ABSTRACT

Title An Observational Study to Evaluate the Long-term Safety of Ivacaftor in Patients With Cystic Fibrosis

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Keywords Ivacaftor, Cystic Fibrosis, Long-term Safety, Disease Progression, Drug Utilization

Rationale and Background Cystic fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality. Ivacaftor (IVA) is an orally bioavailable small molecule that targets the underlying defect in CF and represents the first in a new class of drugs, CFTR potentiators. IVA is intended for chronic, lifelong use. Understanding the long term benefit risk profile is informative to patients, caregivers, prescribers, and payers. This post-authorisation safety study (PASS) evaluated the long-term safety of IVA and disease progression in patients with CF who were treated with IVA, using observational cohorts of patients receiving IVA in a "real-world" setting.

Research Questions and Objectives Primary Objectives:

1. To evaluate the long-term safety of IVA in patients with CF
2. To evaluate outcomes of pregnancy in IVA-treated patients
3. To evaluate the drug utilisation of IVA
4. To evaluate CF disease progression in IVA-treated patients

Study Design This 5-year non-interventional PASS utilised existing real-world data collected by national CF patient registries. Observational cohorts of patients receiving IVA and comparator patients matched in ~1:5 ratio on age, sex, and genotype severity were established annually in each participating registry. Risks of key clinical outcomes were compared between the cohorts in each registry, and disease progression and drug utilization patterns were described annually.

Setting Existing CF patient registries in the US and United Kingdom (UK) served as a source to obtain data on utilisation patterns, and long-term effects of IVA therapy for the purposes of the study. Additional data on drug utilisation were provided by CF patient registries from Ireland and France.

Subjects and Study Size

Cohort sizes used for each of the annual analysis years:

Safety, Pregnancy, and Disease Progression Cohorts: UK		2012	2013	2014	2015	2016 (Final)
Safety Analyses	IVA	-	307	411	432	462
	Comparator	-	1,533	2,069	2,201	2,372
Pregnancy Analyses (subset of Safety Cohorts; females ≥14 years)	IVA	-	97	143	153	158
	Comparator	-	488	725	789	841
Disease Progression Analyses (subset of Safety Cohorts; no change in CFTR modulator treatment and no record of lung transplant from 2013)	IVA	-	293	277	260	247
	Comparator	-	1,433	1,365	1,289	1,230

Safety, Pregnancy, and Disease Progression Cohorts: US		2012	2013	2014	2015	2016 (Final)
Safety Analyses	IVA	807	999	1,256	1,727	1,858
	Comparator	4,035	4,932	6,200	7,329	7,316
Pregnancy Analyses (subset of Safety Cohorts; females ≥14 years)	IVA	256	306	412	528	484
	Comparator	1,265	1,474	1,996	2,110	1,821
Disease Progression Analyses (subset of Safety Cohorts; no change in CFTR modulator treatment and no record of lung transplant from 2012)	IVA	805	752	708	669	635
	Comparator	3,815	3,499	3,249	2,355	1,874

Drug Utilization Cohorts	2012	2013	2014	2015	2016 (Final)
UK	-	307	411	432	462
Ireland	-	131	138	153	160
France	-	68	90	122	132
US	807	999	1,256	1,727	1,858

Variables and Data Sources

All of the study variables (exposure, covariates, safety, disease progression, pregnancy, and drug utilisation endpoints) were collected by the registries in prespecified data collection forms, according to the respective registry data entry guidelines.

Safety endpoints:

- Death
- Organ transplant
- Hospitalisations

- CF complications including but not limited to hepatobiliary, gastrointestinal, and pulmonary conditions
- Pulmonary exacerbations (PEx)
- Serious safety outcomes (composite measure)
- Respiratory microbiology

Pregnancy endpoints:
- Pregnancy frequency
- Pregnancy outcomes (live birth, stillbirth, spontaneous abortion, therapeutic abortion, gestational age, congenital anomalies)

Drug utilisation endpoints:
- Potential off-label use of IVA in patients with CF

CF disease progression endpoints:
- CF lung disease severity based on percent predicted FEV_1
- Clinical signs of CF disease progression

Results The results of annual Safety Cohorts analyses were consistent across two large independent registries (US and UK) and across the analysis years within each registry. Evaluation of outcome patterns of annual analyses over the course of 5 years identified no new safety concerns based on the US and UK registry data analyses. Instead, a number of observations consistently favouring the IVA Safety cohort were made.

The results of each annual analysis demonstrated consistently lower risks of death, organ transplant, PEx, and hospitalisations in IVA-treated versus untreated comparator patients in both registries (results for the rare events of death and transplantation were not statistically significant in the smaller UK CF registry analyses). IVA-treated patients also tended to have lower prevalence of a number of CF-related complications across organ systems and a lower prevalence of a majority of typical CF microbial pathogens, such as *Pseudomonas aeruginosa*.

In addition, a sub-set of patients (predominantly those with at least one *G551D* mutation) with a continuous record of IVA treatment from the first year of commercial availability of IVA (2012 in the US and 2013 in the UK) through 2016 and without organ transplantation over the course of the study, had better preserved lung function and improved nutritional status relative to untreated comparator patients.

There were no notable differences in the outcome of pregnancy among female patients treated with IVA versus untreated comparator female patients.

Analyses of drug utilisation patterns suggested very low prevalence of

potential off-label use in the European countries included in this study. In the final analysis year (2016), there were no potential off-label users in the UK nor Ireland. In France, 1.5% patients treated with IVA in 2016 were potential off label users. The US drug utilisation analyses suggested that in 2016, 13.4% of the patients treated with IVA could potentially be using the drug outside of the labelled indication.

Discussion

The results of annual analyses of real-world observational data from two large, independent CF patient registries from the first year of commercial availability of IVA (2012 in the US and 2013 in the UK) through 2016 indicated no new safety concerns but revealed consistent favourable findings with respect to clinically important outcomes and CF disease progression in IVA treated patients. Findings were consistent with the current understanding of the IVA benefit-risk profile and supported disease modification with IVA in real-world use.

Marketing Authorization Holder

Vertex Pharmaceuticals (Europe) Ltd.