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Original Article

Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-*G551D* gating mutation

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Abstract

Background: Ivacaftor is used to treat patients with CF and a *G551D* gating mutation; the KONNECTION study assessed the efficacy and safety of ivacaftor in patients with CF and a non-*G551D* gating mutation.
Methods: Patients with CF ≥6 -years- old with non-*G551D* gating mutations received ivacaftor 150 mg q12h or placebo for 8 weeks in this 2-part, double-blind crossover study (Part 1) with a 16-week open-label extension (Part 2). The primary efficacy outcome was absolute change in FEV_1 through 8 and 24 weeks of ivacaftor treatment; secondary outcomes were changes in BMI, sweat chloride, and CFQ-R and safety through 8 and 24 weeks of treatment.
Results: Eight weeks of ivacaftor resulted in significant improvements in percent predicted FEV_1, BMI, sweat chloride, and CFQ-R scores that were maintained through 24 weeks. Ivacaftor was generally well tolerated.
Conclusions: Ivacaftor was efficacious in a group of patients with CF who had selected non-*G551D* gating mutations.

Keywords: Ivacaftor; Gating mutation; Potentiator; *G551D*

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive genetic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene [14,17]. These mutations result in a lack of functional CFTR protein or dysfunctional CFTR protein channels at the surface of epithelial cells, which causes impaired chloride transport, dysregulated fluid balance, and thickened mucosal secretions in organ systems such as the lungs, pancreas, sweat glands, and reproductive organs [1,16]. Most available treatments for CF address the symptoms and sequelae of the disease rather than the underlying molecular pathophysiology [8,11].

To date, more than 1,900 mutations in the *CFTR* gene have been identified [5]. Molecular characterization of the *CFTR* mutations has led to classification according to whether the functional defect impacts CFTR protein production, trafficking, function, or stability [2,17]. The opening and closing functions of the CFTR channel, termed gating, are mostly due to conformational changes to the channel driven by ATP binding and hydrolysis in the channel's cytosolic nucleotide-binding domains [10]. Class III mutations limit ATP-dependent channel gating, resulting in loss of CFTR-dependent chloride transport [17,21].

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The most common Class III gating mutation is *G551D*, which accounts for approximately 4% of the CF population worldwide [19]. Other mutations that reduce CFTR channel gating include *G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P,* and *G1349D*; however, these mutations are very rare, jointly accounting for approximately 1% of patients with CF [2]. As for many other *CFTR* mutations, large regional differences in the occurrence of these mutations have been documented [7].

One approach to increasing chloride transport in cells with gating mutations is to use a CFTR potentiator, which is a compound that increases the open probability of CFTR channels at the cell surface [18,21]. In vitro studies showing that ivacaftor improves chloride transport in cells expressing the *G551D* mutation [18] led to clinical studies demonstrating the efficacy and safety of ivacaftor in patients with this mutation [6,13]. Subsequently, ivacaftor was approved for the treatment of CF in patients ≥6 years of age with a *G551D* mutation. However, there is evidence to suggest that other patients with CF may benefit from ivacaftor treatment as well. In vitro research has shown that ivacaftor potentiates chloride transport in cells expressing non-*G551D* gating mutations, including *G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P,* and *G1349D* [21]. Therefore, it was hypothesized that ivacaftor would potentiate chloride transport and improve clinical outcomes in a genetically diverse group of patients with CF who carry one of these non-*G551D* gating mutations.

2. Materials and methods

2.1. Study design

KONNECTION (VX12-770-111) was a 2-part, randomized, controlled study to evaluate the safety and efficacy of ivacaftor in patients with CF ≥6 -years-old with a non-*G551D* gating mutation on at least one allele (ClinicalTrials.gov identifier NCT01614470). This was an international multi-center study of 12 sites in the United States, France, and Belgium. Part 1 of the study was an 8-week, double-blind, placebo-controlled crossover study including a 4-to-8-week washout period. Part 2 was an open-label extension period designed to assess the durability of any observed treatment effects through 24 weeks of continuous treatment (Supplemental Figure S1).

In Part 1, eligible patients were randomized 1:1 to 1 of 2 treatment sequences: ivacaftor 150 mg q12h for 8 weeks followed by placebo q12h for 8 weeks (sequence 1, ivacaftor → placebo) or placebo q12h for 8 weeks followed by ivacaftor 150 mg q12h for 8 weeks (sequence 2, placebo → ivacaftor). In Part 2 of the study, all patients received ivacaftor 150 mg q12h for 16 weeks. Thus, patients randomized to treatment sequence 1 (ivacaftor → placebo) had a maximum of 16 weeks of continuous ivacaftor treatment; patients randomized to treatment sequence 2 had a maximum of 24 weeks of continuous ivacaftor treatment.

The study was conducted in compliance with Institutional Review Board regulations, Good Clinical Practice guidelines, and the Declaration of Helsinki. All patients provided written informed consent or assent, as appropriate.

2.2. Study population

Male and female patients who were ≥6 -years-old and had a confirmed diagnosis of CF [15] and the presence of one of the following *CFTR* mutations on ≥1 allele were eligible for inclusion: *G178R*, *S549N*, *S549R*, *G551S*, *G970R*, *G1244E*, *S1251N*, *S1255P*, or *G1349D*. Patients must have had an FEV_1 ≥40 percent of predicted at screening, based on the Hankinson standard [9] for males ≥18 years and females ≥16 years of age, or the Wang standard [20] for males 6 to 17 years of age and females 6 to 15 years of age. There was no upper limit for percent predicted FEV_1 at screening. Exclusion criteria included the presence of the *G551D* mutation and the use of inhaled hypertonic saline, which was not an approved therapy at the time of this study.

2.3. Outcome measures

In Part 1, the primary outcome measure was the absolute change from baseline in percent predicted FEV_1 through 8 weeks of ivacaftor treatment. Secondary outcome measures included the absolute change from baseline in BMI at 8 weeks of treatment; sweat chloride through 8 weeks of treatment (evaluated using a Macroduct® [Wescor, Logan, UT] collection device; samples were sent to a central laboratory for testing [quantification by coulometric titration]); and respiratory domain score of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) [12] through 8 weeks of treatment.

In Part 2, the primary outcome measure was the absolute change from baseline in percent predicted FEV_1 through 24 consecutive weeks of ivacaftor treatment, which was obtained from patients in treatment sequence 2 only (8 weeks in Part 1, period 2, plus 16 weeks in Part 2). Secondary outcome measures included the absolute change from baseline in BMI at 24 weeks of treatment, sweat chloride through 24 weeks of treatment, and the respiratory domain score of the CFQ-R through 24 weeks of treatment.

Safety and tolerability were assessed throughout the study using AE reports, clinical laboratory values for serum chemistry, hematology, and coagulation, ophthalmologic examinations, electrocardiograms (ECGs), and vital signs. Pulmonary exacerbations, as previously defined, were also evaluated [13].

2.4. Statistical analyses

The full analysis and safety sets included all patients randomized to treatment groups who received at least 1 dose of study drug. In Part 1, the analyses for the absolute change in percent predicted FEV_1, sweat chloride, and CFQ-R were based on a mixed-effects model for repeated measures (MMRM). The model included the absolute change from the baseline in each treatment period as the dependent variable, with sequence, treatment, period, and visit within period as fixed effects, study baseline (for the measure) and age as covariates, and patient nested within sequence as the random effect. The absolute change from baseline in BMI was analyzed using a linear mixed model (LMM), with sequence, period, and treatment as