ABSTRACT

Title

An Observational Study to Evaluate the Utilisation Patterns and Long-term Effects of Lumacaftor and Ivacaftor Combination Therapy in Patients With Cystic Fibrosis

Date of the abstract: 16 November 2021

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Keywords

Lumacaftor/Ivacaftor, Cystic Fibrosis, Long-term Safety, Disease Progression, Drug Utilisation

Rationale and Background

Cystic fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality. The lumacaftor/ivacaftor combination therapy (Orkambi) is indicated for treatment of CF in patients 2 years and older who are homozygous for *F508del* mutation in the CFTR gene. Understanding long-term effects in the overall population of patients receiving treatment and in the specified sub-populations will be informative to patients and their parents, prescribers, and payers. Existing CF registries provide an established source to obtain data on long-term effects of real-world use.

Research Question and Objectives

Primary Objectives:

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

Study Design

Five-year observational cohort study using data collected by existing national CF patient registries in the UK and US (all study objectives), as well as Ireland and France (drug utilisation objective only).

Setting

Existing CF patient registries in the US and UK served as a source to obtain data on utilisation patterns and long-term effects of Orkambi 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 for each annual analysis year by country are as follows:

Country: US

	2016	2017	2018	2019	2020 (Final)
Safety Analyses					
Orkambi	5,553	6,664	4,628	3,182	1,739
Comparator	4,256	4,867	5,666	4,099	2,092
Pregnancy Analyses					
Orkambi	1,917	2,023	892	367	41
Comparator	1,345	1,565	1,603	971	255
Disease Progression Analyses					
Orkambi	5,508	4,821	2,287	969	112
Comparator	3,990	3,759	3,527	1,989	405
Drug Utilisation Analyses	5,777	6,951	7,183	5,193	2,787

Country: UK

	2016	2017	2018	2019	2020 (Final)
Safety Analyses					
Orkambi	-	-	-	-	853
Comparator	-	-	-	-	791
Pregnancy Analyses					
Orkambi	-	-	-	-	-
Comparator	-	-	-	-	-
Disease Progression Analyses					
Orkambi	-	-	-	-	853
Comparator	-	-	-	-	736
Drug Utilisation Analyses	-	-	-	2	1,412

Country: Ireland

	2016	2017	2018	2019	2020 (Final)
Drug Utilisation Analyses	-	318	467	515	426

Country: France

	2016	2017	2018	2019	2020 (Final)
Drug Utilisation Analyses	-	1,088	1,156	1,195	1,749

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
- Respiratory microbiology
- Liver function tests (LFTs)

Pregnancy endpoints:

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

CF disease progression endpoints:

- Percent predicted forced expiratory volume in 1 second ($ppFEV_1$)
- Cystic fibrosis related diabetes (CFRD)
- Distal intestinal obstruction syndrome (DIOS)
- Body mass index (BMI)
- Hospitalisations
- Pulmonary exacerbations

Drug utilisation endpoints:

- Potential off-label use of Orkambi in patients with CF

Results

This final study report focuses on the discussion of 2020 safety, pregnancy, disease progression, and drug utilisation analyses in the US and UK registries, and 2020 drug utilisation analyses in Ireland and France.

In addition, the report discusses the 5 years of safety and disease progression data, from 2016 to 2020, in the US. Of note, following the commercial availability of novel CFTR modulators (tezacaftor/ivacaftor in 2018 and elexacaftor/tezacaftor/ivacaftor in 2019), major attrition of patients from the US Orkambi and Concurrent Comparator Cohorts was observed starting from Year 3 (2018) of this 5-year study as eligible patients initiated novel therapies. This resulted in major changes in cohort size (diminishing over time) and composition (patients remaining in the cohorts tend to be healthier pediatric patients), which should be considered when interpreting the results.

Overall, the results of US data analyses from 2016 through 2020 indicated no new safety concerns and instead a number of observations favouring Orkambi-treated patients were made.

Although only 1 year of data were available for the UK (Orkambi was not commercially available in the country until late 2019), the results were generally consistent with the US results.

The key results, by study objective, are summarised below.

Long-term Safety
Data from the 2020 US registry indicated no new safety concerns. The results

included observations of no deaths and organ transplants in the 2020 Orkambi Cohort patients, and lower risks of hospitalisations, pulmonary exacerbations, and any CF complications in the 2020 Orkambi Safety Cohort versus the Comparator Safety Cohort in crude and age-adjusted analyses. The proportions of patients with elevated LFTs and those with positive bacterial cultures were generally comparable between the Orkambi and Comparator Safety Cohorts.

Overall, none of the 5 annual safety analyses performed using US registry data (2016 through 2020) found imbalances determined to constitute a new safety concern, but a number of observations consistently favouring Orkambi-treated patients were made, as summarised below:

- Risks of deaths and organ transplants were consistently lower in the Orkambi Safety Cohort than in the Comparator Safety Cohort across all years (there were no deaths and no transplants in the Orkambi Cohort in Year 5).
- Risk of hospitalisation was lower in the Orkambi Safety Cohort versus the Comparator Safety Cohort across all years.
- Risk of pulmonary exacerbations was comparable between the 2 cohorts in Years 1 and 2 and was lower in the Orkambi Safety Cohort than the Comparator Safety Cohort during Years 3 through 5.
- Risk of any CF complication was not different between the 2 cohorts in Years 1 and 2 and was slightly lower in the Orkambi Safety Cohort than the Comparator Safety Cohort during Years 3 through 5.

Although only 1 year of safety data were available in UK, the results of 2020 UK safety analyses were generally consistent with the results of 2020 US safety analyses.

Pregnancy
In 2020, there were no pregnancies reported in the US Orkambi Pregnancy Cohort, but the size of the cohort was very small, reflecting the younger age of patients remaining in the Orkambi Cohort in 2020. In Years 1 through 4 of US analyses, the frequency and outcomes of pregnancies were comparable between the US Orkambi and Comparator Pregnancy Cohorts.

Pregnancy analyses based on data from the UK were not feasible because there were no patients eligible to be included in the UK Orkambi Pregnancy Study Cohort, reflecting the young age of patients treated with Orkambi in the UK in 2020.

CF Disease Progression
By the fifth year of follow-up, only 2% of the US Orkambi Disease Progression Cohort remained on Orkambi and were not lost to follow-up and only 10% of the US Comparator Disease Progression Cohort remained untreated and were not lost to follow-up. Patients remaining in the disease progression cohorts in Year 5 were younger and had higher baseline lung function than those who were excluded over the years. Thus, interpretability of the final year (2020) of disease progression analyses is limited. The results of the US disease progression analyses in the prior 4 annual reports are summarised below:

- There was a consistently reduced decline in lung function ($ppFEV_1$) in the Orkambi-treated patients relative to the Comparator patients.
- The proportion of patients with CFRD increased from baseline in both cohorts, with a slightly smaller increase in the Orkambi Disease Progression Cohort relative to the Comparator Disease Progression Cohort.

- The proportion of patients with DIOS decreased from baseline in both cohorts, and the magnitudes of change from baseline were comparable between the 2 cohorts.
- The annual proportion of patients who were hospitalised remained stable or decreased from baseline in the Orkambi Disease Progression Cohort whereas each year showed an increase compared to baseline in the Comparator Disease Progression Cohort.
- Similar to hospitalisations, the annual proportion of patients with any pulmonary exacerbations was generally stable over time in the Orkambi Disease Progression Cohort whereas each year showed an increase compared to baseline in the Comparator Disease Progression Cohort.
- Mean BMI increased from baseline in both cohorts, and a greater increase was observed in the Orkambi-treated patients than in the comparator patients.

Interpretability of the UK disease progression analyses is limited since the patients in the cohorts tended to be younger pediatric patients, reflecting real-world utilisation of Orkambi in the UK in 2020, and the follow-up was limited to 1 year. Nevertheless, lung function decline was slightly lower numerically in the Orkambi Disease Progression Cohort patients than comparators; there was a greater decrease in hospitalisations in the Orkambi Disease Progression Cohort than in comparators; and the annual proportion of patients with pulmonary exacerbations decreased in the Orkambi Disease Progression Cohort while it increased numerically in the comparators. There were also favourable trends in BMI in the Orkambi Disease Progression Cohort relative to comparators.

Drug Utilisation
Analyses of drug utilisation patterns suggested low prevalence of potential off-label use in the US, UK, Ireland, and France.

Discussion

The results of 5 annual analyses of the PASS indicated no new safety concerns but revealed favourable findings with respect to clinically important outcomes in Orkambi-treated patients. The findings are consistent with the current understanding of the Orkambi safety profile and clinical benefits and support CF disease modification with Orkambi in real-world use.

Marketing Authorisation Holder(s)

Vertex Pharmaceuticals (Ireland) Ltd.