5.9
Duration of COPD, months	30.3 ± 28.3
Use of regular respiratory medicines at screening visit, n (%)	
Any	26 (96.3)
Long-acting muscarinic antagonists	21 (77.8)
Long-acting b2 agonists	15 (55.6)
Inhaled corticosteroids	10 (37.0)
Slow release theophylline	4 (14.8)
Mucolytic agents	3 (11.1)
Smoking index, pack-years	61.0 ± 31.8
Pulmonary function tests	
%FEV_1 predicted, %	53.4 ± 12.0
Stage III (30% ≤ %FEV_1 predicted < 50%)	11 (40.7)
Stage II (50% ≤ %FEV_1 predicted < 80%)	16 (59.3)
Ratio of FEV_1/FVC, %	46.8 ± 10.3

Notes: The analyses were used data of all randomized patients set. All data were expressed as mean ± SD and number (%) of patients. Data of pulmonary function tests were obtained 30 mins after inhaled short-acting $β_2$-agonists.
Abbreviations: FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RND, all randomized patients; SD, standard deviation.

than the placebo group; 4.94% (P=0.0128) and 7.52% (P=0.0003), respectively (data not shown).

Imidafenacin 0.1 mg and 0.2 mg resulted in significant improvement in FEV_1 from 1 hr up to 4 hrs and from 1 hr up to 12 hrs compared with placebo, respectively (Figure 3, full data in Table S1). In addition, the differences in the change in FEV_1 between imidafenacin 0.2 mg and placebo at 2 hrs and 3 hrs were 0.128 L (P<0.0001) and 0.115 L

(P=0.0001), respectively (Figure 3). Regarding the maximum change and maximum change rate of FVC from baseline during 24 hrs after administration, imidafenacin 0.2 mg [0.15 L (P=0.0060) and 5.54% (P=0.0076)], but not 0.1 mg [0.08 L (P=0.1120) and 2.67% (P=0.1750)], showed significant increase compared with placebo. For the maximum change and maximum change rate of PEF (Table S2A), MMF (Table S2B), 50 (Table S2C), 25 (Table S2D), and 50/25 (Table S2E), the effects of both doses of imidafenacin did not differ from placebo.

Pharmacokinetics

The pharmacokinetic parameters after a single oral administration of imidafenacin 0.1 mg and 0.2 mg were analyzed by a non-compartment model, and are summarized in Figure 4. The plasma concentrations [mean ± SD, pg/mL at T_{max} (Min – Max)] for imidafenacin 0.1 mg (FAS, n = 26) and 0.2 mg (n = 27) followed similar time-courses, reaching C_{max} [582 ± 136 at 1.96 (0.93–3.83) hrs and 1250 ± 406 at 1.97 (0.92–4.00) hrs, respectively] after administration, and having mean (SD) of $T_{1/2}$ and CL/P of 5.2 (0.97) and 26.7 (10.9) L/hr for imidafenacin 0.1 mg, and 5.3 (0.95) hrs and 25.9 (9.8) L/hr, respectively. The mean (SD) of AUC_{24h} [3910 (1160) with imidafenacin 0.1 mg and 8270 (2690) with imidafenacin 0.2 mg] and AUC_{inf} [4180 (1230) with imidafenacin 0.1 mg and 8680 (2880) with imidafenacin 0.2 mg] increased in roughly dose-dependent manners.

To evaluate the relationship between exposure and efficacy, the plasma imidafenacin concentrations were plotted against the change in FEV_1 from baseline during 24 hrs after administration. The plasma imidafenacin level was

Table 2 Changes In FEV_1 After Oral Imidafenacin When Compared With Placebo

Treatments	Mean (SEM)	Point Estimation [95% CI]	p Value
(A) Maximum Changes in FEV1 (L) From Baseline during 24 hrs After Administration			
Placebo	0.09 (0.01)	–	–
Imidafenacin 0.1 mg	0.15 (0.02)	0.06 [0.01, 0.11]	0.0286*
Imidafenacin 0.2 mg	0.17 (0.02)	0.09 [0.03, 0.14]	0.0017*
(B) AUC of FEV_1 (L·H) From Baseline During 24 hrs After Administration			
Placebo	31.76 (1.83)	–	–
Imidafenacin 0.1 mg	32.56 (1.80)	0.91 [−0.09, 1.91]	0.0729
Imidafenacin 0.2 mg	33.48 (1.80)	1.25 [0.23, 2.26]	0.0175*

Notes: Number of subjects were 24 as per protocol set. Point estimation [95% CI] of maximum changes in FEV_1 and AUC_{24h} of FEV_1 with imidafenacin 0.1 and 0.2 mg were compared to that with placebo by ANCOVA tests, which included this endpoint as the response variable, each baseline value at each test period as covariates, test drug effects, group effects, and period effects as factors, and subjects as random effects. *P <0.05 versus placebo.
Abbreviations: ANCOVA, analysis of covariance; AUC, area under the curve; CI, confidence interval; FEV_1, forced expiratory volume in 1 s; SEM, standard error of mean.
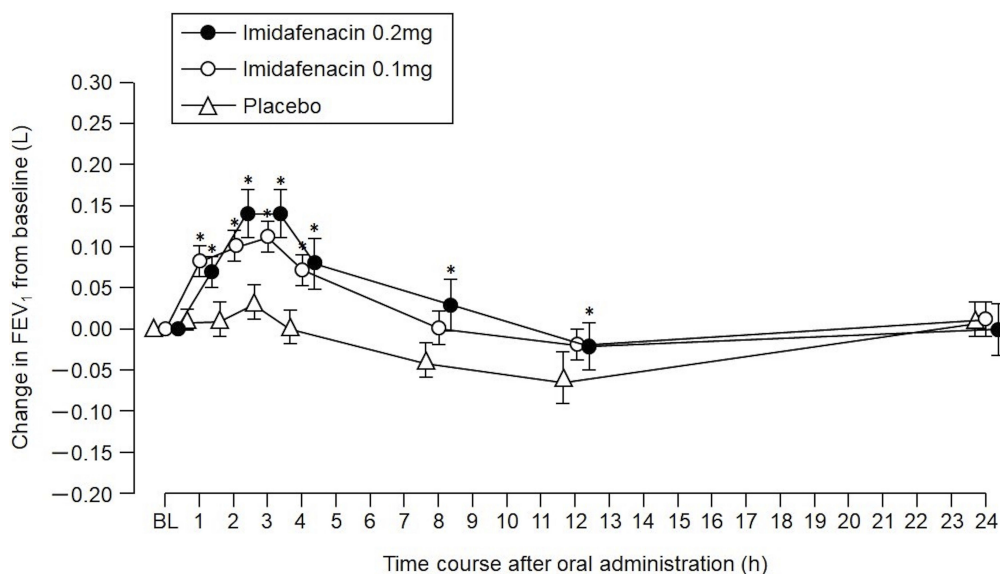
Figure 3 Temporal changes in FEV$_1$ (L). The monitoring period was 24 hrs beginning at the time of oral administration of imidafenacin (analysis set: PPS). All data were represented as means ± SEM. *P<0.05 versus placebo at each time period.
Abbreviations: BL, baseline; FEV$_1$, forced expiratory volume in 1 s; PPS, per protocol set; SEM, standard error of mean.
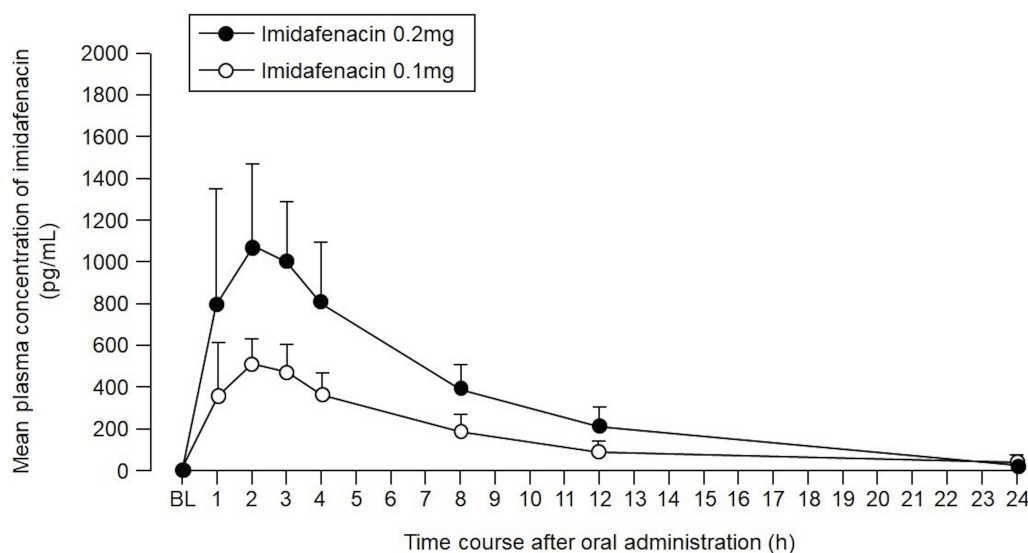

Figure 4 Pharmacokinetic data of plasma concentrations of imidafenacin. Sample sizes as full analysis set of imidafenacin 0.1 mg and 0.2 mg were 26 and 27, respectively. Data were plotted as circles. Standard deviations were expressed as bars.

positively correlated with the change in FEV$_1$ during the 24-hrs period after imidafenacin administration (Figure 5).

Safety Assessments

All 27 subjects received the test drugs and were the targets of the safety analysis. However, one subject revoked consent after finishing Period 2, and did not receive imidafenacin at Period 3. Thus, the safety analysis populations were 27 subjects for placebo and imidafenacin 0.2 mg, and 26 subjects for imidafenacin 0.1 mg. The incidences of AEs

were 11.1% in the imidafenacin 0.2 mg group and 7.7% in the imidafenacin 0.1 mg group, although there were no AEs in placebo group (Table 3). All AEs were mild, but not moderate nor severe. The imidafenacin 0.2 mg group had dry mouth (3.7%), muscle stiffness (3.7%), insomnia (3.7%), and skin exfoliation (3.7%), whereas the imidafenacin 0.1 mg group had thirst (3.8%) and T-wave inversion (3.8%) by ECG as AEs. No meaningful clinical changes in blood pressure or heart rate measured up to 24 hrs after administration were noted in all groups (data not shown).
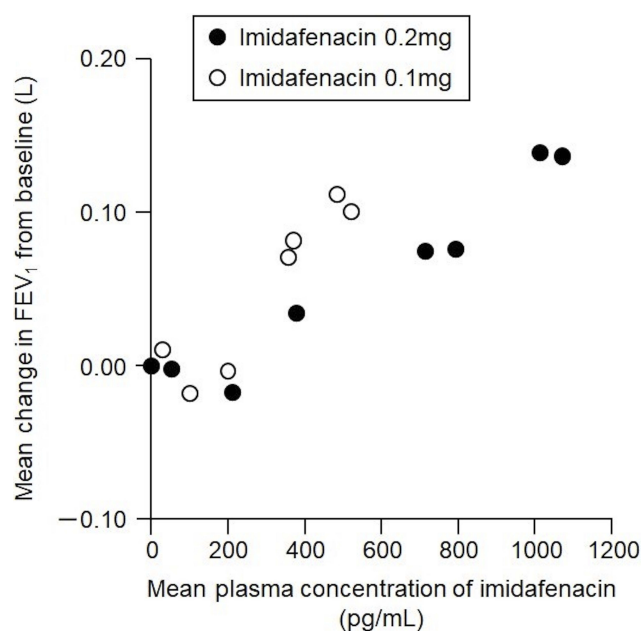
Figure 5 Relationship between plasma imidafenacin concentration and change in FEV_1. Plasma imidafenacin level was positively correlated with change in FEV_1 during the 24-hrs period immediately after imidafenacin administration. Data represent mean values for all patients at each time point.
Abbreviation: FEV_1, forced expiratory volume in 1 s.

There were also no clinically relevant changes in routine laboratory tests from the run-in period to the study completion.

Discussion

This study assessed the efficacy and safety of oral administration of imidafenacin in the treatment of COPD. The results showed that imidafenacin 0.1 mg and 0.2 mg were effective for the primary endpoint (maximum change in FEV_1 from baseline during 24 hrs after administration), and that imidafenacin 0.2 mg, but not 0.1 mg, was effective for the secondary endpoint (AUC_{24h} of FEV_1). However, the imidafenacin 0.1 mg increased the parameters to almost

the levels of statistical significance, when compared with a placebo.

The pharmacokinetic profiles of imidafenacin 0.1 mg and 0.2 mg showed almost identical T_{max}, $T_{1/2}$, and CL/F values with dose-dependent C_{max} and AUC values in patients with COPD. The profiles of kinetics were generally the same as previous observations in healthy subjects.[19] The previous study reported that the minimum change was 0.10 L in trough FEV_1 and has been recommended as the minimum clinically important difference in patients with COPD.[21] Actually, inhaled long-acting bronchodilators such as tiotropium and glycopyrronium bromide improve FEV_1 to exceed 0.10 L over 12 hrs in patients with COPD. Regarding oral imidafenacin 0.2 mg, the changes in FEV_1 were significantly higher than those for placebo from 1 hr up to 12 hrs, especially the changes at 2 hrs and 3 hrs of 0.128 L ($P<0.0001$) and 0.115 L ($P=0.0001$), respectively.

The treatment with imidafenacin 0.1 mg and 0.2 mg was well tolerated, as all subjects completed the trial without moderate or severe AEs including dysuria or glaucoma attacks in our study. Transient dry mouth and thirst and T-wave inversion by ECG might be related with imidafenacin as anticholinergic effects. All AEs (Table 3) were mild and also already known previously.[15,22,23] Neither clinically meaningful changes in vital signs nor clinically relevant changes occurred for both doses of imidafenacin in laboratory tests. Imidafenacin is predominantly metabolized by cytochrome P450 3A4 and uridine 5′-diphospho-glucurono-syltransferase 1A4 in liver.[24] The prevalence of COPD increases with age. Although the oral clearance of imidafenacin is decreased with advancing age, it has been reported that the effect of age on oral clearance was limited.[25] Previous studies supported our results that oral imidafenacin showed better tolerances and was safer than other anticholinergics in patients with overactive bladder disorder.[14–16]

Table 3 Summary of Adverse Events

Treatments	Placebo	Imidafenacin 0.1 mg	Imidafenacin 0.2 mg
n, SAF	27	26	27
Total occurrence, n (%)	0 (0)	2 (7.7)	3 (11.1)
Dry mouth	0 (0)	0 (0)	1 (3.7)
Thirst	0 (0)	1 (3.8)	0 (0)
Muscle stiffness	0 (0)	0 (0)	1 (3.7)
ECG T-wave inversion	0 (0)	1 (3.8)	0 (0)
Insomnia	0 (0)	0 (0)	1 (3.7)
Skin exfoliation	0 (0)	0 (0)	1 (3.7)

Abbreviations: ECG, electrocardiogram; SAF, safety analysis set.

Regarding the balance of pharmacological benefits and risks on chronic airway diseases between oral and inhaled administration, oral administration may have more effects on central to peripheral airway as benefits, but may exert more influences systemically as risks. Both doses of oral imidafenacin did not improve peripheral airway function, indicated in parameters of MMF, 25, 50, and 50/25 (Table S2A–E). Our results showed that treatment with oral imidafenacin had benefits with the improvement of FEV_1 safety in patients with COPD who had difficulty mastering inhalation techniques.[13] Oral imidafenacin was less effective in improving lung function than approval inhaled LAMAs, such as tiotropium, glycopyrronium, or umeclidinium. However, many studies have demonstrated that oral medications improve patient satisfaction and adherence compared with inhaled drugs.[26–28] Oral administration may contribute to pharmacological adherences significantly.

Our study demonstrated the efficacy and safety of a single dose of oral imidafenacin. Comparisons of efficacy between once-daily and twice-daily LAMAs are limited in the management for patients with COPD.[29,30] Using a network meta-analysis of randomized controlled trials, the twice-daily dosing had the efficacy of similar improvement in the lung function, health-related quality of life, and dyspnea when compared with once-daily dosing of LAMAs.[29,30] However, the twice-daily dosing may have more benefits than once-daily doing 12 hrs to 24 hrs after initial administration.[31] Aclidinium, twice-daily dosing, provided more bronchodilation during the nighttime, improvement of early-morning and nighttime symptoms, and early-morning limitation of activity than tiotropium, a once-daily dosing of LAMAs, in patients with moderate to severe COPD.[32] Imidafenacin should be administrated twice-daily clinically as like the treatment of patients with overactive bladder.

Our study has some limitations. First, imidafenacin showed no improvement of peripheral airway function. The sample size might be too small to find evidence since we calculated the sample size based on the estimated difference of FEV_1, primary endpoint, between imidafenacin and placebo. Second, the study was conducted only with the oral single administration. Thus, the efficacy of twice-daily dosing of oral imidafenacin is still unclear. Further studies are needed to evaluate the effects, tolerances, and safety of long-term usage. Third, the efficacy and safety of long-term imidafenacin therapy is still unknown in patients with COPD. Further studies are necessary to address these limitations.

Conclusion

In conclusion, the present study showed the potential usefulness and tolerability of oral imidafenacin for improving the pulmonary function of patients with COPD.

Abbreviations

AEs, adverse events; ANCOVA, analysis of covariance; AUC, area under the curve; AUC_{24h}, AUC from baseline to 24 hrs; AUC_{inf}, AUC from time 0 to infinity; CL/F, clearance; C_{max}, maximum plasma concentration of analyte; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; FAS, full analysis set; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MedDRA, Medical Dictionary for Regulatory Activities; MMF, mid-maximum flow; PEF, peak expiratory flow; PPS, per protocol set; RND, randomized patients; SAF, safety analysis set; SD, standard deviation; $T_{1/2}$, elimination half-life; T_{max}, time to reach C_{max}; V25, 25% vital capacity; V50, 50% vital capacity.

Ethics Approval And Consent To Participate

The study was approved by the Ethics Committee of each of the participating institutions and all subjects gave written informed consent.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgments

Author Contributions

Dr. Machida, Dr. Kawayama, Dr. Kinoshita, Dr. Tsuda, Dr. Takata, Dr. Koto, Dr. Yoshida, Dr. Ashihara, and Dr. Inoue were investigators for this study. Dr. Ichinose was the medical advisor for this study. All authors contributed to

data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

Dr. Kinoshita received honoraria from GlaxoSmithKline K.K., Daiichi Sankyo Co. Ltd., Novartis Pharma K.K., Takeda Pharmaceutical Co. Ltd., and Astellas Pharma Inc. Dr. Tsuda received honoraria from Novartis Pharma K.K., Pfizer Japan Inc., and Nippon Boehringer Ingelheim Co. Ltd. Mr. Kawashima and Dr. Suna are full-time employees of Ono Pharmaceutical Co. Ltd., Japan. Dr. Inoue received research grants from Asahi Kasei Corporation, Astellas Pharma Inc., Nippon Boehringer Ingelheim Co. Ltd., Chugai Pharmaceutical Co. Ltd., Sumitomo Dainippon Pharma Co. Ltd., Eisai Co. Ltd., MSD K.K., Nippon Kayaku Co. Ltd., Shionogi & Co. Ltd., Taisho Toyama Pharmaceutical Co. Ltd., and Teijin Pharma Ltd.; gave lectures and acted on advisory committees for Asahi Kasei Corporation, Astellas Pharma Inc., AstraZeneca K.K., Nippon Boehringer Ingelheim Co. Ltd., Chugai Pharmaceutical Co. Ltd., Eisai Co. Ltd., GlaxoSmithKline K.K., Eli Lilly Japan K.K., Kyorin Pharmaceutical Co. Ltd., MSD K.K., Meiji Seika Pharma Co. Ltd., Novartis Pharma K.K., Otsuka Pharmaceutical Co. Ltd., Pfizer Japan Inc., Shionogi & Co. Ltd., Taisho Pharmaceutical Co. Ltd., and Teijin Pharma Ltd. The authors report no other conflicts of interest in this work.

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