**43 Patient-reported outcomes in Phase 3 trials of ivacaftor in subjects with CF who have the G551D-CFTR mutation**

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**Objectives:** Two Phase 3 studies were conducted to evaluate the effect of ivacaftor in CF subjects with a G551D mutation. Change in Cystic Fibrosis Questionnaire-revised (CFQ-R) scores was evaluated in both studies.

**Methods:** Both were randomized, double-blind, placebo-controlled studies. Subjects received placebo or ivacaftor 150 mg q12h for 48 weeks in addition to prescribed therapies. In STRIVE, 161 subjects ≥12 years were dosed. In ENVISION, 52 subjects 6–11 years were dosed. The CFQ-R is a patient-reported outcome measure with multiple domains each scored on a 100-point scale. Higher numbers indicate fewer symptoms. In the respiratory domain, a difference of at least 4 points is considered the minimal clinically important difference (MCID). MCIDs for other domains have not been established.

**Results:** The treatment difference in the mean pooled CFQ-R Respiratory Symptoms scores for ivacaftor vs. placebo through Week 48 was 8.6 points (P < 0.0001) in STRIVE and 5.1 points (P = 0.1354) in ENVISION. Differences between groups were detected by Day 15 in both studies and were maintained at subsequent visits in STRIVE. In STRIVE, the treatment difference for ivacaftor was 4.4 points (P = 0.0055) for the Physical Functioning scale, 4.3 points (P = 0.0026) for Social Functioning scale, 3.3 points (P = 0.0021) for Eating Disturbances scale, and 3.3 points (P = 0.0419) for Treatment Burden scale.

**Conclusions:** Both studies demonstrated clinically meaningful improvements in respiratory symptoms that were rapid, durable, and of comparable magnitude. There were statistically significant improvements in other domains, though the MCID for those domains has not been established.

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**44 Pulmonary exacerbations in a Phase 3 trial of ivacaftor in subjects with cystic fibrosis who have the G551D-CFTR mutation**

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**Objectives:** Pulmonary exacerbations have been associated with a worsening decline in lung function and are a major cause of morbidity in CF. Pulmonary exacerbations were evaluated in a Phase 3 study of ivacaftor (STRIVE) in subjects with CF who have a G551D-CFTR mutation.

**Methods:** This was a randomized, double-blind, placebo-controlled, multicenter study in which subjects received placebo or ivacaftor 150 mg q12h for 48 weeks in addition to their prescribed therapies. 161 subjects with CF who were ≥12 years of age and had percent predicted FEV1 at screening of 40%–90% were dosed. Pulmonary exacerbations were identified by modified Fuchs’ criteria.

**Results:** The pulmonary exacerbation-free rate was 67% in the ivacaftor group compared to 41% in the placebo group from baseline through Week 48. The rate of pulmonary exacerbations through 48 weeks in the ivacaftor group was less than half that of the placebo group (rate ratio = 0.426; P = 0.0003). There was a 55% reduction in risk of a pulmonary exacerbation for subjects in the ivacaftor group relative to subjects in the placebo group through Week 48 (hazard ratio: 0.455; P = 0.0012). The mean number of days with pulmonary exacerbation, adjusted for time on study, was significantly less in the ivacaftor group than in the placebo group through Week 48 (11.5 versus 36.7 days; P = 0.0007). The most commonly reported adverse events were respiratory in nature. The incidence of adverse events through Week 48 was similar between groups.

**Conclusions:** Treatment with ivacaftor resulted in marked improvement in the risk of experiencing a pulmonary exacerbation, as well as the frequency and duration of pulmonary exacerbations.

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**45 Drug–drug interactions between ivacaftor and midazolam or rosiglitazone in healthy volunteers**

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**Objectives:** Iva: The selectivity of cystic fibrosis transmembrane conductance regulator (CFTR), demonstrated substantial, durable improvements in lung function, respiratory symptoms and weight gain, as well as sustained improvements in CFTR function in subjects with CF. In vitro studies demonstrated that ivacaftor and its metabolite M1 were reversible inhibitors of CYP2C8 and weak inhibitors of CYP3A. Therefore, ivacaftor may have drug–drug interactions with CYP3A (e.g., midazolam) or CYP2C8 (e.g., rosiglitazone).

**Methods:** A single-center, open-label, 2-period, 1-sequence crossover study was conducted with 24 healthy subjects between 18 and 55 years of age. The effects of co-administration of steady-state ivacaftor on the pharmacokinetic parameters of:

1. a single dose of the CYP3A substrate midazolam and its metabolite 1′-hydroxy-midazolam; and
2. a single dose of the CYP2C8 substrate rosiglitazone, were evaluated in this study.

**Results:** Co-administration of ivacaftor at steady-state slightly increased the midazolam Cmax and AUC0–∞ by 1.4-fold [CI: 1.26, 1.52] and 1.5-fold [CI: 1.39, 1.69], respectively. Midazolam metabolite 1′-hydroxymidazolam Cmax and AUC0–∞ were similar with and without ivacaftor (0.92-fold (0.82, 1.03) and 1.10-fold (0.98, 1.25), respectively). Co-administration of ivacaftor at steady-state did not affect the exposure of a CYP2C8 substrate rosiglitazone.

**Conclusions:** Ivacaftor is a weak CYP3A inhibitor. Caution is warranted when a sensitive CYP3A substrate with narrow therapeutic index is co-administered with ivacaftor. No dose adjustment is required when ivacaftor is co-administered with CYP2C8 substrates. Suggested by Vertex.

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**46 Hyperpolarized Gas MRI of ivacaftor therapy in subjects with cystic fibrosis who have the G551D-CFTR mutation**

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**Objectives:** Hyperpolarized Gas MRI (HG-MRI) allows direct, high-resolution imaging of certain non-radioactive isotopes of noble gases, such as He-3. Images with patients from CF show numerous “ventilation defects” – areas of the lung into which inhaled gas does not flow due to airway obstruction. Ventilation defects correlate with disease severity. Ivacaftor improves FEV1 in patients with CF who have the G551D-CFTR mutation.

**Methods:** This single-center, Phase 2, single-blind, placebo-controlled study evaluated the effects of ivacaftor on ventilation as revealed by HG-MRI in 8 subjects with CF who have the G551D-CFTR mutation and to assess the utility of HG-MRI as a biomarker of lung disease. Subjects were required to have FEV1 ≥40% predicted to enroll. Subjects received ivacaftor 150 mg q12h for 4w and placebo for a total of 4w.

**Results:** HG-MRI revealed ventilation defects at baseline in all subjects, including those with FEV1 >90% predicted. 28d treatment with ivacaftor led to a substantial reduction in total ventilation defects [8.20% as determined by human reader (HR) (P = 0.0547) and 12.81% by computer algorithm (CA) (P = 0.0078)] and total defect volume [0.48 L as determined by HR (P = 0.0313) and 0.68 L by CA (P = 0.0078)] as assessed by HG-MRI. This correlated with an increase in FEV1% predicted of 12.8% (P = 0.0078).

**Conclusions:** HG-MRI could provide a novel endpoint in clinical trials of CF, one that both corroborates traditional pulmonary function testing and provides unique information, including absolute quantification of disease burden, information on burden in each lung or lobe, and assessment of burden in patients with relatively normal spirometry.

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