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Short Communication

Effect of bronchodilators in healthy individuals receiving lumacaftor/ivacaftor combination therapy

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Abstract

In an open-label, single-center phase 1 pharmacokinetic study in healthy subjects who received lumacaftor (LUM) in combination with ivacaftor (IVA), review of spirometry data showed a transient decline in percent predicted forced expiratory volume in 1 s ($ppFEV_1$) within 4 h of drug administration. An additional cohort of healthy subjects with normal baseline $ppFEV_1$ values was studied to evaluate the $ppFEV_1$ response to LUM/IVA administration and assess the effect of long-acting bronchodilators (LABDs) and short-acting bronchodilators (SABDs) on $ppFEV_1$ response. The $ppFEV_1$ decline observed at 4 h was attenuated following administration of an LABD and reversed following administration of an SABD. Concomitant administration of LUM/IVA with bronchodilators was well tolerated. These data show that a transient decline in $ppFEV_1$ was observed in healthy subjects following administration of LUM/IVA combination therapy, which can be ameliorated with LABDs or SABDs.

1. Introduction

In 2 phase 3 studies, treatment with the combination of lumacaftor (LUM) and ivacaftor (IVA) resulted in clinically meaningful improvements in lung function, rate of pulmonary exacerbations and nutritional status in patients aged 12 years or older with cystic fibrosis (CF) who were homozygous for the *F508del-CFTR* mutation [1]. LUM/IVA was generally well tolerated; however, the incidence of certain respiratory adverse events (AEs), including dyspnea and chest tightness, was higher in LUM/IVA-treated patients than placebo-treated patients. These AEs were often associated with initiation of therapy and generally resolved within the first few weeks of treatment [1]. In a phase 2 study of patients with CF who had an *F508del-CFTR* mutation, dose-dependent reductions in percent predicted forced expiratory volume in 1 s ($ppFEV_1$) were observed during the 28-day period of LUM monotherapy [2]. Review of spirometry data from an open-label, single-center phase 1 pharmacokinetic study in healthy volunteers [3] revealed a transient decline in $ppFEV_1$ within 4 h of administration of LUM/IVA combination therapy. To better understand this decline, a cohort was added to the latter study to evaluate $ppFEV_1$ response within 4 h of LUM/IVA administration and assess the effect of long-acting bronchodilators (LABDs) and short-acting bronchodilators (SABDs) on $ppFEV_1$ response.

2. Methods

Healthy male and female volunteers aged 18 to 55 years with $ppFEV_1$ 80 or higher, body mass index 18 to 31 kg/m^2 and body weight more than 50 kg were eligible; those with a history of regular alcohol consumption, smoking and bronchodilator use within the previous 28 days were excluded. Participants were randomized to 1 of 4 dosing sequences (1:1:1:1), each of which included 3 dosing periods (period 1: days −2 to 2; period 2: days 6 to 9; period 3: days 13 to 16). Once during each dosing period on days 1, 8 and 15, LUM 200 mg was administered in combination with IVA 250 mg orally in the morning. The peak concentrations in healthy subjects administered LUM 200 mg/IVA 250 mg were projected to be comparable to the peak concentrations in patients

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with CF administered LUM 400 mg/IVA 250 mg. As shown in Figs. 1 and 2, an SABD (albuterol 2.5 mg or ipratropium 0.5 mg) was administered by inhalation via nebulizer during each dosing period (after the 4-h spirometry assessment) and an LABD (indacaterol 75 μg or tiotropium 18 μg) was administered via inhalation in dosing periods 2 and 3 (12 h prior to and 12 h after LUM/IVA administration); spirometry assessments were performed throughout the study.

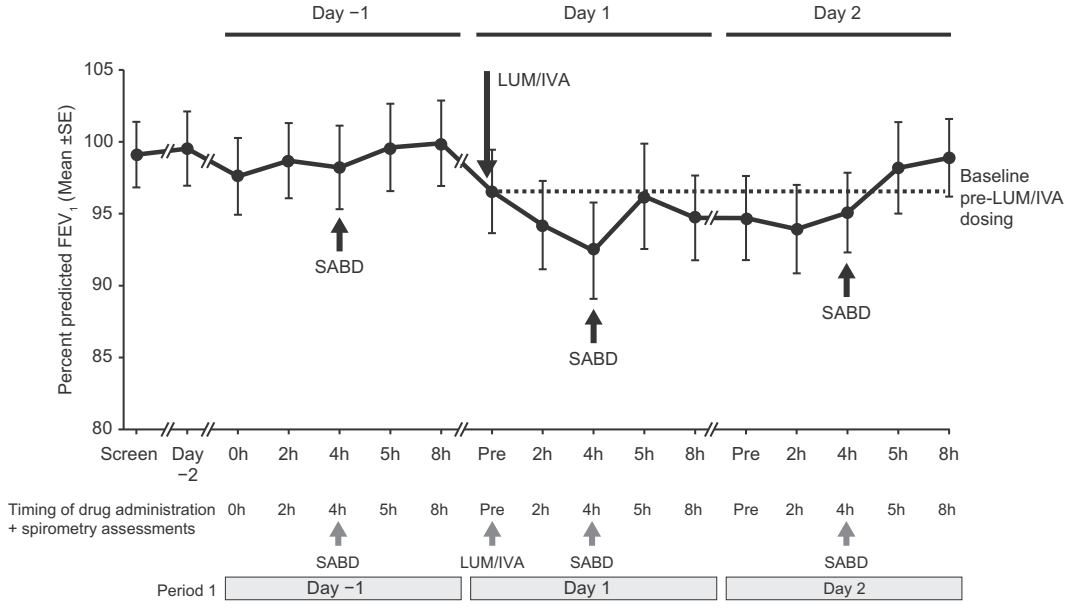
The primary outcome measure was the absolute change in $ppFEV_1$ from before to 4 h after LUM/IVA administration. Safety was assessed by the incidence of treatment emergent AEs, vital signs, clinical laboratory tests, electrocardiograms, spirometry and physical examinations. A mixed model for repeated measures was used to evaluate the overall effect of LABDs by comparing the absolute change in $ppFEV_1$ from before LUM/IVA to 4 h post LUM/IVA in the presence and absence of LABDs. The model included sequence and treatment (albuterol + ipratropium, indacaterol, tiotropium) as fixed effects, period baseline $ppFEV_1$ as a covariate and subject nested within sequence as a random effect. Data for $ppFEV_1$ were pooled for administration of an SABD (albuterol, ipratropium) and an LABD (indacaterol, tiotropium).

3. Results

A total of 26 participants was enrolled; 24 (92.3%) completed the study and 2 (7.7%) withdrew consent and were discontinued after dosing period 1. Baseline characteristics were well balanced for participants in each dosing sequence. The mean age (SD) was 36.5 (10.5) years and mean $ppFEV_1$ (SD) was 96.6 (14.8).

We observed a transient decline in $ppFEV_1$ after a single dose of LUM/IVA (mean absolute change [SD] on day 1 at 4 h was −4.1 [5.6] percentage points). The absolute change in $ppFEV_1$ for each individual subject is shown in Fig. 3. The decline in $ppFEV_1$ was rapidly reversed following administration of an SABD (Fig. 1). The mean (SD) difference in absolute change in $ppFEV_1$ from 4 h to 5 h post LUM/IVA following administration of an SABD in the absence of an LABD was 3.8 (5.8) percentage points ($p = 0.003$); similar results were observed with beta agonists and anticholinergics (4.0 [5.5] percentage points for albuterol and 3.5 [6.3] percentage points for ipratropium). Moreover, when an LABD was administered 12 h before LUM/IVA, the decline in $ppFEV_1$ was attenuated (Fig. 2). The mean absolute change (SD) was −1.4 (4.1) percentage points on days 8 and 15 (average) at 4 h post LUM/IVA. The least squares (LS) mean (SE) difference for attenuation of the decline in $ppFEV_1$ in the presence of all LABDs vs in the absence of LABDs was 2.9 (1.4) percentage points ($p = 0.046$); findings were similar for beta agonists and anticholinergics (LS mean [SE]: 3.1 [1.6] percentage points for indacaterol and 2.8 [1.6] percentage points for tiotropium). As shown in Fig. 2, an SABD administered 4 h post LUM/IVA in the presence of an LABD led to further improvement in $ppFEV_1$.

Overall, 11 participants (42.3%) reported AEs, all of which were mild (n = 9) or moderate (n = 2) in severity. AEs occurring in more than one participant included oropharyngeal



	Day 1					Day 2 (Time matched)				
Percent predicted FEV_1	Pre	2h	4h	5h	8h	Pre	2h	4h	5h	8h
Mean	96.6	94.2	92.4	96.2	94.7	94.7	93.9	95.1	98.2	98.9
Absolute difference		−2.3	−4.1	−0.3	−1.8		−0.8	0.4	3.5	4.2

Fig. 1. Percent predicted FEV_1 before and after LUM/IVA administration in the absence of LABD (period 1). Data are mean $ppFEV_1$ during period 1 and error bars indicate standard error. FEV_1, forced expiratory volume in 1 s; LUM/IVA, lumacaftor/ivacaftor; SABD, short-acting bronchodilator; SE, standard error.