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Original Article

Lumacaftor/ivacaftor in patients with cystic fibrosis and advanced lung disease homozygous for *F508del-CFTR*☆

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Abstract

Objective: Evaluation of the safety, tolerability, and efficacy of lumacaftor/ivacaftor in patients with cystic fibrosis (CF) with severe lung disease.
Methods: Patients with CF 12 years of age and older, homozygous for *F508del-CFTR*, with percent predicted forced expiratory volume in 1 second ($ppFEV_1$) < 40 received lumacaftor 400 mg/ivacaftor 250 mg every 12 h (full dose) for 24 weeks in an open-label, prospective study (NCT02390219). Dose modification to half dose for 1–2 weeks (including at initiation) was permitted. Safety and tolerability were the primary outcome measures; clinical outcomes were also assessed.
Results: Of 46 patients (initiated on full dose: n = 28; initiated on half dose: n = 18), 35 (76%) completed 24 weeks of treatment. The most common adverse events included infective pulmonary exacerbation, abnormal respiration, cough, and dyspnea. Compared with patients initiating on full dose, patients initiating at half dose had less frequent respiratory events (56% vs 71%) of shorter median duration (4 vs 9 days). No dose modifications or discontinuations as a result of respiratory events occurred in patients initiating on half dose who were then increased to the full dose over 2 weeks (versus three each for patients on full dose). Following an initial reduction, $ppFEV_1$ was similar to baseline from week 4 throughout the remainder of the study (least squares mean [95% confidence interval] at week 24: −0.4 [−1.9, 1.1]; p = 0.6249). Compared with the 24 weeks prior to study, the annualized hospitalization rate was lower (rate ratio: 0.41; p = 0.00026) and the duration of intravenous antibiotics was shorter (mean [standard deviation] difference: −8.52 [24.91] days; p = 0.0369) through study week 24.
Conclusions: Compared with patients with higher lung function, respiratory events were more common in patients with $ppFEV_1$ < 40; aside from these events, the lumacaftor/ivacaftor safety profile was consistent with previous studies. Results suggest that patients with $ppFEV_1$ < 40 may benefit from treatment initiation at a lower dose with augmented monitoring before increasing to the full dose.

Keywords: Cystic fibrosis; *F508del*; Lumacaftor; Ivacaftor; Severe lung dysfunction; Advanced lung disease

Abbreviations: AE, adverse event; AESI, adverse event of special interest; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CF, cystic fibrosis; CFQ-R, Cystic Fibrosis Questionnaire–Revised; CI, confidence interval; IV, intravenous; IVA, ivacaftor; LS, least squares; LUM, lumacaftor; MMRM, mixed-effects model for repeated measures; PEx, pulmonary exacerbations; $ppFEV_1$, percent predicted forced expiratory volume in 1 s; q12h, once every 12 h; ULN, upper limit of normal.

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1. Introduction

In patients with cystic fibrosis (CF) who were ≥ 12 years of age and homozygous for the *F508del-CFTR* mutation, lumacaftor/ivacaftor (LUM/IVA) combination therapy improved lung function, nutritional status, and pulmonary exacerbations (PEx) compared with placebo (ClinicalTrials.gov identifiers: NCT01807923 and NCT01807949) [1]. These clinical benefits of LUM/IVA were sustained for up to 120 weeks on treatment and were associated with a reduced rate of decline in percent predicted forced expiratory volume in 1 s ($ppFEV_1$) compared with the Cystic Fibrosis Foundation registry control population [2].

Compared with patients with higher lung function (ie, $ppFEV_1 > 40$), patients with CF and advanced lung disease ($ppFEV_1 < 40$) have a greater burden of disease, with an increased frequency of PEx, worse nutritional status, a greater likelihood of lung transplantation, and an increased risk of mortality [3–6]. Assessing therapeutic options that are both safe and effective is of particular interest for patients with CF and advanced lung disease.

While the eligibility criteria to enroll in LUM/IVA pivotal clinical studies required patients to have a $ppFEV_1$ of 40–90 at screening [1], a subgroup analysis of phase 3 LUM/IVA clinical studies examined the safety and efficacy of LUM/IVA in patients whose $ppFEV_1$ fell below 40 between the screening and baseline study visits [7]. Treatment benefits in patient with $ppFEV_1 < 40$ were consistent with the overall patient population; however, an increased incidence of respiratory events, including dyspnea and chest tightness, were observed [7]. In the clinical practice setting, there have been reports of increased frequency in respiratory adverse events (AEs) in patients with $ppFEV_1 < 40$ initiating treatment with LUM/IVA [8–10]. This study evaluated the safety and efficacy of LUM/IVA in patients with CF who were homozygous for the *F508del-CFTR* mutation and had advanced lung disease ($ppFEV_1 < 40$) in a prospective, open-label, 24-week clinical study.

2. Methods

This was a phase 3b open-label study of LUM/IVA (Orkambi, Vertex Pharmaceuticals Incorporated, Boston, MA, USA) in patients with CF who were homozygous for the *F508del-CFTR* mutation and had advanced lung disease ($ppFEV_1 < 40$) (ClinicalTrials.gov identifier: NCT02390219). The study was conducted in accordance with Good Clinical Practice guidelines and was reviewed and approved by institutional review boards. All patients of age of consent (per local requirements) provided written informed consent; for patients below the local age of consent, the patient's parent/legal guardian provided written informed consent, and the patient provided assent when applicable per local requirements.

This study was conducted at six sites in the United States between February 19, 2015, and October 3, 2016. Eligible patients with a diagnosis of CF were 12 years of age or older, homozygous for the *F508del-CFTR* mutation, and had a $ppFEV_1$ value < 40 adjusted for age, gender, and height at screening [11,12] ($ppFEV_1 \geq 40$ at baseline was permitted). Key exclusion criteria included (1) current use of invasive mechanical ventilation; (2) a history of any significant comorbidity or laboratory abnormality that, in the investigator's judgment, might have interfered with study assessments or posed an undue risk for the patient; and (3) abnormal liver (at least 3 of aspartate aminotransferase [AST], alanine aminotransferase (ALT), gamma-glutamyl transpeptidase, and alkaline phosphatase ≥ 3 times the upper limit of normal (ULN); or ALT or AST > 5 times ULN; or bilirubin > 2 times ULN) or renal function (glomerular filtration rate ≤ 45 ml/min/1.73 m^2, calculated by the Counahan-Barratt equation [13]). Target enrollment was 100 to 200 patients.

Patients received LUM 400 mg every 12 h (q12h) in combination with IVA 250 mg q12h orally for 24 weeks. Based on the observation early in this study of a serious AE of respiratory chest tightness, the study protocol was amended to permit the option of modification to half dose of study drug (LUM 200 mg q12h in combination with IVA 125 q12h) for up to 7 days at the discretion of the treating physician following discussion with and approval by the medical monitor. This included the option of initiating the study on half dose of study drug. The dose modification could be extended by the treating physician; no patient was on the modified dose for > 15 days.

Patient visits were as follows: screening (within 4 weeks of study initiation), days 1 and 2, weeks 2, 4, 8, 16, and 24, and follow-up 4 weeks after the last dose of study drug (Fig. 1). Spirometry was performed at all patient visits and the Cystic Fibrosis Questionnaire–Revised (CFQ-R), weight, height, pregnancy test, vital signs, pulse oximetry, and information on AEs and concomitant medications, treatments, and procedures were collected at all study visits. All questionnaires were completed before the start of any other assessments scheduled at that visit. In addition, telephone interviews were conducted at day 3, week 12, and week 20 to assess patients' status, any AEs, concomitant medications, treatments, and procedures.

2.1. Outcomes

The primary endpoint was the safety and tolerability of LUM/IVA based on treatment-emergent AEs (Medical Dictionary for Regulatory Activities [MedDRA] version 19), including respiratory adverse events of special interest (AESIs; defined as asthma, bronchial hyperreactivity, bronchospasm, chest discomfort, dyspnea, respiration abnormal, and wheezing), clinical laboratory values (hematology and serum chemistry), and standard digital 12-lead electrocardiograms. Safety evaluations also included physical examinations, vital signs (including nutritional status parameters), pulse oximetry, and day 2 spirometry. Secondary endpoints included absolute change from baseline in $ppFEV_1$ at each study visit up to week 24, absolute change from baseline in the CFQ-R respiratory domain score through week 24, absolute change from baseline in sweat chloride to the average of day 15 and week 4, total number of days of intravenous (IV) antibiotics for sinopulmonary signs and symptoms through week 24, and total number of all-cause hospitalizations through week 24. Absolute change from baseline in body mass index (BMI) was evaluated as an additional safety assessment and was also evaluated for efficacy.

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