Journal of Pulmonary & Respiratory Medicine

Lange et al., J Pulm Respir Med 2014, 4:4
DOI: 10.4172/2161-105X.1000196

Research Article Open Access

The 24 Hour Lung Function Time Profile of Olodaterol Once Daily Versus Placebo and Tiotropium in Patients with Moderate to Very Severe Chronic Obstructive Pulmonary Disease

Peter Lange[1*], Joseph-Leon Aumann[2], Alan Hamilton[3], Kay Tetzlaff[4], Naitee Ting[5] and Eric Derom[6]

[1]*Hvidovre Hospital, Hvidovre/Section of Social Medicine, Department of Public Health, Copenhagen University, Copenhagen, Denmark*

[2]*Jesse Ziekenhuis, Hasselt, Belgium*

[3]*Boehringer Ingelheim, Burlington, Ontario, Canada*

[4]*Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany*

[5]*Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, Connecticut, USA*

[6]*Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium*

[*]**Corresponding author:** Peter Lange, Hvidovre Hospital, Section of Respiratory Medicine and Department of Public Health, University of Copenhagen, Kettegård Allé 30, DK-2650 Hvidovre, Denmark, Tel: +45 2687 9020; E-mail: peter.lange@sund.ku.dk

Received date: Apr 16, 2014, **Accepted date:** Jul 01, 2014, **Published date:** Jul 04, 2014

Abstract

Background: Olodaterol is a once-daily long-acting β2-agonist being investigated for the treatment of chronic obstructive pulmonary disease, with ≥ 24 hour bronchodilator activity.

Methods: Two replicate, randomized, double-blind, four-way crossover (6-week treatment periods), active (tiotropium 18 µg via HandiHaler®)- and placebo-controlled trials were conducted to evaluate the 24 hour forced expiratory volume in 1 second (FEV1) profile of olodaterol (5 and 10 µg) once daily (via Respimat®). Patients continued with inhaled corticosteroids and xanthines. Spirometry was performed at baseline and over the entire 24 hour post-dose period at week 6 of each treatment phase. Co-primary end points were change from study baseline (response) in FEV1 area under the curve from 0–12 hours (AUC0–12) and FEV1 AUC from 12–24 hours (AUC12–24); key secondary end point was FEV1 AUC from 0–24 hours response.

Results: In study 1222.39, there was a significant difference from placebo in FEV1 AUC0–12 and AUC12–24 responses (P<0.0001) with olodaterol 5 µg (0.185 and 0.131 L) and 10 µg (0.207 and 0.178 L) at 6 weeks; similar results were observed for tiotropium (0.173 and 0.123 L). In study 1222.40, responses were 0.197 and 0.153 L with olodaterol 5 µg, 0.221 and 0.170 L with 10 µg, and 0.221 and 0.164 L with tiotropium versus placebo (P<0.0001). Incidence of adverse events was comparable across treatments.

Conclusions: These data confirm the 24 hour lung-function efficacy profile of once-daily olodaterol, with FEV1 responses comparable to tiotropium.

Keywords: Bronchodilators; Chronic disease; Pharmacology

Abbreviations:

AE: Adverse Event; AUC0–3: Area under the curve from 0–3 hours; AUC0–12: Area under the curve from 0–12 hours; AUC0–24: Area under the curve from 0–24 hours; AUC12–24: Area under the curve from 12–24 hours; COPD: Chronic Obstructive Pulmonary Disease; ECG: Electrocardiogram; FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; GOLD: Global initiative for Chronic Obstructive Lung Disease; LABA: Long-acting β2-agonist; LAMA: Long-Acting Muscarinic Antagonist; QD: Once Daily

Background

Bronchodilators are central to maintenance treatment of Chronic Obstructive Pulmonary Disease (COPD), with long-acting β2-agonists (LABAs) and Long-Acting Muscarinic Antagonists (LAMAs) being established therapies, as supported by international recommendations [1]. The twice-daily LABAs formoterol and salmeterol have been available for a number of years. More recently, β-agonists with a longer duration of action have been developed that may allow more convenient once-daily (QD) dosing, with the potential to improve adherence [2].

Olodaterol is a LABA that has almost full β-agonistic activity with high β2 selectivity and ≥ 24 hour bronchodilator activity [3,4]. The efficacy and tolerability of olodaterol has been demonstrated in single-dose studies and studies of QD dosing for 4 weeks in COPD [5-7] and asthma [8,9]. Further evaluation of olodaterol has been undertaken in an integrated phase III program, consisting of five pairs of replicate studies to assess lung function, symptomatic relief, 24 hour bronchodilation profile, and effects on exercise in patients with moderate to very severe COPD.

The doses of olodaterol evaluated in the phase III program (5 and 10 μg QD) were based on the results of two phase II studies [7,10]. As part of the phase III evaluation, the two replicate studies presented here were designed to evaluate the 24 hour Forced Expiratory Volume in 1 second (FEV1) profile of olodaterol (5 and 10 μg) QD (via the Respimat®) in comparison to placebo and to the QD LAMA tiotropium (via the HandiHaler®) over 6 weeks in patients with Global initiative for chronic Obstructive Lung Disease (GOLD) 2–4 COPD.

Methods

Patients

Patients with stable moderate to very severe COPD (GOLD 2–4) were included if they had a post-bronchodilator FEV1 <80% of predicted normal and a post-bronchodilator FEV1/forced vital capacity (FVC) <70%. Patients were current or ex-smokers with a smoking history of >10 pack-years. Key exclusion criteria included significant disease other than COPD (i.e. a disease that may put the patient at risk because of participation, may influence the results of the study, or cause concern regarding the patient's ability to participate in the study), a history of asthma, myocardial infarction in the previous year, unstable or life-threatening cardiac arrhythmia, or hospitalization for heart failure within the previous year. Patients with unstable doses of oral or inhaled corticosteroid (<6 weeks on a stable dose) or who used doses of oral corticosteroids greater than the equivalent of 10 mg per day or 20 mg every other day were also excluded.

Study design

Study 1222.39 (NCT01040689) and study 1222.40 (NCT01040728) were replicate, randomized, double-blind, double-dummy, four-way crossover (6-week treatment periods separated by a 21 day washout), placebo- and active-controlled trials. Following an initial screening visit (Figure 1), patients entered a baseline period of 2–6 weeks to ensure that their COPD was clinically stables (i.e. no exacerbations). Eligible patients then proceeded into the 4×6-week double-blind crossover period during which they received olodaterol 5 μg and 10 μg administered QD by the Respimat® inhaler, tiotropium (18 μg) QD via the HandiHaler®, or placebo (both Respimat® and HandiHaler®) in a randomized sequence (Figure 1). Each treatment phase was separated by a 21 day washout period.

Patients were evaluated for an additional 21 days following completion of the last of four 6-week periods of randomized treatment, or, in case of discontinuation, after the final dose of study medication. The overall duration of the study was 38–42 weeks (depending on the length of screening) for each patient. Study drug was self-administered (according to a double-dummy blinding approach) between 7:00 AM and 10:00 AM daily; patients inhaled olodaterol (or placebo) from the Respimat® inhaler first (two actuations) followed by tiotropium (or placebo) from the HandiHaler®. The trial was carried out in compliance with the principles laid down in the Declaration of Helsinki and in accordance with the International Conference on Harmonised Tripartite Guideline for Good Clinical Practice. Prior to study initiation, the protocol was approved by the local Institutional Review Board, Independent Ethics Committee, and the Competent Authority. All patients provided written, informed consent prior to the study commencing. Details of the local Institutional Review Board/Independent Ethics Committee are provided in Supplementary Information in e-Table 1.

	Study 1222.39 (n=108)	**Study 1222.40 (n=122)**
Male, n (%)	83 (76.9)	75 (61.5)
Age, mean (SD), years	61.7 (8.8)	62.7 (7.9)
COPD diagnosis, mean (SD), years	9.4 (8.1)	9.3 (8.1)
Pre-bronchodilator		
Mean (SD) FEV1, L	1.483 (0.532)	1.233 (0.489)
Post-bronchodilator		
Mean (SD) FEV1, L	1.656 (0.527)	1.456 (0.516)
Mean (SD) FEV1 change from		
pre-bronchodilator, L	0.181 (0.162)	0.223 (0.152)
Mean (SD) FEV1/FVC, %	48.1 (11.7)	45.5 (11.1)
Mean (SD) % of predicted normal FEV1	56.4 (15.2)	50.5 (14.2)
GOLD, n (%)		
2	69 (63.9)	63 (51.6)
3	32 (29.6)	48 (39.3)
4	5 (4.6)	11 (9.0)

Body mass index, mean (SD), kg/m2	27.5 (4.4)	27.0 (6.3)
Current smoker, n (%)	46 (42.6)	66 (54.1)
Smoking history, mean (SD), pack-years	41.5 (19.3)	47.4 (23.5)
Baseline pulmonary medications		
Any pulmonary medication, n (%)	86 (79.6)	106 (86.9)
SAMA,a n (%)	14 (13.0)	17 (13.9)
LAMAb (tiotropium), n (%)	42 (38.9)	51 (41.8)
SABAc (inhaled), n (%)	62 (57.4)	74 (60.7)
LABAb (inhaled), n (%)	52 (48.1)	66 (54.1)
Steroids, n (%)		
Inhaledd	50 (46.3)	63 (51.6)
Orald	1 (0.9)	4 (3.3)
Xanthinesd, n (%)	9 (8.3)	7 (5.7)

Table 1: Baseline patient demographics

aNot permitted during treatment period.

bPatients switched to study medication during treatment period.

cAll patients were provided with SABA as a rescue medication during this study.

dPermitted during treatment period.

COPD: Chronic Obstructive Pulmonary Disease; FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; LABA: Long-acting β2-agonist; LAMA: Long-acting muscarinic antagonist; SABA: Short-acting β-agonist; SAMA: Short-acting muscarinic antagonist; SD: Standard Deviation.

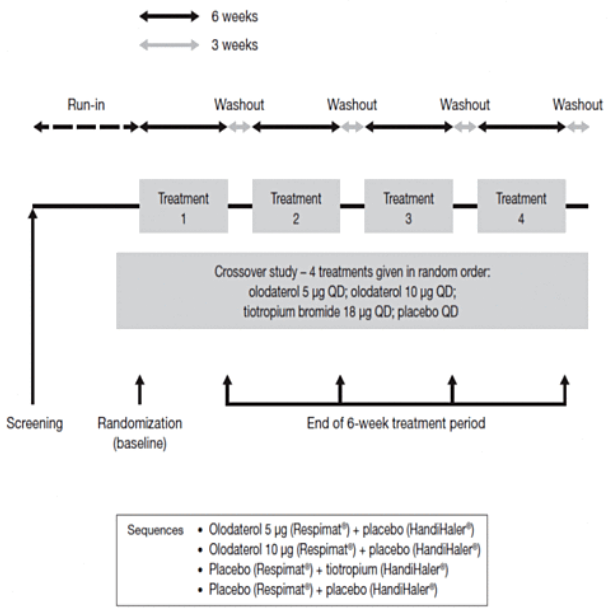

Figure 1: Design of study 1222.39 and study 1222.40.

QD: once daily.

Short-acting muscarinic antagonists, LAMAs, and LABAs were not permitted during the treatment periods; however, patients were required to continue treatment with inhaled corticosteroids, oral corticosteroids (≤ 10 mg prednisone per day or ≤ 20 mg prednisone every other day [or equivalent]), or methylxanthines, if being used as maintenance therapy at study entry.

End points

The primary efficacy variable was FEV1. There were two co-primary efficacy end points: FEV1 area under the curve from 0–12 hours (AUC0–12) response (change from study baseline) and FEV1 area under the curve from 12–24 hours (AUC12–24) response after 6 weeks of treatment. These were calculated from zero time to 12 hours and from 12–24 hours, respectively, using the trapezoidal rule and divided by the corresponding duration (i.e. 12 hours) to give the results in liters.

FEV1 area under the curve from 0–24 hours (AUC0–24) was identified as a key secondary end point. Other secondary efficacy end points included FEV1 area under the curve from 0–3 hours (AUC0–3), trough FEV1, as well as the corresponding FVC end points (FVC AUC0–12, FVC AUC12–24, FVC AUC0–24, FVC AUC0–3, and trough FVC). In addition, a pre-specified analysis of pooled data from the two studies was conducted focusing on the comparison of olodaterol (5 μg, 10 μg) and tiotropium. Safety end points included adverse events (AEs) and serious AEs, vital signs, blood chemistry, and electrocardiogram (ECG).

Assessments

At the start of each treatment period, spirometry was conducted at 1 hour and at 10 minutes prior to administration of the morning dose of study medication and 30 minutes and 1, 2, and 3 hours post-dose. At the end of each 6-week treatment period, spirometry was repeated at 30 minutes prior to administration of the morning dose and for 24 hours post-dose (30 minutes, 1, 2, 3, 4, 6, 8, 10, 12, 22, and 23 hours, and 23 hours 50 minutes post-dose). At each time point, spirometric measurements were conducted in triplicate and the highest FEV1 and FVC from an acceptable maneuver was recorded.

At each visit, all AEs reported by the patient were recorded, irrespective of causality, and the severity of the AE was classified by a clinician. Blood pressure and pulse rate were measured prior to spirometry at all visits (and ≤ 3 hours post-dose at baseline at all treatment visits). Clinical laboratory testing (hematology, blood chemistry, and urinalysis) was performed at screening, after each randomized treatment period, and in case of premature withdrawal from the study. A standard 12 lead ECG was performed at screening for all patients. At each subsequent study visit, ECGs were performed pre-dose and repeated ~40 minutes post-dose.

Statistical analysis

It was estimated that with 80 completed patients, each study would be able to detect treatment differences of 0.060 L for FEV1 AUC0–12 response (standard deviation 0.160 L) with 91% power, and 0.060 L for FEV1 AUC12–24 response (standard deviation 0.140 L) with 96% power. Based on an estimated dropout rate of 20%, it was planned that 100 patients would be randomized.

Adjusted mean FEV1 AUC0–12 and FEV1 AUC12–24 responses were analyzed using a mixed model for repeated measurements. This model included treatment and period as fixed effects, patient as a random effect, and study baseline as a continuous covariate. For all continuous secondary end points, a mixed model for repeated measurements was performed as described for the primary analysis. Compound symmetry was used as the covariance structure for within-patient variation.

All efficacy analyses were performed on the full analysis set, which was defined as all randomized patients who received at least one dose of treatment and had a baseline and at least one post-baseline measurement.

No formal statistical analysis was planned for the safety comparisons; summary statistics are presented based on the pooled safety population (defined as all randomized patients who received at least one dose of treatment).

Results

Patient disposition and baseline characteristics

A total of 230 patients were randomized to treatment in the two studies (Figures 2a and 2b): 108 in study 1222.39 and 122 in study 1222.40. Study 1222.39 was conducted at 15 centers in Belgium, Denmark, Germany, and Hungary, while study 1222.40 was conducted at 12 centers in Germany, The Netherlands, Norway, and the US. Both studies were conducted between January 2010 and January 2011.

All randomized patients received at least one dose of study drug and the majority completed all four treatment periods (84.3% in study 1222.39 and 78.7% in study 1222.40). AEs, including worsening of COPD, were the most frequent reasons cited for discontinuation.

The baseline demographic characteristics of patients in the two studies are shown in Table 1. Baseline FEV1 was somewhat lower in study 1222.40 than study 1222.39, with a greater proportion of current smokers and higher usage of inhaled corticosteroids. However, patients in study 1222.40 experienced a slightly greater difference between pre-bronchodilator and post-bronchodilator FEV1 than patients in study 1222.39.

Efficacy

For FEV1 at individual time points at week 6, there were statistically significant differences between olodaterol (both doses) and placebo (P<0.001) at each time point from 30 minutes pre-dose through to 23 hours 50 minutes post-dose (Figures 3a and 3b and Supplementary Information [e-Figure 1]). The 24 hour FEV1 time profiles for tiotropium were generally similar to olodaterol. FVC profiles were generally consistent with the FEV1 results (Supplementary Information [e-Figures 2a and 2b]).

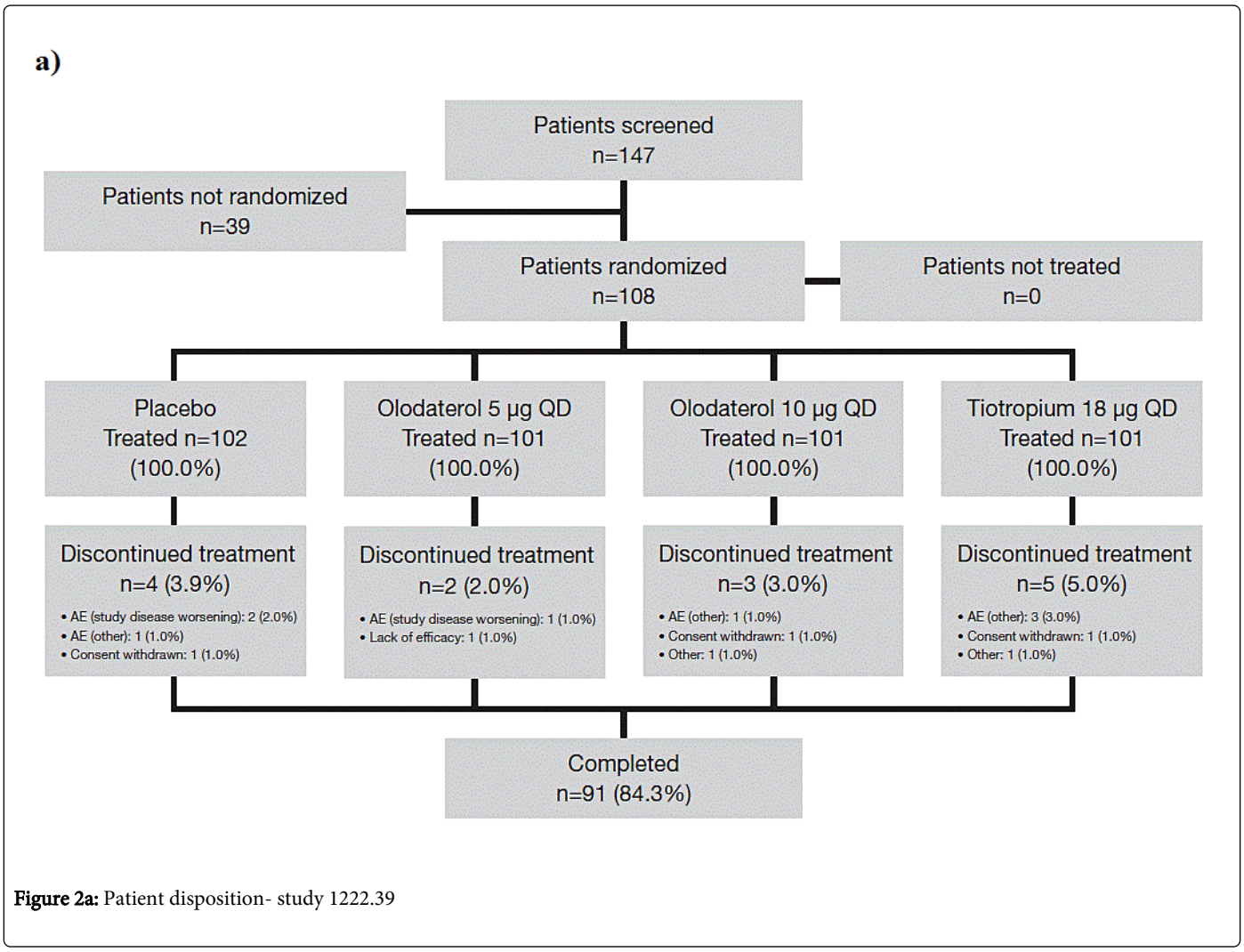

Figure 2a: Patient disposition- study 1222.39

Primary and key secondary end points

At week 6, statistically significant (P<0.0001) improvements in both FEV1 AUC0–12 and FEV1 AUC12–24 responses were observed for both doses of olodaterol and tiotropium compared to placebo in both studies (Tables 2 and 3). The responses were generally higher in study 1222.40 than study 1222.39.

In both studies, there were also statistically significant (P<0.0001) improvements in the key secondary end point FEV1 AUC0–24 response for both doses of olodaterol and tiotropium compared to placebo.

Other secondary end points

Results for the other secondary end points supported the primary end points and are presented in table 4 and Supplementary Information [e-Tables 2–5], with significant (P<0.0001) improvements in FEV1 AUC0–3 and trough FEV1 responses for both doses of olodaterol and tiotropium compared to placebo at week 6. In addition, there were significant improvements in FVC AUC0–12, FVC AUC12–24, FVC AUC0–3, and trough FVC compared to placebo at week 6.

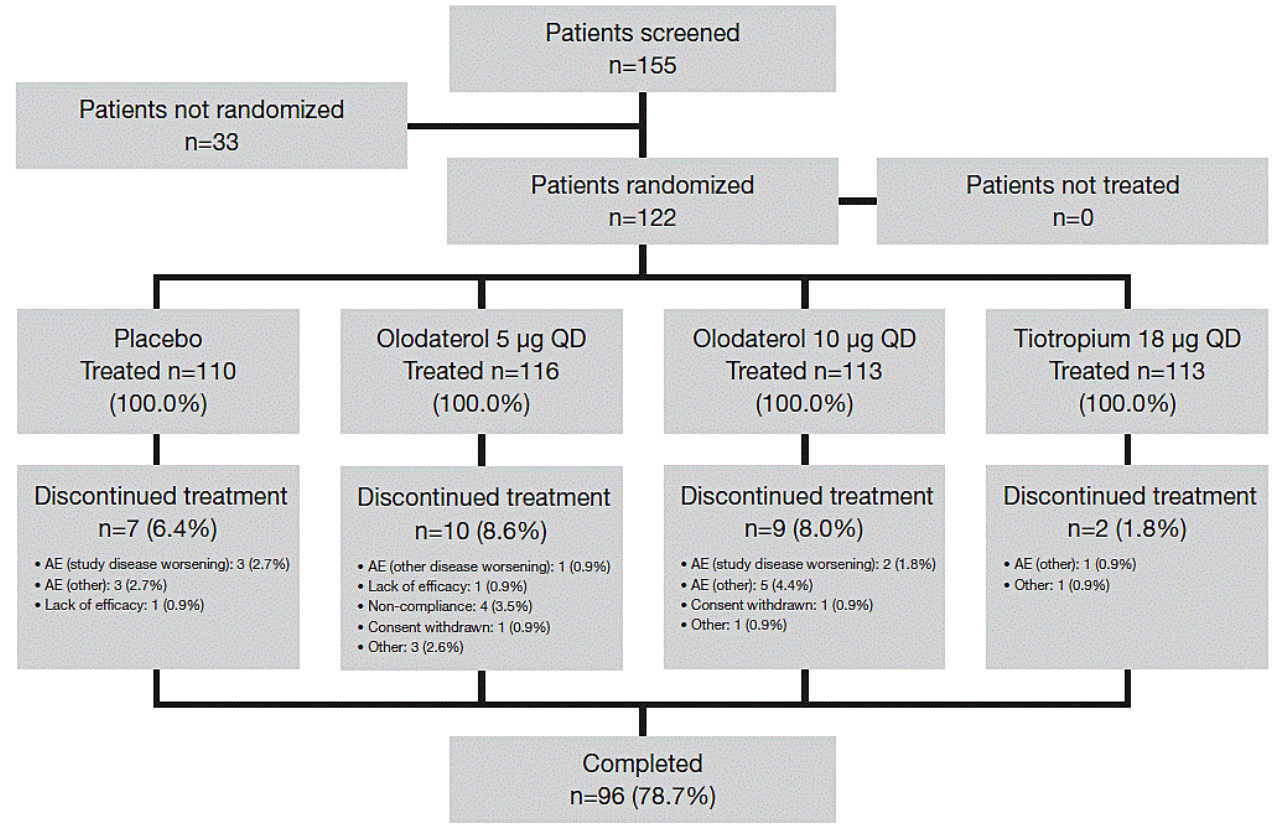

Figure 2b: Patient disposition- study 1222.40.

AE: adverse event; QD: once daily.

	Treatment		**Adjusteda mean difference from placebo**		
Trial/treatment	n	Adjusted mean (SE)	Mean (SE)	P value	95% CI
Study 1222.39					
Placebo	99	-0.054 (0.020)			
Olodaterol 5 µg	100	0.131 (0.020)	0.185 (0.020)	<0.0001	0.145, 0.224
Olodaterol 10 µg	99	0.152 (0.020)	0.207 (0.020)	<0.0001	0.167, 0.246
Tiotropium 18 µg	99	0.119 (0.020)	0.173 (0.020)	<0.0001	0.133, 0.212
Study 1222.40					
Placebo	105	-0.008 (0.019)			
Olodaterol 5 µg	115	0.189 (0.019)	0.197 (0.017)	<0.0001	0.163, 0.231
Olodaterol 10 µg	106	0.213 (0.019)	0.213 (0.019)	<0.0001	0.186, 0.255
Tiotropium 18 µg	112	0.213 (0.019)	0.221 (0.017)	<0.0001	0.187, 0.255

Table 2: FEV1 AUC0–12 responses (L) after 6 weeks.

aAdjusted for baseline and period.

AUC0–12: Area under the curve from 0–12 hours; CI: Confidence Interval; FEV1: Forced Expiratory Volume in 1 second; SE: Standard Error.

	Treatment		**Adjusteda mean difference from placebo**		
Trial/treatment	n	Adjusted mean (SE)	Mean (SE)	P value	95% CI
Study 1222.39					
Placebo	99	-0.095 (0.021)			
Olodaterol 5 µg	100	0.036 (0.021)	0.131 (0.021)	<0.0001	0.090, 0.173
Olodaterol 10 µg	99	0.082 (0.021)	0.178 (0.021)	<0.0001	0.136, 0.219
Tiotropium 18 µg	99	0.027 (0.021)	0.123 (0.021)	<0.0001	0.081, 0.164
Study 1222.40					
Placebo	105	-0.059 (0.018)			
Olodaterol 5 µg	115	0.094 (0.018)	0.153 (0.018)	<0.0001	0.117, 0.188
Olodaterol 10 µg	107	0.111 (0.018)	0.170 (0.018)	<0.0001	0.134, 0.205
Tiotropium 18 µg	112	0.105 (0.018)	0.164 (0.018)	<0.0001	0.128, 0.199

Table 3: FEV1 AUC12–24 responses (L) after 6 weeks.

aAdjusted for baseline and period.

AUC12–24: Area under the curve from 12–24 hours; CI: Confidence Interval; FEV1: Forced Expiratory Volume in 1 second; SE: Standard Error.

Treatment comparison: pre-specified pooled analysis

There were no differences between olodaterol 5 µg and tiotropium in FEV1 AUC0–12, AUC12–24, or AUC0–24 responses at week 6 (Supplementary Information [e-Table 6]). There was a numerical difference in the FEV1 AUC12–24 response between olodaterol 10 µg and tiotropium at week 6 (P<0.05); differences in FEV1 AUC0–12 and AUC0–24 responses showed P values >0.05. Other than for FEV1 AUC12–24, there were no significant differences between olodaterol 5 and 10 µg (Supplementary Information [e-Table 6]).

Safety

No deaths were reported during the studies. Incidence of AEs was similar across the treatment groups (Table 5), and the most frequent AEs were nasopharyngitis (19.4%), worsening of COPD (13.9%), dyspnea (6.5%), and cough (5.6%). Most events were mild or moderate in intensity and not considered related to treatment. There was a low incidence of AEs leading to discontinuation of study medication: 3.8% with placebo, 1.4% with olodaterol 5 µg, 3.3% with olodaterol 10 µg, and 2.8% with tiotropium. The most common reason for discontinuation was worsening of COPD, which occurred more frequently with placebo. Serious AEs were recorded for the individual trials by the investigators; there were 10 and 17 patients in the 1222.39 and 1222.40 studies, respectively. Two patients discontinued treatment with olodaterol 10 µg due to atrial fibrillation. In one case (a patient with a history of hypertension and an FEV1:FVC ratio of 32.5% on entry to the study), the investigator considered there was a reasonable probability of a relationship between the atrial fibrillation and treatment with olodaterol (as well as salbutamol); following discontinuation of study treatment and initiation of digitalis, the atrial fibrillation resolved. Cardiac disorders by treatment, primary system organ class, and preferred term are described in the Supplementary Information in e-Table 7 and overall blood potassium changes are included in e-Table 8.

No changes indicative of an AE were seen for any laboratory parameters, vital signs, or ECG in either study.

	Treatment		**Adjusteda mean (95% CI) difference from placebo at 6 weeks**		
Trough FEV1	n	Adjusted mean (SE)	Mean (SE)	P value	95% CI
Study 1222.39					
Placebo	99	-0.043 (0.020)			
Olodaterol 5 µg	100	0.090 (0.020)	0.133 (0.019)	<0.0001	0.096, 0.170
Olodaterol 10 µg	99	0.104 (0.020)	0.147 (0.019)	<0.0001	0.110, 0.184
Tiotropium 18 µg	99	0.054 (0.020)	0.097 (0.019)	<0.0001	0.060, 0.134

Study 1222.40					
Placebo	105	0.003 (0.019)			
Olodaterol 5 µg	115	0.137 (0.019)	0.134 (0.019)	<0.0001	0.097, 0.171
Olodaterol 10 µg	107	0.146 (0.019)	0.143 (0.019)	<0.0001	0.105, 0.181
Tiotropium 18 µg	112	0.161 (0.019)	0.158 (0.019)	<0.0001	0.120, 0.195
FEV1 AUC0–3					
Study 1222.39					
Placebo	99	-0.045 (0.019)			
Olodaterol 5 µg	100	0.161 (0.019)	0.206 (0.019)	<0.0001	0.170, 0.243
Olodaterol 10 µg	99	0.170 (0.019)	0.215 (0.018)	<0.0001	0.179, 0.252
Tiotropium 18 µg	99	0.137 (0.019)	0.182 (0.019)	<0.0001	0.146, 0.219
Study 1222.40					
Placebo	105	0.011 (0.020)			
Olodaterol 5 µg	115	0.225 (0.019)	0.214 (0.019)	<0.0001	0.178,0.251
Olodaterol 10 µg	106	0.255 (0.020)	0.245 (0.019)	<0.0001	0.208,0.282
Tiotropium 18 µg	112	0.246 (0.019)	0.235 (0.019)	<0.0001	0.199, 0.271
FEV1 AUC0–24					
Study 1222.39					
Placebo	99	-0.075 (0.020)			
Olodaterol 5 µg	100	0.083 (0.020)	0.158 (0.019)	0.158 (0.019)	0.121, 0.196
Olodaterol 10 µg	99	0.117 (0.020)	0.192 (0.019)	<0.0001	0.155, 0.230
Tiotropium 18 µg	Tiotropium 18 µg	0.073 (0.020)	0.148 (0.019)	<0.0001	0.110, 0.185
Study 1222.40					
Placebo	105	-0.033 (0.019)			
Olodaterol 5 µg	115	0.142 (0.018)	0.175 (0.017)	<0.0001	0.141, 0.208
Olodaterol 10 µg	107	0.158 (0.018)	0.191 (0.017)	<0.0001	0.157, 0.225
Tiotropium 18 µg	112	0.159 (0.018)	0.192 (0.017)	<0.0001	0.159, 0.226

Table 4: Secondary efficacy end point: FEV1 responses (L) after 6 weeks.

aAdjusted for baseline and period.

AUC0–3: area under the curve from 0–3 hours; AUC0–24: area under the curve from 0–24 hours; CI: confidence interval; FEV1: forced expiratory volume in 1 second; SE: standard error.

AE	Placebo (n=211)	Olodaterol 5 µg (n=216)	Olodaterol 10 µg (n=214)	Tiotropium 18 µg (n=214)
Any AE, n (%)	72 (34.1)	73 (33.8)	78 (36.4)	73 (34.1)
Nasopharyngitis	12 (5.7)	14 (6.5)	8 (3.7)	11 (5.1)
COPD	10 (4.7)	14 (6.5)	9 (4.2)	6 (2.8)
Dyspnea	5 (2.4)	5 (2.3)	5 (2.3)	6 (2.8)

Cough	6 (2.8)	1 (0.5)	7 (3.3)	5 (2.3)
Headache	4 (1.9)	4 (1.9)	2 (0.9)	3 (1.4)
Hypertension	2 (0.9)	2 (0.9)	2 (0.9)	2 (0.9)
Back pain	3 (1.4)	2 (0.9)	0	3 (1.4)

Table 5: AEs occurring with an overall incidence of ≥3%a (pooled data).

aCalculated as the sum of the patients reporting AEs across all treatments in both trials divided by 230 (i.e. the safety population).

AE: Adverse Event; COPD: Chronic Obstructive Pulmonary Disease.

Discussion

These replicate studies in patients with moderate to very severe COPD demonstrated that QD olodaterol 5 and 10 µg resulted in significant improvements in FEV1 over the entire 24 hour dosing period, as demonstrated by the FEV1 AUC0–12, FEV1 AUC12–24, and FEV1 AUC0–24 responses after 6 weeks.

The tiotropium–olodaterol comparison is of particular value, as it allows the responses observed with olodaterol to be viewed in the context of those with the well-established "gold standard" treatment in COPD with a QD profile.

Similar results were observed for olodaterol 5 and 10 µg and tiotropium; while the FEV1 AUC12–24 response for olodaterol 10 µg was numerically higher than for tiotropium (P<0.05), no account was taken of multiple testing and, therefore, limited conclusions can be drawn regarding their comparative or differential efficacy.

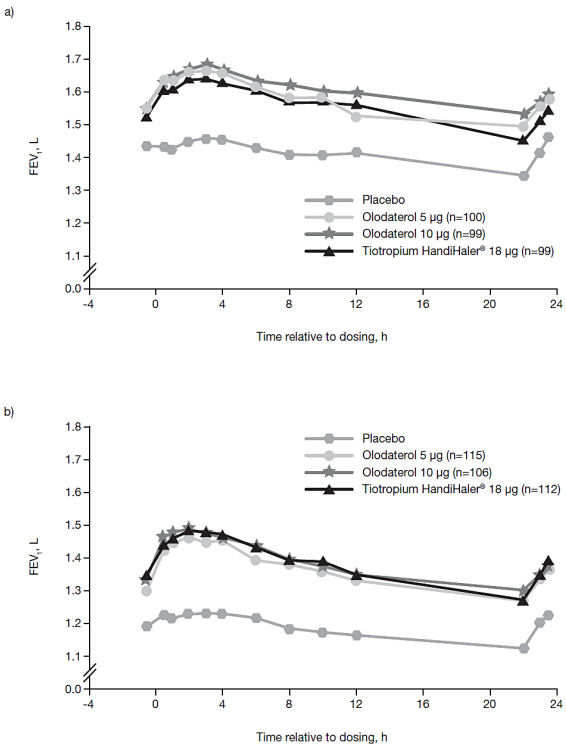

Figure 3: FEV1 at individual time points at week 6: (a) study 1222.39; (b) study 1222.40. All comparisons versus placebo (P<0.0001).

FEV1: forced expiratory volume in 1 second.

The results for the secondary efficacy end points support those of the primary end points. Indeed, the inclusion of both peak (FEV1 AUC0–3) and trough FEV1 end points (i.e. at both ends of the daily dosing profile) provide further evidence to confirm the 24 hour activity of olodaterol. These end points are of interest as they allow comparison with results from the pivotal studies within the olodaterol phase III clinical program,

which were conducted under different trial conditions. In two sets of replicate studies, the mean FEV1 AUC0–3 responses (difference from placebo) ranged from 0.129–0.172 L with olodaterol 5 μg and 0.143–176 L with olodaterol 10 μg QD (ranges for trough FEV1 were 0.047–0.091 L and 0.048–0.101 L, respectively) [11,12]. These responses are lower than in the present studies, reflecting the fact that patients in the previous studies were allowed to continue on background COPD therapies, including tiotropium. This highlights the importance of assessing the characteristics of the patient populations and background therapies when interpreting effect sizes [13].

Differences in the magnitude of the responses observed in the two studies, with larger effects generally seen in study 1222.40, may be a reflection of different baseline characteristics in the study populations. While pre-bronchodilator FEV1 was higher in study 1222.39, FEV1 responsiveness was greater in study 1222.40; this difference in the responsiveness of the study populations is reflected in the higher FEV1 AUC0–3 responses observed in study 1222.40. Since the studies were designed and managed as replicate studies, the differences in baseline characteristics are likely due to random sampling effects.

Similar lung function responses were observed in two independent, replicate, 6-week studies of olodaterol 5 and 10 μg in comparison with twice-daily formoterol [14]. FEV1 AUC0–12 and FEV1 AUC0–24 were also used as primary end points in these trials and, taken together, the two sets of replicate studies provide a valid and rigorous means of characterizing the pharmacologic activity of olodaterol, based on 24 hour spirometry.

Further support is available from earlier phase II studies using the same primary end points, demonstrating that olodaterol 5 and 10 μg administered QD provide significant and identical bronchodilation over the complete 24 hour dosing period [5,7].

The data from these trials add to the comprehensive set of evidence for the efficacy and safety of QD olodaterol in COPD derived from the wider phase III olodaterol clinical program [11,12,14]; this includes the 12 hour lung function testing performed in a subset of patients at 12 weeks in two replicate 48-week studies [11].

In general, the frequency of AEs was similar with olodaterol to placebo and tiotropium, although in study 1222.40 slightly more events were observed with the 10 μg dose. The incidence of AEs typically associated with LABAs was low; while two patients were discontinued from olodaterol 10 μg due to atrial fibrillation, only in one case did the investigator consider that there was a reasonable probability of it being related to study medication.

While the studies were designed to characterize the bronchodilatory profile of olodaterol over the full 24 hour period, one limitation was the gap in the 24 hour spirometry between 12 and 22 hours post-dose, which corresponds to the time when patients were allowed to sleep in the clinic (or in a hotel close to the clinic). While this is usual practice for such studies, it might be argued that interim measurements could have been performed. However, the validity of such interim measurements is unclear, since patients would be required to conduct effort-dependent spirometric maneuvers immediately after waking during the middle of the night. Furthermore, the interrupted sleep might have impacted on the quality of the spirometry performed the following morning. As shown in Figure 3, FEV1 time profiles over the 24 hour post-dose period were still achievable even with this necessary 8 hour interruption and indicate that olodaterol provides bronchodilation throughout the 24 hour observation period without abolishing the circadian variation.

Conclusions

These data confirm the 24 hour lung-function efficacy profile of olodaterol 5 and 10 μg QD, with FEV1 responses over 24 hours that were comparable to tiotropium. FEV1 responses were comparable between olodaterol 5 and 10 μg QD and support the selection of the 5 μg dose for later use in clinical practice. These results add to the wider evidence from the olodaterol clinical program supporting its clinical profile as an effective QD bronchodilator.

Acknowledgments

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. They take full responsibility for the scope, direction, content of, and editorial decisions relating to, the manuscript, were involved at all stages of development, and have approved the submitted manuscript. The authors received no compensation related to the development of the manuscript. Medical writing assistance was provided by Rob Kite, BSc, of Complete HealthVizion, which was contracted and compensated by Boehringer Ingelheim Pharma GmbH & Co. KG.

Funding

These studies were funded by Boehringer Ingelheim Pharma GmbH & Co. KG.

Competing interests

Dr P Lange: has received grant monies and consultancy fees from pharmaceutical companies.

Dr J-L Aumann: has nothing to disclose.

Dr A Hamilton, Dr K Tetzlaff, and Dr N Ting: are employees of Boehringer Ingelheim.

Dr E Derom: has acted as a consultant to Boehringer Ingelheim and Actelion, as a speaker for Boehringer Ingelheim and GlaxoSmithKline, and on advisory boards for Chiesi and AstraZeneca.

This work was supported by Boehringer Ingelheim Pharma GmbH & Co. KG.

Author contributions

Dr P Lange: contributed to the study conception and design, and provided oversight of the studies.

Dr J-L Aumann: contributed to the study conception and design, and provided oversight of the studies and analysis of the data.

Dr A Hamilton: contributed to the study conception and design, and provided oversight of the studies and analysis of the data.

Dr K Tetzlaff: contributed to the study conception and design.

Dr N Ting: contributed to the study conception and design, and provided oversight of the studies and analysis of the data.

Dr E Derom: contributed to the study conception and design, and provided oversight of the studies and analysis of the data.

All authors were responsible for the drafting, review, and final approval of the manuscript.

References

1. Global Initiative for Chronic Obstructive Lung Disease (2013) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease.
2. Cazzola M, Calzetta L, Matera MG (2011) b2-adrenoceptor agonists: current and future direction. Br J Pharmacol 163: 4-17.
3. Bouyssou T, Casarosa P, Naline E, Pestel S, Konetzki I, et al. (2010) Pharmacological characterization of olodaterol, a novel inhaled b2-adrenoceptor agonist exerting a 24-hour-long duration of action in preclinical models. J Pharmacol Exp Ther 334: 53-62.
4. Casarosa P, Kollak I, Kiechle T, Ostermann A, Schnapp A, et al. (2011) Functional and biochemical rationales for the 24-hour-long duration of action of olodaterol. J Pharmacol Exp Ther 337: 600-609.
5. van Noord JA, Smeets JJ, Drenth BM, Rascher J, Pivovarova A, et al. (2011) 24-hour bronchodilation following a single dose of the novel b2-agonist olodaterol in COPD. Pulm Pharmacol Ther 24: 666-672.
6. van Noord JA, Korducki L, Hamilton A, Koker P (2009) Four weeks once daily treatment with BI 1744 CL, a novel long-acting b2-agonist, is effective in COPD patients. Am J Respir Crit Care Med 179: abs A6183.
7. Joos G, Aumann JL, Coeck C, Korducki L, Hamilton AL, et al. (2012) Comparison of 24-hour FEV1 profile for once-daily versus twice-daily treatment with olodaterol, a novel long-acting B2-agonist, in patients with COPD. Am J Respir Crit Care Med 185: abs A2930.
8. O'Byrne PM, van der Linde J, Cockcroft DW, Gauvreau GM, Brannan JD, et al. (2009) Prolonged bronchoprotection against inhaled methacholine by inhaled BI 1744, a long-acting b2-agonist, in patients with mild asthma. J Allergy Clin Immunol 124: 1217-1221.
9. O'Byrne PM, D'Urzo T, Gahlemann M, Hart L, Wang F, et al. (2012) Dose-finding study of once-daily treatment with olodaterol, a novel long-acting b2-agonist, in patients with asthma. Am J Respir Crit Care Med 185: abs A3963.
10. van Noord JA, Korducki L, Hamilton AL, Koker P (2012) Four weeks once daily treatment with BI 1744, a novel long-acting b2-agonist, is effective in COPD patients. Poster presented at the American Thoracic Society International Conference, San Francisco, California, USA, May 18-23.
11. Ferguson G, Feldman G, Hofbauer P, Hamilton A, Allen L, et al. (2013) Lung function efficacy of olodaterol QD delivered via Respimat® in COPD patients: Results from two 48-week studies. Eur Respir J 42 (Suppl 57): 5s, abs 187.
12. Koch A, Pizzichini E, Hamilton A, Hart L, Korducki L, et al. (2013) Lung function efficacy of olodaterol QD delivered via Respimat® versus placebo and formoterol BID in patients with COPD: two 48-week studies. Poster P764 presented at the European Respiratory Society Annual Congress, Barcelona, Spain, 7-11 September.
13. Cazzola M, MacNee W, Martinez FJ, Rabe KF, Franciosi LG, et al. (2008) Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 31: 416-469.
14. Feldman G, Bernstein J, Hamilton A, Nivens C, Wang F, et al. (2013) The 24-hour FEV1 time profile of olodaterol once daily (QD) via Respimat® and formoterol twice daily (BID) via Aerolizer® in patients with COPD: results from two 6-week studies. Abstract 749A presented at CHEST, Chicago, Illinois, USA, October 26-31.