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 FEV1 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 FEV1, 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.

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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].
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 FEV1 ≥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 FEV1 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 FEV1 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 FEV1 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 FEV1, 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
fixed effects, visit within period and the treatment by visit interaction as random effects, and adjustment for study baseline age and percent predicted FEV₁ as covariates; visit was treated as a continuous variable. The absolute changes from baseline in percent predicted FEV₁ at (2, 4, and 8 weeks) and BMI, sweat chloride, and CFQ-R (at 8 weeks) were compiled by genotype.

In Part 2, the absolute change from baseline in percent predicted FEV₁ through 24 weeks of treatment for patients originally randomized to placebo was defined as the average of non-missing measurements after 2, 4, 8, 16, and 24 weeks of treatment. Secondary outcome measures in Part 2 were also summarized.

3. Results

3.1. Patients

Thirty-nine patients were enrolled and randomized to treatment groups; in Part 1, 20 patients were randomized to treatment sequence 1 (ivacaftor → placebo) and 19 to treatment sequence 2 (placebo → ivacaftor; Supplemental Figure S2). At baseline, defined as the measure closest to but before the first dose of study drug, the mean age of patients was 22.8 years and the mean percent predicted FEV₁ was 78.4 (Table 1). The majority of patients were white and not Hispanic or Latino (28/39, 71.8%). The mean sweat chloride of patients was high (97.5 mmol/L), and most patients were pancreatic insufficient (79.5%). All baseline characteristics were similar between treatment sequences and similar to G551D patient populations (Table 1). Three patients discontinued treatment during Part 1. One patient was lost to follow-up (sequence 2) and 2 patients (1 in each sequence group) discontinued due to the need for antibiotic therapy that extended the between-period washout (classified as “other”). Eighteen patients from each treatment sequence in Part 1 completed Part 2.

3.2. Efficacy

3.2.1. Part 1: Double-blind, 8-week crossover study

3.2.1.1. Overall. Patients receiving ivacaftor demonstrated a significant ($P < 0.0001$) improvement in absolute percent predicted FEV₁ (7.5 percentage points) through 8 weeks of treatment, whereas FEV₁ declined in patients receiving placebo (−3.2 percentage points; Fig. 1a). The model- adjusted absolute mean treatment difference between the ivacaftor and placebo groups was 10.7 percentage points (95% CI: 7.3, 14.1). Statistically significant effects of ivacaftor treatment were also observed at weeks 2 and 4 ($P < 0.0001$ at both time points) when compared with placebo. The model- adjusted mean differences between ivacaftor and placebo groups at weeks 2 and 4 were 8.3 percentage points (95% CI: 4.5, 12.1) and 10.0 percentage points (95% CI: 6.2, 13.8), respectively. Additional analyses showed that the treatment sequence had no significant impact on the observed effects (data not shown).

Improvements in response to ivacaftor treatment were also observed in the model-adjusted mean changes from baseline in BMI, sweat chloride, and CFQ-R (Figs. 1b–d). The model-adjusted absolute mean change from baseline in BMI at week 8 was greater during treatment with ivacaftor (0.7 kg/m²) compared with placebo (0.02 kg/m²), resulting in a treatment difference of 0.7 kg/m² (95% CI: 0.34, 0.99; $P < 0.0001$; Fig. 1b). Similarly, the model-adjusted absolute mean change from baseline in BMI-for-age $z$-score showed a significant improvement (0.24 points) at week 8 in ivacaftor-treated patients compared with patients receiving placebo (−0.04 points), resulting in a treatment effect of 0.28 points (95% CI: 0.12, 0.45; $P = 0.0010$).

The model-adjusted mean change from baseline in sweat chloride through 8 weeks of treatment with ivacaftor was −52.3 mmol/L compared with −3.1 mmol/L during the placebo period (Fig. 1c). The resulting treatment effect was −49.2 mmol/L (95% CI: −57.0, −41.4; $P < 0.0001$). Ivacaftor treatment led to a significant decline in sweat chloride as early as week 2 (model-adjusted mean change, −48.2 mmol/L; 95% CI: −54.0, −37.5; $P < 0.0001$) that was sustained through week 8.

The model-adjusted mean change from baseline in the pooled (all questionnaire versions) CFQ-R respiratory domain score through week 8 was significantly greater in patients treated with ivacaftor (8.9 points) compared with patients receiving placebo.
The resulting treatment difference was 9.6 points (95% CI: 4.5, 14.7; P = 0.0004). The improvement in CFQ-R score was observed as early as week 2 of ivacaftor treatment (model-adjusted mean change, 6.1 points; 95% CI: 0.61, 12.8; P = 0.03). At week 8, 28/38 patients treated with ivacaftor (73.7%) had an increase in CFQ-R score of ≥4 points, which is considered to be the minimal clinically important difference, compared with 11/37 patients (29.7%) on placebo.

3.2.1.2. By genotype. All genotype subgroups showed positive mean numerical changes from baseline in BMI, CFQ-R score, and FEV₁ at week 8 of treatment (Table 2), with high variability among and within subgroups. Mean changes in sweat chloride were also similar among the genotype subgroups, with the exception of the G970R subgroup, which showed a reduction in sweat chloride that was markedly lower relative to the other mutation subgroups.

3.2.2. Part 2: Open-label, 16-week extension study

All 36 patients who completed Part 1 of the study entered Part 2 and completed the 16-week open-label extension study, 18 of whom are represented in the 24-week outcome measures. The mean absolute change from baseline in percent predicted FEV₁ through week 24 of ivacaftor treatment was 13.5 percentage points (range, −6.9 to 36.5; Fig. 2). Examination of secondary outcome measures revealed that the mean absolute change from baseline in BMI at week 24 was 1.3 kg/m² (range, 0.16 to 2.9); the mean absolute change from baseline in sweat chloride through week 24 was −59.2 mmol/L (range, −93.5 to 40.5); and the mean absolute change from baseline in CFQ-R respiratory domain score was 11.4 (range, −16.7 to 33.3).

3.3. Safety

In Part 1, adverse events were reported by 83.8% (31/37) of patients receiving placebo and 73.7% (28/38) of patients receiving ivacaftor (Table 3). The most commonly reported AEs in both treatment groups were infections, respiratory disorders, and gastrointestinal disorders. Within the placebo group, pulmonary exacerbations (11/37; 29.7%), cough (7/37; 18.9%), and headache (5/37; 13.5%) were the most commonly reported AEs. The most commonly reported AEs in the ivacaftor group were pulmonary exacerbation (9/38; 23.7%) and cough (6/38; 15.8%). Seven patients (18.9%) in the placebo group and 4 (10.5%) patients in the ivacaftor group experienced serious AEs (SAEs). The SAEs were six pulmonary exacerbations and one event each of appendiceal mucocoele, intussusception, pneumothorax, and paranasal cyst in the placebo group; and two pulmonary exacerbations, one distal ileal obstruction syndrome event, and one intervertebral disc protrusion event in the ivacaftor group.

During Part 2, AEs were reported by 83.3% (15/18) of patients in either treatment sequence in part one (Table 3). During the 16-week open-label extension, the most commonly reported AEs overall were respiratory disorders, infections, and gastrointestinal disorders. In the group continuing on ivacaftor, the most commonly reported AEs were cough (3/18; 16.7%)
and pulmonary exacerbation (3/18; 16.7%). The most commonly reported AEs in the ivacaftor → placebo group were headache (4/18; 22.2%) and pulmonary exacerbation (3/18; 16.7%). Overall, three patients reported six SAEs; there were generally well tolerated; during Part 1, the number of reported AEs and serious AEs was comparable in the placebo and ivacaftor groups. The specific AEs reported throughout the study were similar to those previously reported in STRIVE and ENVISION—Phase 3 studies of ivacaftor in patients with CF and the G551D-CFTR gating mutation [6,13].

Although the studies cannot be compared directly, the treatment effects observed in the KONNECTION study were similar in direction and magnitude to the treatment effects reported in the STRIVE and ENVISION studies [6,13]. In STRIVE and ENVISION, the effects of ivacaftor treatment on percent predicted FEV1, sweat chloride, and CFQ-R respiratory domain scores in patients with CF and a non-G551D gating mutation. Improvements in percent predicted FEV1, sweat chloride, and CFQ-R respiratory domain score were detectable by week 2 of treatment and sustained through 8 weeks of treatment; moreover, the results from the open-label extension period supported the durability of improvements in lung function through 24 weeks. Treatment with ivacaftor was generally well tolerated; during Part 1, the number of reported AEs and serious AEs was comparable in the placebo and ivacaftor groups. The specific AEs reported throughout the study were similar to those previously reported in STRIVE and ENVISION —Phase 3 studies of ivacaftor in patients with CF and the G551D-CFTR gating mutation [6,13].

The examination of efficacy outcomes according to CFTR gating mutation indicated that there were varying degrees of clinical improvement after 8 weeks of treatment with ivacaftor. Sample sizes for each mutation were extremely small, so conclusions about the relative efficacy of ivacaftor by genotype should not be drawn at this stage; some genotype subgroups included as few as two patients, and intraindividual variability in these clinical measures is expected. In this study, there was no upper limit to FEV1 as an entry criterion; in some patients, a ceiling effect may be present. However, while the mean

<table>
<thead>
<tr>
<th>Mutation</th>
<th>n</th>
<th>Absolute change from baseline in % predicted FEV1, % points, mean (min, max)</th>
<th>Absolute change from baseline in sweat chloride at week 8, mmol/L, mean (min, max)</th>
<th>Absolute change from baseline in BMI at week 8, kg/m², mean (min, max)</th>
<th>Absolute change from baseline in CFQ-R Score at week 8, points, mean (min, max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1244E (5)</td>
<td>11.08 (−5.20, 25.41)</td>
<td>5.54 (−4.63, 12.95)</td>
<td>8.36 (−0.93, 18.37)</td>
<td>−55.10 (−75.0, −34.0)</td>
<td>0.63 (0.34, 1.32)</td>
</tr>
<tr>
<td>G1349D (2)</td>
<td>19.42 (5.49, 33.36)</td>
<td>18.48 (1.60, 35.37)</td>
<td>19.67 (2.97, 36.37)</td>
<td>−80.25 (−81.5, −79.0)</td>
<td>1.15 (1.07, 1.22)</td>
</tr>
<tr>
<td>G178R (5)</td>
<td>7.46 (1.42, 16.99)</td>
<td>10.23 (−2.31, 20.53)</td>
<td>8.37 (−0.77, 17.56)</td>
<td>−52.50 (−64.5, −35.0)</td>
<td>0.85 (0.33, 1.46)</td>
</tr>
<tr>
<td>G551S (2)</td>
<td>−3.09 (−4.69, 5.41)</td>
<td>0.29 (−5.32, 5.89)</td>
<td>3.12</td>
<td>−6.72 (0.52, 12.61)</td>
<td>6.76 (1.21, 14.23)</td>
</tr>
<tr>
<td>G797R (4)</td>
<td>6.72 (0.52, 12.61)</td>
<td>6.76 (1.21, 14.23)</td>
<td>2.55 (−1.30, 4.52)</td>
<td>−6.25 (−16.0, −2.0)</td>
<td>0.48 (−0.38, 1.75)</td>
</tr>
<tr>
<td>S1251N (8)</td>
<td>2.14 (−23.28, 19.95)</td>
<td>7.66 (−13.20, 26.03)</td>
<td>8.70 (−19.57, 21.38)</td>
<td>−54.38 (−84.0, −7.0)</td>
<td>0.73 (0.08, 1.83)</td>
</tr>
<tr>
<td>S1255P (2)</td>
<td>11.10 (8.25, 13.94)</td>
<td>8.73 (4.74, 12.73)</td>
<td>3.14 (−1.42, 7.70)</td>
<td>−77.75 (−82.0, −73.5)</td>
<td>1.62 (1.39, 1.84)</td>
</tr>
<tr>
<td>S549R (6)</td>
<td>10.55 (5.11, 15.93)</td>
<td>8.06 (−9.29, 19.30)</td>
<td>11.31 (−2.40, 19.78)</td>
<td>−74.25 (−92.5, −53.0)</td>
<td>0.79 (0.00, 1.91)</td>
</tr>
<tr>
<td>S549R (4)</td>
<td>3.47 (−3.55, 7.59)</td>
<td>4.11 (−3.78, 10.00)</td>
<td>5.18 (−3.07, 12.74)</td>
<td>−60.67 (−70.5, −53.5)</td>
<td>0.53 (0.33, 0.80)</td>
</tr>
<tr>
<td>Overall</td>
<td>7.23 (−23.28, 33.36)</td>
<td>7.55 (−13.20, 35.37)</td>
<td>8.13 (−19.57, 36.37)</td>
<td>−55.82 (−92.5, −2.0)</td>
<td>0.75 (−0.38, 1.91)</td>
</tr>
</tbody>
</table>

* Only one patient with the G551S mutation completed 8 weeks of ivacaftor treatment.

Fig. 2. Mean absolute change from baseline in percent predicted FEV1 over 24 weeks of ivacaftor treatment for patients from treatment sequence 2 (placebo → ivacaftor).
improvement in FEV₁ was within the range of responses seen in other small subgroups, there were much smaller sweat chloride responses in these individuals relative to the other genotype subgroups studied. Additional studies will be required to elucidate the effects of ivacaftor in patients with the G970R mutation, which is complicated by the fact that there are fewer than a dozen known individuals with this mutation worldwide [4]. Notwithstanding the G970R mutation (which showed an in vitro response comparable to other gating mutations), in vitro studies have accurately predicted patient response to ivacaftor treatment in 8 of the 9 gating mutations tested. For instance, in vitro results were predictive of the positive clinical results in the ivacaftor Phase 3 studies of patients with the G551D mutation [18,6,13]. Likewise, the negative clinical results in patients who are homozygous for the F508del mutation was predicted by in vitro data [3,21]. These examples, together with the results of this study, support the continued use of these in vitro models.

The KONNECTION study illustrates the utility of a non-traditional approach to Phase 3 clinical study design (crossover vs. parallel-group) that may be useful for therapeutic areas with ultra-rare patient types; using a crossover design with an open-label extension allowed both a within-subjects analysis and longer-term evaluation of ivacaftor, whereas a more typical parallel-group design would not have provided adequate statistical power in this small population. In the future, “N of 1” trials may be considered for even rarer genotypes. Moreover, this study illustrates the importance of using in vitro models that accurately characterize a mutation or patient group in a manner that predicts clinical response to a treatment.

The KONNECTION study demonstrates that patients with CF who have selected non-G551D gating mutations show clinical and pharmacodynamic improvements in response to treatment with ivacaftor that are similar to the benefits observed in patients with CF who have a G551D gating mutation. The findings in KONNECTION support grouping patients on the basis of knowledge about the functional consequences of their mutation types, and underscore the importance of developing in vitro models that can aid in the accurate characterization of mutation types. Continued global cooperation among cell biologists, physicians, patients, and registries may build on this progress to help ensure that ultra-rare mutation types can become better understood and appropriate care made available to greater numbers of patients with CF.

Disclosures and acknowledgments

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Conflicts of interest

K. De Boeck has served as an investigator on Boehringer Ingelheim, Gilead, Pharmaxis, PTC, and Vertex Pharmaceuticals Incorporated studies and has participated in advisory boards for Ablynx, Aptalis, Galapagos, Gilead, Pharmaxis, PTC, and Vertex Pharmaceuticals Incorporated. A. Munck has served as an investigator for Boehringer Ingelheim, Gilead, Pharmaxis, Novartis, and Vertex Pharmaceuticals Incorporated studies and has participated in advisory boards for Novartis and Vertex Pharmaceuticals Incorporated. S. Walker has received support for clinical trials from Gilead, Novartis, and Vertex Pharmaceuticals Incorporated and participated in scientific advisory boards for Vertex Pharmaceuticals Incorporated. A. Faro has served as an investigator on Vertex Pharmaceuticals Incorporated, PTC, Novartis, Pfizer, Insmed, CF Therapeutics, and NIH-sponsored studies and participated on advisory boards for Gilead. P. Hiatt has served as an investigator on Vertex Pharmaceuticals Incorporated, Gilead, Novartis, CF Therapeutics, and NIH-sponsored studies. G. Gilmartin is a former employee of Vertex Pharmaceuticals Incorporated. M. Higgins is an employee of Vertex Pharmaceuticals Europe (Limited)
and may own stock or stock options in Vertex Pharmaceuticals Incorporated.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcf.2014.09.005.

References