26 March 2026
EMADOC-1700519818-2827731
Committee for Medicinal Products for Human Use (CHMP)

Assessment Report

Orkambi

International non-proprietary name: Lumacaftor / Ivacaftor

Procedure No. EMA/VR/0000320822

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Vertex Pharmaceuticals (Ireland) Limited submitted to the European Medicines Agency on 22 December 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.11.b	C.I.11.b Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment by the competent authority is required	Variation type II

Submission of the final report from study VX18-809-128 (study 128), listed as an obligation in the Annex II of the Product Information. This is a 6-year, observational, post-authorization efficacy study (PAES) in young children with cystic fibrosis (CF) aged 1 through 5 years at the time of Orkambi initiation. This study evaluated disease progression and safety using observational cohorts of children receiving therapy in a "real-world" setting. The Annex II and the RMP version 12.0 are updated accordingly.

The requested variation(s) proposed amendments to the Annex II and to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

The Marketing Authorisation Holder (MAH) for Orkambi (lumacaftor/ivacaftor – LUM(IVA) has submitted this type II variation in compliance with the agreed post-approval commitments (see procedure EMEA/H/C/003954/X/0078/G).

Data from the final clinical study report (CSR) for the post-authorization efficacy study (PAES) **VX18-809-128** have been submitted in line with CHMP requests: this PAES was a commitment at the time of authorization for Orkambi in patients 2 through 5 years of age. The PAES protocol was subsequently amended, based on CHMP's request, to extend the study to include patients aged 1 to <2 years of age. The final PAES protocol was dated 06 June 2023.

Study **VX18809128** was a six-year, observational, registry-based PAES designed to characterise disease progression and safety in children with cystic fibrosis (CF) homozygous for *F508del* (F/F) who initiated lumacaftor/ivacaftor (Orkambi) at 1 through <2 years of age or 2 through 5 years of age in routine care.

The main research question was whether children treated earlier in life develop a less advanced disease as they grow older, compared with children who either never received a CFTR modulator or initiated Orkambi later in their life. The study leverages two independent, mature data sources - the European Cystic Fibrosis Society Patient Registry (ECFSPR) and the US Cystic Fibrosis Foundation Patient Registry (CFFPR) - and contextualises findings against an F/F historical cohort, the UK Kalydeco PAES F/F comparator cohort, and Study 110 (including older, 6–11 year old Orkambi-treated children from a clinical trial programme).

Matching for concurrent cohort comparisons was 1:1 on age, sex, and BMI-forage z-score; analyses were predominantly descriptive by protocol.

For the **2–5y cohorts**, Orkambi and matched F/MF (and, in ECFSPR only, matched F/F) comparators had cohort entry aligned with each region's market availability (US CFFPR: 2018–2019; ECFSPR: 2019–2020) with follow-up to 31 Dec 2024. The **1–<2y cohorts** had entry in 2022–2023 (US) and 2023 (EU) with follow-up planned through 2024, yielding necessarily short observation time.

Effectiveness endpoints included growth parameters (BMI/height/weight z-scores and percentiles; weight-for-length for 1–<2y), pulmonary exacerbations (definitions registry-specific), all-cause hospitalisations, ppFEV$_1$ (when available), CF medication use (inhaled antibiotics, oral corticosteroids), CF complications (distal intestinal obstruction syndrome - DIOS, CF-related diabetes - CFRD), and pulmonary microbiology (*H. influenzae, P. aeruginosa, S. aureus*/MRSA). Safety endpoints included liver function test (LFT) elevations (ALT/AST; US CFFPR only), organ transplantation, and death.

Despite methodological constraints inherent to observational registry research and pronounced post-2021/2022 attrition - chiefly due to transitions to newer CFTR modulators - the convergent patterns across two independent registries support that initiating Orkambi at ages 2–5 years was associated with better growth, reduced PEx and hospitalisations, stable lung function, and no new safety concerns versus matched comparators and historical experience. Some of these data are considered of potential relevance to prescribers and were included in Section 5.1 of the SmPC (see the annexed SmPC for details).

Evidence in the 1–<2-year-old cohorts remains preliminary because of limited follow-up and extensive censoring because of treatment switch. Overall, the limited available data can still be considered suggestive of improvements in growth after Orkambi initiation, and no obvious safety concerns were observed in younger children. However, no robust inference can be made on pulmonary endpoints or longer-term outcomes, and changes in clinical practice make the possibility to collect additional prospective data in this population unrealistic.

Overall, the submitted data can be considered supportive of the clinical benefit of earlier initiation of CFTR modulation with Orkambi while acknowledging the limits on precision and durability of estimates late in follow-up. The available real-word data are considered overall consistent with the established overall benefit-risk profile of Orkambi.

The benefit-risk balance of Orkambi remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		**Type**
C.I.11.b	C.I.11.b Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment by the competent authority is required	Variation type II

Submission of the final report from study VX18-809-128 (study 128), listed as an obligation in the Annex II of the Product Information. This is a 6-year, observational, post-authorization efficacy study (PAES) in young children with cystic fibrosis (CF) aged 1 through 5 years at the time of Orkambi initiation. This study evaluated disease progression and safety using observational cohorts of children receiving therapy in a "real-world" setting.

The section 5.1 of the SmPC is updated, as well as Annex II of the PI, and the RMP version 12.0,.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to the SmPC section 5.1, Annex II and to the Risk Management Plan are recommended.

The following obligation has been fulfilled, and therefore it is recommended that it be deleted from the Annex II to the Opinion:

- **Obligation to conduct post-authorisation measures:**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-Authorisation Efficacy Study (PAES) Based on an agreed protocol, the Applicant should conduct a long-term effectiveness study to compare disease progression among children with CF homozygous for *F508del-CFTR* and are aged 1 through 5 years at the time of Orkambi treatment initiation versus disease progression among concurrent matched cohort of children with CF who have never received Orkambi treatment, in addition to a longitudinal historical cohort.	Interim Analysis: December 2022 Final Report: December 2025

Annex: Rapporteur’s assessment comments on the type II variation

4. Introduction

The Marketing Authorisation Holder (MAH) has filed this type II variation in compliance with the post-approval commitments for the Marketing Authorization (MA) for lumacaftor/ivacaftor (LUM/IVA, Orkambi, see procedure EMEA/H/C/003954/X/0078/G).

The MAH has submitted the final clinical study report (CSR) for the post-authorization efficacy study (PAES) VX18-809-128 to fulfil the recommendation from the CHMP. This PAES was a commitment at the time of authorization for Orkambi in patients 2 through 5 years of age. The PAES protocol was subsequently amended based on CHMP's request to extend the study to include patients 1 to <2 years of age. The final PAES protocol (dated 06 June 2023) was agreed upon with CHMP. Annual reporting milestones were completed for the interim analysis (see Table below).

Table 1: Study 128 milestones

Milestone	Planned Date
Start of data collection[a]	June 2019 (date when US CFFPR 2018 data became available for analyses)
End of data collection[a]	June 2025
Interim Analysis (ECFSPR and US CFFPR data through December 2021)	December 2022 submission
Final report of study results (ECFSPR and US CFFPR data through December 2024)	December 2025 submission

Source: Study 128 Protocol Version 3.0/Table 3

CFFPR: CF Foundation Patient Registry; ECFSPR: European CF Society Patient Registry; US: United States

[a] Per EU Good Pharmacovigilance Practices VIII.A.1, the start of data collection in case of secondary use of data is the date from which data extraction starts and end of data collection is when the analytical datasets are completely available.

Results showed no new safety concerns and favourable trends in terms of early efficacy in children who initiated LUM/IVA at the ages of 2 through 5 years.

5. Post-Authorisation efficacy study (PAES) results

Study VX18-809-128 (Study 128) was a 6-year, observational, post-authorization efficacy study (PAES) in young children with cystic fibrosis (CF) aged 1 through 5 years at the time of LUM/IVA (Orkambi) initiation. This study evaluated disease progression and safety using observational cohorts of children receiving therapy in a "real-world" setting. The main objective of study VX18-809-128 was to assess whether children with CF homozygous for *F508de*l (F/F) who are treated with LUM/IVA early in life have less advanced disease when they become older compared to those who were never treated with LUM/IVA (or another CFTR modulator) or who initiated LUM/IVA therapy at a later age.

5.1. Methods – analysis of data submitted

Study design

This was a 6-year, observational, retrospective cohort study using data collected by existing CF patient registries in Europe and the US. The source populations for the main study analyses were children included in the ECFSPR (European CF Society Patient Registry) and US CFFPR (CF Foundation Patient Registry). Results from the Kalydeco PAES UK F/F Comparator Cohort and Study 110 were also used to provide additional context to the disease patterns observed in the analyses of the ECFSPR and US CFFPR data.

The cohort entry periods and follow-up periods are shown in figures below for all ECFSPR and US CFFPR

cohorts; the Kalydeco PAES UK F/F Comparator Cohort; and the Study 110 Treatment Cohort Period 1:

Figure 1: Schematic of ECFSPR and US CFFPR Cohorts

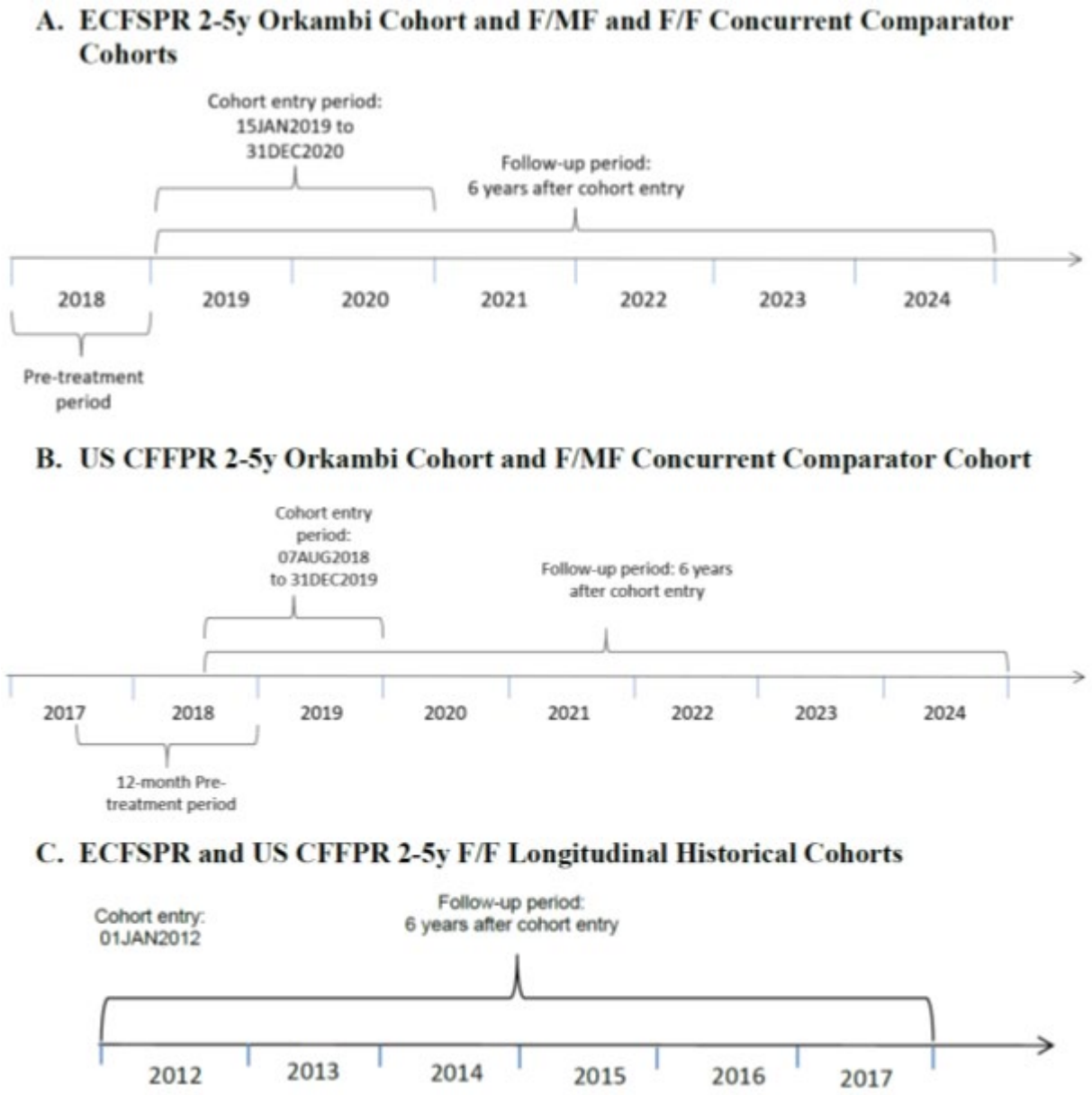
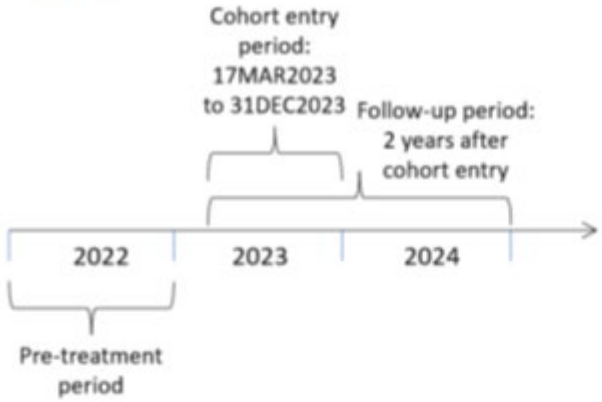
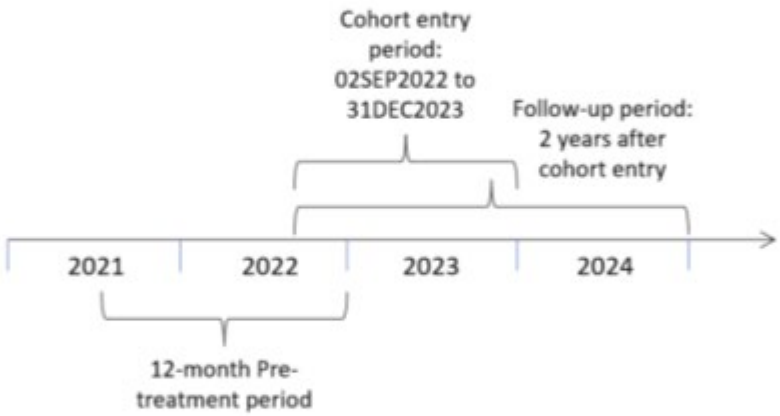


Figure 1: Schematic of ECFSPR and US CFFPR Cohorts

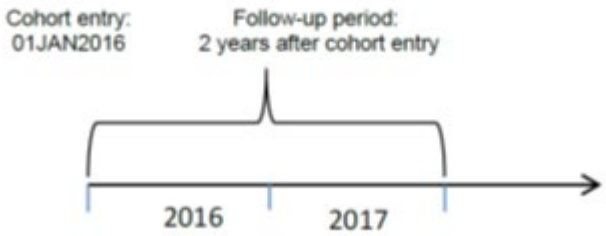
A. ECFSPR 1-<2y Orkambi Cohort and F/MF and F/F Concurrent Comparator Cohorts



B. US CFFPR 1-<2y Orkambi Cohort and F/MF Concurrent Comparator Cohort



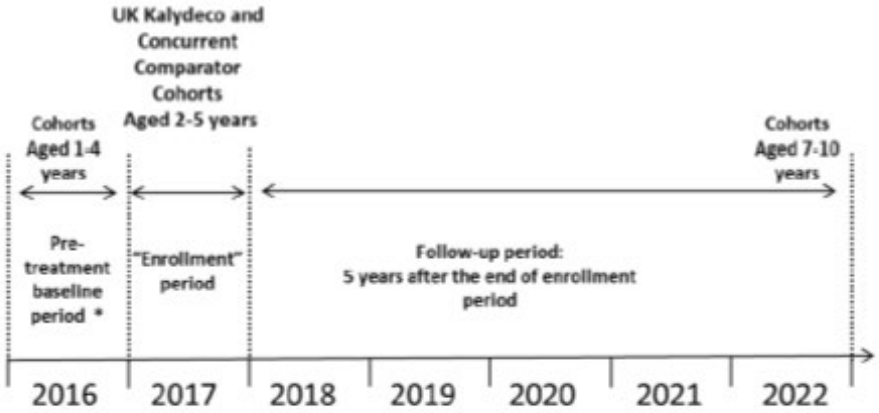
C. ECFSPR and US CFFPR 1-<2y F/F Longitudinal Historical Cohorts



Source: Study 128 Protocol Version 3.0/Figure 1

CFFPR: Cystic Fibrosis Foundation Patient Registry; CFTR: cystic fibrosis transmembrane conductance regulatory protein; ECFSPR: European Cystic Fibrosis Society Patient Registry; F/F: homozygous for *F508del* mutation; F/MF: heterozygous for *F508del* and a second mutation that results in minimal CFTR function

Figure 2: Schematic of Kalydeco PAES UK F/F Comparator Cohort

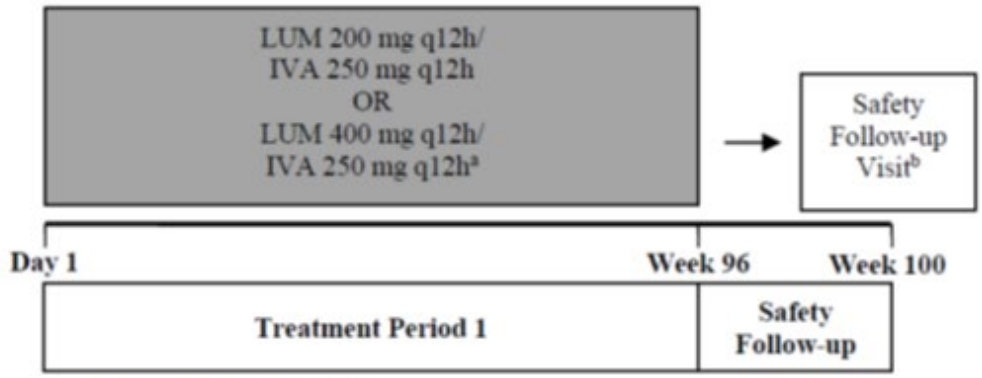


Source: Study 770-125 Final CSR/Figure 11-3

CF: cystic fibrosis; F/F: homozygous for *F508del*; PAES: post-authorization efficacy study

* Kalydeco was commercially available for treatment of children with CF 2 through 5 years of age in the UK in January 2017; 2016 represents the full calendar year prior to Kalydeco availability for young children.

Figure 3: Schematic of Study 110 Treatment Cohort Period 1



Source: Study 110 CSR/Figure 2-1

IVA: ivacaftor; LUM: lumacaftor; q12: every 12 hours

[a] Subjects who turned 12 years of age in the previous (parent) study or on Day 1 of this rollover study began receiving LUM 400 mg q12h/IVA 250 mg q12h on Day 1. Subjects who turned 12 years of age after the Day 1 Visit of this rollover study began receiving LUM 400 mg q12h/IVA 250 mg q12h at their next scheduled visit.

[b] The Safety Follow-up Visit occurred 4 weeks (± 7 days) after the last dose of study drug.

Main inclusion/exclusion criteria

The main inclusion criteria are summarised in Table below.

Table 2: Study Cohorts Established in the ECFSPR and US CFFPR

Cohorts	ECFSPR	US CFFPR
2-5y Cohorts		
2-5y Orkambi Cohort[a]	All children who: • Are from one of participating countries with commercial access to Orkambi[b] • Have F/F genotype • Initiate Orkambi during the cohort entry period[c] • Aged 2 through 5 years at Orkambi initiation • Have available data in 2018 (pre-treatment)	All children who: • Have F/F genotype • Initiate Orkambi during the cohort entry period[b] • Aged 2 through 5 years at the time of Orkambi initiation • Have 12 months of available data before initiation of Orkambi
2-5y F/MF Concurrent Comparator Cohort[a]	All children who: • Are from the same countries as 2-5y Orkambi Cohort children[b] • Have F/MF genotype • Aged 2 through 5 years during the cohort entry period[c] • Have never received Orkambi or any other CFTR modulator as of cohort entry date • Have available data in 2018	All children who: • Have F/MF genotype • Aged 2 through 5 years during the cohort entry period[b] • Have never received Orkambi or any other CFTR modulator as of cohort entry date • Have 12 months of available data before cohort entry date
2-5y F/F Concurrent Comparator Cohort[a]	All children who: • Are from one of the participating countries without commercial access to Orkambi[d] • Have F/F genotype • Have never received Orkambi or any other CFTR modulator as of cohort entry date • Aged 2 through 5 years as of cohort entry date • Have available data in 2018	N/A (not feasible due to high uptake of Orkambi in the US F/F population)
2-5y F/F Longitudinal Historical Cohort	All children who: • Are from the same countries as 2-5y Orkambi Cohort children[b] • Have F/F genotype • Aged 2 through 5 years as of 01 January 2012 • Had continuous enrollment in the registry until death or 31 December 2017 • Have never received Orkambi or any other CFTR modulator as of 01 January 2012	All children who: • Have F/F genotype • Aged 2 through 5 years as of 01 January 2012 • Had continuous enrollment in the registry until death or 31 December 2017 • Have never received Orkambi or any other CFTR modulator as of 01 January 2012
1-<2y Cohorts		
1-<2y Orkambi Cohort[a]	All children who: • Are from one of participating countries with commercial access to Orkambi[e] • Have F/F genotype • Initiate Orkambi during the cohort entry period[f] • Aged 1 to <2 years at Orkambi initiation	All children who: • Have F/F genotype • Initiate Orkambi during the cohort entry period[b] • Aged 1 to <2 years at the time of Orkambi initiation
1-<2y F/MF Concurrent Comparator Cohort[a]	All children who: • Are from the same countries as 1-<2y Orkambi Cohort children[e] • Have F/MF genotype • Aged 1 to <2 years during the cohort entry period[f]	All children who: • Have F/MF genotype • Aged 1 to <2 years during the cohort entry period[b]

Table 2: Study Cohorts Established in the ECFSPR and US CFFPR

Cohorts	ECFSPR	US CFFPR
	• Have never received Orkambi or any other CFTR modulator as of cohort entry date	• Have never received Orkambi or any other CFTR modulator as of cohort entry date
1-<2y F/F Concurrent Comparator Cohort[a]	All children who: • Are from one of the participating countries without commercial access to Orkambi[g] • Have F/F genotype • Aged 1 to <2 years as of cohort entry date • Have never received Orkambi or any other CFTR modulator as of cohort entry date	N/A (not feasible due to high uptake of Orkambi in the US F/F population)
1-<2y F/F Longitudinal Historical Cohort	All children who: • Are from the same countries as 1-<2y Orkambi Cohort children[a] • Have F/F genotype • Aged 1 to <2 years as of 01 January 2016 • Had continuous enrollment in the registry until death or 31 December 2017 • Have never received Orkambi or any other CFTR modulator as of 01 January 2016	All children who: • Have F/F genotype • Aged 1 to <2 years as of 01 January 2016 • Had continuous enrollment in the registry until death or 31 December 2017 • Have never received Orkambi or any other CFTR modulator as of 01 January 2016

Source: Study 128 Protocol Version 3.0/Table 5; Study 128 SAP Version 2.0

CFFPR: Cystic Fibrosis Foundation Patient Registry; CFTR: cystic fibrosis transmembrane conductance regulatory protein; ECFSPR: European Cystic Fibrosis Society Patient Registry; F/F: homozygous for *F508del* mutation; F/MF: heterozygous for *F508del* and a second mutation that results in minimal CFTR function; MF: minimal function mutation; N/A: not applicable; US: United States

[a] The Orkambi Cohort children were matched to the Concurrent Comparator Cohort children on age, sex, and BMI-for-age z-score. In addition, supplementary analyses without matching were performed to evaluate outcomes in all children eligible to be included in the Orkambi Cohort, including those who could not be matched to the Concurrent Comparator Cohort children.

[b] Countries participating in the ECFSPR with commercial access to Orkambi for children aged 2 through 5 years as of 31 December 2020: Austria, Denmark, France, Germany, Ireland, Luxembourg, The Netherlands, Slovenia, Sweden, Switzerland, and UK

[c] ECFSPR 2-5y Orkambi and F/F and F/MF Concurrent Comparator Cohort entry period: 15 January 2019 through 31 December 2020

[d] Countries participating in the ECFSPR without commercial access to Orkambi for children aged 2 through 5 years as of 31 December 2020 and with comparable standard of care to countries with commercial access to Orkambi: Croatia, Czech Republic, Italy, Latvia, Norway, and Poland

[e] Countries participating in the ECFSPR with commercial access to Orkambi for children aged 1 to <2 years as of 31 December 2023: Austria, Denmark, France, Germany, Ireland, Norway, Sweden, UK

[f] ECFSPR 1-<2y Orkambi and F/F and F/MF Concurrent Comparator Cohort entry period: 17 March 2023 through 31 December 2023.

[g] Countries participating in the ECFSPR without commercial access to Orkambi for children aged 1 to <2 years as of 31 December 2023: Croatia, Czech Republic, Greece, Italy, Latvia, Luxemburg, Netherlands, Poland, Portugal, Spain, Slovenia, and Switzerland

[h] US CFFPR 2-5y Orkambi and F/MF Concurrent Comparator Cohort entry period: 07 August 2018 through 31 December 2019

[i] US CFFPR 1-<2y Orkambi and F/MF Concurrent Comparator Cohort entry period: 02 September 2022 through 31 December 2023

For the 2-5y Orkambi and Concurrent Comparator Cohorts for both registries, the start of the cohort entry period was the date of marketing authorization; the end of the cohort entry period was 31 December 2019 for the US CFFPR and 31 December 2020 for the ECFSPR. These cohorts were followed through 31 December 2024.

For the 1-<2y Orkambi and Concurrent Comparator Cohorts, the start of the cohort entry period was the date of marketing authorization; the end of the cohort entry period was 31 December 2023. These

cohorts were followed through 31 December 2024.

For the 2-5y Longitudinal Historical Cohorts for both registries, the cohort entry date was 01 January 2012. These cohorts were followed through 31 December 2017.

For the 1-<2y Longitudinal Historical Cohorts for both registries, the cohort entry date was 01 January 2016. These cohort were followed through 31 December 2017.

Results from the Kalydeco PAES UK F/F Comparator Cohort and Study 110 are discussed to provide additional context to the disease patterns observed in the concurrent cohorts. Patients were censored based on death, loss to follow-up treatment, and lack of evidence of treatment to Orkambi.

Main study objectives

1. To evaluate disease progression in F/F children aged 2 through 5 years at Orkambi initiation in context of the following cohorts:
    a) Matched Concurrent Comparator Cohorts of children aged 2 through 5 years, who have never received Orkambi or other CFTR modulator treatment, and who are
        a. heterozygous for F508del and a minimal function mutation (F/MF), or
        b. F/F (if feasible)
    b) Longitudinal Historical Cohort of F/F children aged 2 through 5 years who have never received Orkambi (or other CFTR modulator) (where data are available)
    c) F/F children from the Kalydeco™ PAES (VX15-770-125 [Study 770-125]) Comparator Cohort from the UK CF Registry aged 2 through 5 years who have never received Orkambi (or other CFTR modulator)
    d) F/F children from Study VX15-809-110 Treatment Cohort Period 1 (Study 110) who were aged 6 through 11 years at Orkambi initiation
2. To evaluate the safety outcomes in F/F children aged 2 through 5 years at Orkambi initiation
3. To evaluate disease progression in F/F children aged 1 to <2 years at Orkambi initiation in the context of the following:
    a. Matched Concurrent Comparator Cohorts of children aged 1 to <2 years who have never received Orkambi (or other CFTR modulator) treatment, and who are
        i. F/MF, or
        ii. F/F (if feasible)
    b. Longitudinal Historical Cohort of F/F children aged 1 to <2 years who have never received Orkambi (or other CFTR modulator)
4. To evaluate the safety outcomes in F/F children aged 1 to <2 years at Orkambi initiation

Data Sources and Measurement

Data from the ECFSPR and US CFFPR were used for the main study analyses.

The ECFSPR database contains data from over 52,000 consenting people with CF from:

- 20 countries with a national registry: data is collected on a national level with the national registry's software system
- 19 countries with individual centers: CF clinicians and other clinical staff input data directly in

the software system ECFSTracker.

The data in the ECFSPR database represents, in most countries, ⩾80% of people with CF. Data are collected annually and included in pre-defined fields in the online software ECFSTracker. The system adheres to the current European data protections regulations. A Data Report with aggregated annual data, relevant for this study, is provided to Vertex.

The US CFFPR tracks the treatments and health of patients with CF across the US. Information is collected on patients who receive care at >120 CFF-accredited care centers and who agree to participate in the registry. In 2020, the US CFFPR included >31,000 CF patients, representing 81% to 84% of all people with CF in the country. This registry utilizes PortCF, an online registry application, for data entry by staff at CF-accredited care centers. Data are entered throughout the year for encounter-based visits and annual patient visits. All data entered into PortCF are transferred nightly to the CF Foundation using a secure SSH File Transfer Protocol. The data are then processed, stored, and encrypted to meet the standards of the HITECH Act. Data collected by the US CFFPR are then provided to Vertex as a data report only.

Statistical analyses

Exposure: Orkambi exposure for each patient was determined based on record of Orkambi treatment as identified in the ECFSPR and US CFFPR. Children were considered exposed to Orkambi until there was no evidence of treatment in the registry. If the registry data showed that a child was no longer exposed to Orkambi, the child was censored from the Orkambi Cohort. If an interruption period was ⩽90 days in duration, patients were considered continuously exposed until censorship; patients were censored if interruptions were >90 days in duration. In these cases, exposure duration was calculated through the last date of exposure or first encounter date where exposure was not reported, depending on the registry and available data (i.e., date of censoring).

Covariates: outcomes in the Orkambi and Concurrent Comparator Cohorts were stratified by age. There were slight differences in the age stratification approach used across analyses, due to differences in cohort entry and baseline periods between the analyses with and without matching and between the registries.

Effectiveness Endpoints: the effectiveness endpoints that were evaluated in the ECFSPR and US CFFPR cohorts, Kalydeco PAES UK F/F Comparator Cohort, and Study 110 cohort are summarized in Table below. Any differences are due to differences across the registry data collection methods and study designs.

Table 3: Effectiveness Endpoints, by Cohort

Endpoint	US CFFPR		ECFSPR			
	Orkambi and F/MF Concurrent Comparator Cohorts	F/F Historical Comparator Cohort	Orkambi and F/MF and F/F Concurrent Comparator Cohorts	F/F Historical Comparator Cohort	Kalydeco PAES UK F/F Comparator Cohort	Study 110 Cohort
Growth Parameters						
BMI-for-age, height-for-age, and weight-for-age z-scores	Yes	Yes	Yes	Yes	Yes	Yes
Weight-for-length z-score[a]	Yes	Yes	Yes	Yes	No	No
BMI, height, and weight percentiles	Yes	Yes	Yes	Yes	Yes	No
Weight-for-length percentile[a]	Yes	Yes	Yes	Yes	No	No
PEx						
PEx leading to hospitalization and/or home IV antibiotics	Yes	Yes	No	No	No	No
PEx leading to hospitalization[b]	Yes	Yes	Yes	No	Yes	No
PEx based on physician assessment at each visit as recorded in the registry	Yes	No	No	No	No	No
Hospitalizations (any)[c]	Yes	Yes	Yes	No	Yes[h]	No
ppFEV$_1$[d]	Yes	Yes	Yes	No	Yes	Yes
CF medications						
Inhaled antibiotics (tobramycin, colistin, aztreonam)	Yes	Yes	Yes[g]	No	Yes[i]	No
Oral corticosteroids	Yes	Yes	Yes	No	No	No
CF complications (DIOS and CFRD[e])	Yes	Yes	Yes	No	Yes	No

Table 3: Effectiveness Endpoints, by Cohort

Endpoint	US CFFPR		ECFSPR			
	Orkambi and F/MF Concurrent Comparator Cohorts	F/F Historical Comparator Cohort	Orkambi and F/MF and F/F Concurrent Comparator Cohorts	F/F Historical Comparator Cohort	Kalydeco PAES UK F/F Comparator Cohort	Study 110 Cohort
Pulmonary microorganisms (*P. aeruginosa*, *H. influenzae*, and *S. aureus* [including methicillin-resistant *S. aureus*])[f]	Yes	Yes	Yes	No	Yes	No

BMI: body mass index; CF: cystic fibrosis; CFFPR: Cystic Fibrosis Foundation Patient Registry; CFRD: CF-related diabetes; CFTR: cystic fibrosis transmembrane conductance regulatory protein; DIOS: distal intestinal obstruction syndrome; ECFSPR: European Cystic Fibrosis Society Patient Registry; F/F: homozygous for *F508del* mutation; F/MF: heterozygous for *F508del* and a second mutation that results in minimal CFTR function; *H. influenzae: Haemophilus influenzae;* IV: intravenous; PAES: post-authorization efficacy study; PEx: pulmonary exacerbation; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; *P. aeruginosa: Pseudomonas aeruginosa; S. aureus: Staphylococcus aureus;* UK: United Kingdom; US: United States

[a] Weight-for-length z-score and percentile were evaluated for the 1-<2y cohorts only.

[b] For US CFFPR, PEx leading to hospitalization was characterized by IV antibiotic treatment in the hospital; % of patients with PEx leading to hospitalization and number of PEx per patient were evaluated. For ECFSPR, % of patients with PEx leading to hospitalization was derived based on total days on IV antibiotics in the hospital; number of PEx per patient cannot be derived.

[c] For US CFFPR % of patients with any hospitalization and number of hospitalizations per patient was evaluated. For ECFSPR, % of patients with any hospitalization was derived based on total days in the hospital; number of hospitalizations per year cannot be derived.

[d] $ppFEV_1$ data were unavailable before patients reached the age of 6 years during follow-up.

[e] For US CFFPR, % of patients with CFRD was evaluated. For ECFSPR, % of patients with diabetes treated with insulin, which may include patients with diabetes not related to CF, was evaluated; % of patients with CFRD cannot be derived.

[f] For US CFFPR, % of patients with a positive bacterial culture for each pulmonary microorganism during the analysis year was evaluated. For ECFSPR, % of patients with a positive bacterial culture for *H. influenzae* during the analysis year and % of patients with chronic infection of *P. aeruginosa* and *S. aureus* based on the Leeds criteria were evaluated.

[g] For ECFSPR, any kind of inhaled antibiotics was evaluated.

[h] In the Kalydeco PAES UK analysis, hospitalizations was defined as hospitalizations for reasons other than PEx, which is different from the definition of hospitalizations used for the concurrent cohorts (i.e., any hospitalizations).

[i] In the Kalydeco PAES UK analysis, use of CF medications was evaluated using a different set of medications compared with those reported by the ECFSPR and US CFFPR.

Safety Endpoints: the following safety endpoints were evaluated in the ECFSPR and US CFFPR cohorts:

- Liver function test (LFT) elevations (US CFFPR only):
    - o Alanine transaminase (ALT)
    - o Aspartate transaminase (AST)
- Organ transplantations
- Deaths

Continuous variables were summarized using the following descriptive summary statistics: number of observations (n), mean, SD, SE, median, range (minimum, maximum value), and 95% CI for the mean, as appropriate.

Categorical variables were summarized using counts and percentages, as appropriate.

Analysis of ECFSPR and US CFFPR Orkambi and Concurrent Comparator Cohorts

For the matched analyses, children in the Orkambi Cohort were matched 1:1 to children in the Concurrent Comparator Cohorts on age, sex, and BMI-for-age z-score at baseline.

Statistical assessments were performed to compare children in the Orkambi Cohort to children in the Concurrent Comparator Cohorts, using descriptive summary statistics, relative risks, 95% CI, and/or P values.

Summary statistics of effectiveness outcomes in the Orkambi and Concurrent Comparator Cohorts during the baseline period and each year of follow-up were provided for the overall cohorts and by age subgroups. In addition, change from baseline was estimated for the growth parameters.

Summary statistics of safety outcomes for the Orkambi and Concurrent Comparator Cohorts during each year of follow-up were provided. Results of LFT elevations were provided for the overall cohorts and by age subgroups for the US CFFPR.

Analysis of ECFSPR and US CFFPR F/F Longitudinal Historical Cohorts

For the F/F Longitudinal Historical Cohorts, descriptive summary statistics of outcomes for each year of follow-up were provided. Results from the F/F Longitudinal Historical Cohorts were used for additional context for interpreting results of the Orkambi and Concurrent Comparator Cohorts. No statistical comparisons using the F/F Longitudinal Historical Cohort were carried out.

Missing Values

The ECFSPR and US CFFPR have robust systems in place to minimize missing data. Where data on outcomes were missing, the at-risk population was defined by those patients with non-missing data. As such, the at-risk population differed slightly across outcomes. Missing values were not imputed.

Quality Control

Data processors in the centres and national registries are responsible for ensuring that data submitted to the ECFSPR is accurate, complete, and up to date. In the software, data validation is applied on different levels with automated data validation checks and controls to minimize duplication, errors and/or issues. The statisticians perform the final validation checks.

Inconsistencies in the data were reported back to the centre and national registries, who corrected or confirmed the reported issues. In 2018, the ECFSPR started a validation program at source level in the centres in Europe, that enters the data directly into the ECFSTracker, to foster higher accuracy of data entry. This program is also available for use in the countries with a national registry. The overall results of the validation visits showed $\geqslant$92% data completeness for the subset of variables examined for the year 2020 and data accuracy of $\geqslant$81% for the variables examined for 2016, 2017, and 2020.

The responsibility for the quality of the US CFFPR data lies with the CF centres. The annual grants application signed by all centre directors has a clause that states that the registry data provided by the centre is accurate to the best of the centre director's knowledge. Some of the key data entries (e.g., death dates) are verified with the centre's data entry staff after the end of the reporting year. There is also documented evidence about an almost perfect match between the registry data and the data from the clinical studies that involve patients with CF. Audits performed between 2013 and 2018 demonstrated

a high degree of US CFFPR data accuracy, with 95% to 99% concordance between registry records and electronic medical record values across major data categories.

5.2. Results

Study Size

The study size was based on the registry-based cohorts and was dependent on the patterns of Orkambi use in children aged 1 through 5 years in routine clinical practice in the US and participating European countries during the cohort entry periods. The Table below displays the sizes of the patient populations at the end of the cohort entry periods.

Table 4: Sizes of the Patient Populations, ECFSPR and US CFFPR

	ECFSPR	US CFFPR
2-5y Matched Concurrent Cohorts		
Orkambi Cohort and F/MF Concurrent Comparator Cohort	677 matched pairs	779 matched pairs
Orkambi Cohort and F/F Concurrent Comparator Cohort	210 matched pairs	NA
2-5y F/F Longitudinal Historical Cohort	1282	1441
1-<2y Matched Concurrent Cohorts		
Orkambi Cohort and F/MF Concurrent Comparator Cohort	118 matched pairs	161 matched pairs
Orkambi Cohort and F/F Concurrent Comparator Cohort	69 matched pairs	NA
1-<2y F/F Longitudinal Historical Cohort	291	305

Sources: Study 128 ECFSPR 2-5y Concurrent Cohorts Tables and Figures/Figure 1.1b; Study 128 ECFSPR 2-5y Historical Cohort Tables and Figures/Figure 1; Study 128 US CFFPR 2-5y Concurrent Cohorts Tables and Figures/Figure 1.0b; Study 128 US CFFPR 2-5y Historical Cohort Tables and Figures/Figure 1; Study 128 ECFSPR 1y Concurrent Cohorts Tables and Figures/Figures 1.1b and 1.2b; Study 128 ECFSPR 1y Historical Cohort Tables and Figures/Figure 1; Study 128 US CFFPR 1y Concurrent Cohorts Tables and Figures/Figure 1.0b; and Study 128 US CFFPR 1y Historical Cohort Tables and Figures/Figure 1.0

CF: cystic fibrosis; CFFPR: CF Foundation Patient Registry; ECFSPR: European CF Society Patient Registry; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a second mutation that results in minimal CFTR function; NA: not applicable; US: United States

In the Concurrent Cohorts Analyses, baseline was defined as follows:

Baseline period

In the ECFSPR analyses, the calendar year prior to the start of the cohort entry period was considered the baseline period.

- o 2-5y cohorts: baseline measure was from 2018 (Orkambi EEA approval in 2019)
- o 1-<2y cohorts: baseline measure was from 2022 (Orkambi EEA approval in 2023)

In the US CFFPR analyses, the baseline period was the 12-month period before the cohort entry date for the Orkambi Cohorts (in both the matched and unmatched analyses) as well as for the Matched F/MF Concurrent Comparator Cohorts.

- o 2-5y cohorts: baseline period was from 07 August 2017 through 31 December 2018
- o 1-<2y cohorts: 17 March 2022 through 31 December 2022

For the Unmatched F/MF Concurrent Comparator Cohorts, since there was no index date, the 2018

calendar year was used as the baseline period for the 2-5y cohort and the 2022 calendar year was used as the baseline period for the 1-<2y cohort.

Outcomes

ECFSPR

ECFSPR 2-5y Orkambi and Concurrent Comparator Cohorts

As of the end of the ECFSPR 2-5y cohort entry period (31 December 2020), there were 992 patients who initiated Orkambi and were aged 2 through 5 years at treatment initiation.

During the same period, there were 795 patients eligible for inclusion in the 2-5y F/MF Concurrent Comparator Cohort and 226 patients eligible for inclusion in the 2-5y F/F Concurrent Comparator Cohort.

Following individual 1:1 matching on age, sex, and BMI-for-age z-score, 677 matched pairs were formed between the 2-5y Orkambi Cohort and 2-5y F/MF Concurrent Comparator Cohort, and 210 matched pairs were formed between the 2-5y Orkambi Cohort and 2-5y F/F Concurrent Comparator Cohort.

Pre-treatment baseline demographic and clinical characteristics for the patients prior to matching and those for the matched cohorts are shown in the Table below.

Table 5: Baseline Demographic and Clinical Characteristics for the ECFSPR 2-5y Orkambi and Concurrent Comparator Cohorts by Matching Status

	Before Matching ("Unmatched")			Matched to F/MF Comparator		Matched to F/F Comparator	
Characteristic	**2-5y Orkambi Cohort N = 992**	**2-5y F/MF Concurrent Comparator Cohort N = 795**	**2-5y F/F Concurrent Comparator Cohort N = 226**	**2-5y Orkambi Cohort N = 677**	**2-5y F/MF Concurrent Comparator Cohort N = 677**	**2-5y Orkambi Cohort N = 210**	**2-5y F/F Concurrent Comparator Cohort N = 210**
Age at baseline, years, mean (SD)[a]	2.8 (1.31)	3.3 (1.55)	3.1 (1.65)	2.9 (1.36)	2.9 (1.37)	2.9 (1.56)	3.0 (1.58)
Female sex, n (%)	485 (48.9)	372 (46.8)	108 (47.8)	315 (46.5)	315 (46.5)	103 (49.0)	103 (49.0)
Country, n (%)							
Austria	18 (1.8)	30 (3.8)	-	*	28 (4.1)	*	-
Denmark	43 (4.3)	*	-	34 (5.0)	*	14 (6.7)	-
France	234 (23.6)	201 (25.3)	-	160 (23.6)	177 (26.1)	52 (24.8)	-
Germany	167 (16.8)	224 (28.2)	-	116 (17.1)	191 (28.2)	34 (16.2)	-
Ireland	68 (6.9)	21 (2.6)	-	54 (8.0)	17 (2.5)	19 (9.0)	-
Luxembourg	*	*	-	0 (0.0)	*	0 (0.0)	-
The Netherlands	58 (5.8)	21 (2.6)	-	42 (6.2)	19 (2.8)	19 (9.0)	-
Slovenia	*	*	-	0 (0.0)	*	*	-
Sweden	32 (3.2)	13 (1.6)	-	25 (3.7)	12 (1.8)	*	-
Switzerland	*	36 (4.5)	-	*	32 (4.7)	*	-
UK	360 (36.3)	234 (29.4)	-	225 (33.2)	187 (27.6)	56 (26.7)	-
Croatia	-	-	15 (6.6)	-	-	-	14 (6.7)
Czech Republic	-	-	*	-	-	-	*
Italy	-	-	111 (49.1)	-	-	-	103 (49.0)
Latvia	-	-	*	-	-	-	*
Norway	-	-	12 (5.3)	-	-	-	*
Poland	-	-	72 (31.9)	-	-	-	68 (32.4)

BMI-for-age z-score, mean (SD)	0.0 (1.17)	-0.1 (1.13)	-0.5 (1.32)	-0.1 (1.18)	-0.1 (1.17)	-0.3 (1.19)	-0.4 (1.32)
BMI percentile, mean (SD)	49.9 (30.5)	48.7 (29.65)	39.0 (31.97)	47.9 (30.31)	48.1 (30.14)	41.9 (31.15)	40.7 (32.29)
PEx leading to hospitalization, n/N1 (%)	164/990 (16.6)	116/793 (14.6)	56/224 (25.0)	116/676 (17.2)	100/675 (14.8)	25/210 (11.9)	54/208 (26.0)
Hospitalizations, n/N1 (%)	347/980 (35.4)	235/790 (29.7)	116/221 (52.5)	243/668 (36.4)	197/674 (29.2)	72/208 (34.6)	111/205 (54.1)
CF medication use, n/N1 (%)							
Inhaled antibiotics	151/991 (15.2)	126/793 (15.9)	30/226 (13.3)	95/676 (14.1)	106/676 (15.7)	20/210 (9.5)	27/210 (12.9)
Oral corticosteroids	10/991 (1.0)	5/793 (0.6)	8/190 (4.2)	8/676 (1.2)	4/676 (0.6)	0/210 (0.0)	6/176 (3.4)
Pulmonary microbiology, n/N1 (%)							
P. aeruginosa	19/990 (1.9)	16/795 (2.0)	4/225 (1.8)	14/675 (2.1)	13/677 (1.9)	2/209 (1.0)	4/209 (1.9)
H. influenzae	358/990 (36.2)	248/795 (31.2)	44/192 (22.9)	246/675 (36.4)	192/677 (28.4)	77/209 (36.8)	41/178 (23.0)
S. aureus (including MRSA)	184/990 (18.6)	170/795 (21.4)	90/202 (44.6)	131/675 (19.4)	148/677 (21.9)	47/209 (22.5)	85/188 (45.2)
DIOS, n/N1 (%)	28/984 (2.8)	14/793 (1.8)	1/221 (0.5)	23/671 (3.4)	12/676 (1.8)	4/210 (1.9)	1/205 (0.5)
CFRD, n/N1 (%)	1/991 (0.1)	3/795 (0.4)	0/226 (0.0)	1/676 (0.1)	2/677 (0.3)	0/210 (0.0)	0/210 (0.0)

Sources: Study 128 ECFSPR 2-5y Concurrent Cohorts Tables and Figures/Tables 1.1a, 1.1b, and 1.6b

BMI: body mass index; CF: cystic fibrosis; CFRD: CF-related diabetes; DIOS: distal intestinal obstruction syndrome; ECFSPR: European CF Society Patient Registry; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a second mutation that results in minimal CFTR function; *H. influenzae:* IA: interim analysis; MRSA: methicillin-resistant *Staphylococcus aureus*; n: number of patients with an event; N: total cohort size; N1: number of patients with a non-missing measurement; PEx: pulmonary exacerbation; *P. aeruginosa; Pseudomonas aeruginosa;* SD: standard deviation; *S. aureus: Staphylococcus aureus;* UK: United Kingdom

Note: Denominators for percentages are the total cohort size (i.e., N) unless shown otherwise, in which case the denominator is N1, the number of patients with a non-missing measurement of the outcome.

Note: Cells denoted by an asterisk (*) have been redacted at the time of publication on the EMA website due to low numbers of participants (n ≤11). In cases where suppressed cells can be calculated using the total n value/percentages of a column, complimentary cell suppression was applied to the next lowest cell.

[a] Age as of 31 December 2018

After matching, the cohorts were well balanced on pre-treatment baseline values of age, sex, and BMI-for-age z-score. However, some residual numeric imbalances existed in terms of other baseline characteristics (e.g., risk of PEx and hospitalizations)

All 2-5y matched concurrent cohorts experienced pronounced attrition starting from 2022, primarily due to initiation of other CFTR modulators (Symkevi therapy became available for Orkambi Cohort patients 6 to 11 years of age in 2020 and Kaftrio therapy became available for Orkambi and F/F and F/MF Concurrent Comparator Cohorts patients 6 to 11 years of age in 2022 and 2 to 5 years of age in 2023). The proportions of patients remaining in each cohort as of 2024 (last year of follow-up) were as follows:

- Within the 2-5y Orkambi Cohort matched to the 2-5y F/MF Concurrent Comparator Cohort, only 9 out of 677 (1.3%) patients were still being treated with Orkambi (and did not meet any other censoring criteria) while only 35 out of 677 (5.2%) patients in the 2-5y F/MF Concurrent Comparator Cohort remained untreated with a CFTR modulator (and were not censored due to other reasons)
- Similarly, within the 2-5y Orkambi Cohort matched to the 2-5y F/F Concurrent Comparator Cohort, only 3 out of 210 (1.4%) patients were still being treated with Orkambi (and did not meet any other censoring criteria) while only 8 out of 210 (3.8%) patients in the 2-5y F/F Concurrent Comparator Cohort remained untreated with a CFTR modulator (and were not censored due to other reasons)

To understand the impact of attrition on study result interpretation, baseline characteristics of the initial patient cohorts were compared to baseline characteristics of patients who remained in the cohorts in each follow-up year. These analyses showed that:

- In both matched sets of 2-5y cohorts (Orkambi matched to F/MF comparator and Orkambi matched to F/F comparator), patients remaining in the cohort were generally younger than the initial cohorts. Patients remaining in the 2-5y Orkambi Cohorts and F/MF Concurrent Comparator Cohort generally had lower growth parameter values at baseline than the initial cohorts, whereas patients remaining in the F/F Concurrent Comparator Cohort had higher growth parameter values at baseline than the initial cohort. There were other numeric differences from the initial cohorts, however no other discernible trends could be identified.
- Furthermore, as a result of attrition, starting from 2022, both sets of matched cohorts were no longer balanced on baseline BMI-for-age z-score (patients remaining in Orkambi cohorts had lower baseline score than patients remaining in comparator cohorts) and baseline age (patient remaining in Orkambi cohorts were younger at baseline than those remaining in the comparator cohorts).

Therefore, given the significant differential attrition in the 2-5y concurrent cohorts starting from 2022 and small sample sizes after 2022, the results of analyses post-2022 should be interpreted with caution.

Distributions of Orkambi exposure duration in the ECFSPR 2-5y Matched Orkambi Cohorts are summarized in Table below:

Table 6: Orkambi Exposure Duration in the ECFSPR 2-5y Matched Orkambi Cohorts

Orkambi Exposure Duration (months) as of:	Orkambi Cohort Matched to F/MF Concurrent Comparator Cohort N = 677		Orkambi Cohort Matched to F/F Concurrent Comparator Cohort N = 210	
	n	Mean (SD)	n	Mean (SD)
31 December 2019[a]	674[b]	1.8 (3.08)	209[c]	2.0 (3.29)
31 December 2020	677	10.9 (5.52)	210	11.1 (5.82)
31 December 2021	625	22.9 (5.73)	199	23.1 (5.87)
31 December 2022	300	32.5 (4.57)	100	31.7 (4.22)
31 December 2023	60	42.4 (4.13)	28	43.0 (3.79)
31 December 2024	9	56.4 (4.34)	3	57.9 (1.90)

Sources: Study 128 ECFSPR 2-5y Concurrent Cohorts Tables and Figures/Tables 2.1b and 2.2b

CF: cystic fibrosis; ECFSPR: European CF Society Patient Registry; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a second mutation that results in minimal *CFTR* function; n: number of subjects with data; N: number of subjects in the analysis set; SD: standard deviation

[a] Exposure duration among all patients, including those who initiated Orkambi in 2020 (i.e., unexposed to Orkambi in 2019).

[b] Discrepancy between N and n is due to the lack of records in the total Orkambi cohort of 3 patients in 2019.

[c] Discrepancy between N and n is due to the lack of records in the total Orkambi cohort of 1 patient in 2019.

ECFSPR 2-5y F/F Longitudinal Historical Cohort

The ECFSPR 2-5y F/F Longitudinal Historical Cohort included 1,282 patients in 2012. Baseline demographic and clinical characteristics for the ECFSPR F/F Longitudinal Historical Cohort are presented in Table below:

Table 7: Demographic and Clinical Characteristics for the ECFSPR 2-5y F/F Longitudinal Historical Cohort

Characteristic	2-5y F/F Longitudinal Historical Cohort N = 1282
Age as of 01 January 2012, years, mean (SD)	4.0 (1.15)
Female sex, n (%)	669 (52.2)
Country, n (%)	
Austria	35 (2.7)
Denmark	*
France	299 (23.3)
Germany	205 (16.0)
Ireland	73 (5.7)
Netherlands	91 (7.1)
Slovenia	*
Sweden	29 (2.3)
Switzerland	31 (2.4)
UK	486 (37.9)
BMI-for-age z-score, mean (SD)	0.0 (1.06)
BMI percentile, mean (SD)	50.4 (29.10)

Sources: Study 128 ECFSPR 2-5y Historical Cohort Tables and Figures/Tables 1.0, 2.1.1, and 2.2.1

BMI: body mass index; CF: cystic fibrosis; ECFSPR: European CF Society Patient Registry; F/F: homozygous for *F508del*; n: number of subjects with data; N: number of subjects in the analysis set; SD: standard deviation; UK: United Kingdom

Notes: The cohort entry date was 01 January 2012. Attrition from the cohort over time is permitted as subjects become exposed to CFTR modulators, death or first year of loss to follow-up. The cohort was followed through 31 December 2017.

Note: Cells denoted by an asterisk (*) have been redacted at the time of publication on the EMA website due to low numbers of participants (n ≤11). In cases where suppressed cells can be calculated using the total n value/percentages of a column, complimentary cell suppression was applied to the next lowest cell.

Over the course of 6 years of follow-up, a total of 88 (6.9%) patients were censored, 1 due to death, 55 due to loss to follow-up, and 32 due to a record of CFTR modulator use.

Kalydeco PAES UK F/F Comparator Cohort

The Kalydeco PAES UK F/F Comparator Cohort included 236 patients. Baseline demographic and clinical characteristics for the Kalydeco PAES UK F/F Comparator Cohort are presented in Table below.

Table 8: Baseline Demographic and Clinical Characteristics for the Kalydeco PAES UK F/F Comparator Cohort

	Concurrent Comparator Cohort N = 236
Age as of 31 December 2016, years	
Mean (SD)	3.4 (1.3)
Sex	
Female, n (%)	108 (45.8)
BMI-for-age *z*-score as of 31 December 2016	
Mean (SD)	0.3 (1.0)
PEx and hospitalizations	
PEx (hospitalization) n (%)	65 (27.5)
Non-PEx hospitalization, n (%)	47 (19.9)
Medications	
Inhaled corticosteroids, n (%)	22 (9.3)
Inhaled tobramycin, n (%)	1 (0.4)
Inhaled aztreonam, n (%)	0 (0.0)
Pulmonary microbiology	
P. aeruginosa, n (%)	59 (25.0)
H. influenzae, n (%)	86 (36.4)
S. aureus – any, n (%)	52 (22.0)
MRSA, n (%)	3 (1.3)
Complications	
DIOS, n (%)	3 (1.3)
CFRD, n (%)	0 (0.0)

Source: Study 770-125 Final CSR/Table 12-9

BMI: body mass index; CFRD: CF-related diabetes; DIOS: distal intestinal obstruction syndrome; F/F: homozygous for *F508del*; *H. influenzae*: *Haemophilus influenzae*; MRSA: methicillin-resistant *Staphylococcus aureus*; n: number of subjects or observations; *P. aeruginosa*: *Pseudomonas aeruginosa*; PAES: Post-authorization efficacy study; PEx: pulmonary exacerbation; *S. aureus*: *Staphylococcus aureus*; SD: standard deviation; UK: United Kingdom

The Kalydeco PAES UK F/F Comparator cohort experienced pronounced attrition over time with 70/236 (29.7%) patients followed in 2020 and only 5/236 (2.1%) followed in 2022. The attrition was primarily due to initiation of new CFTR modulators.

When the baseline characteristics of the initial patient cohorts were compared to the baseline characteristics of patients who remained in the cohorts in each follow-up year, the attrition appeared to be differential starting from the fourth year of follow-up, with patients remaining in the cohort being younger than the initial cohort (similar to patterns observed in the Orkambi cohorts in this study).

Study 110

Study 110 was a Phase 3, multicenter study in subjects aged 6 years and older with CF with the F/F genotype who had participated in parent studies (Study 109 or Study 011B). The Study 110 LUM/IVA to LUM/IVA group (L/I-L/I) consisted of 143 subjects who were treated with LUM/IVA in either parent study. Baseline demographic and clinical characteristics for subjects in the Study 110 L/I-L/I group are presented in Table below.

Table 9: Baseline Demographic and Clinical Characteristics for Subjects in Study 110 L/I-L/I Group

Characteristic	Study 110 L/I-L/I N = 143
Age at baseline, mean (SD)	8.9 (1.56)
Female sex, n (%)	83 (58.0)
Region, n (%)	
North America	102 (71.3)
Europe	25 (17.5)
Australia	16 (11.2)
BMI-for-age z-score, mean (SD)	-0.09 (0.88)
ppFEV$_1$, mean (SD)	89.3 (13.7)

Sources: Study 110 CSR/Tables 10-2 and 10-3

BMI: body mass index; L/I: lumacaftor/ivacaftor; n: number of subjects or observations; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; SD: standard deviation

The mean age at parent study baseline was 8.9 years.

It is not appropriate to directly compare the characteristics of the subjects in Study 110 to the Orkambi Cohorts, mainly because Study 110 included children who were older (6 through 11 years of age) at Orkambi treatment initiation and therefore had more advanced CF disease.

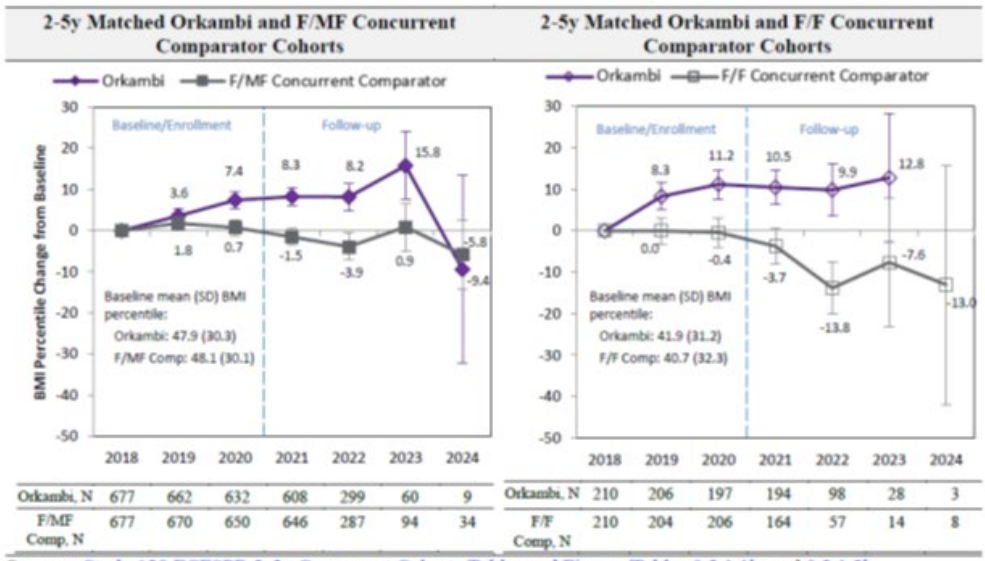
Study 110 disease progression patterns on key outcomes of growth parameters and lung function serve as additional context to interpret the patterns observed in the Orkambi Cohort children who were younger at treatment initiation.

ECFSPR Effectiveness Endpoints

Growth Parameters

BMI percentile change from baseline in the matched concurrent cohorts, height percentile change from baseline in the matched concurrent cohorts and weight percentile change from baseline in the matched concurrent cohorts are presented in Figures below.

Figure 4: BMI Percentile Change from Baseline in the ECFSPR 2-5y Matched Orkambi and F/MF and F/F Concurrent Comparator Cohorts

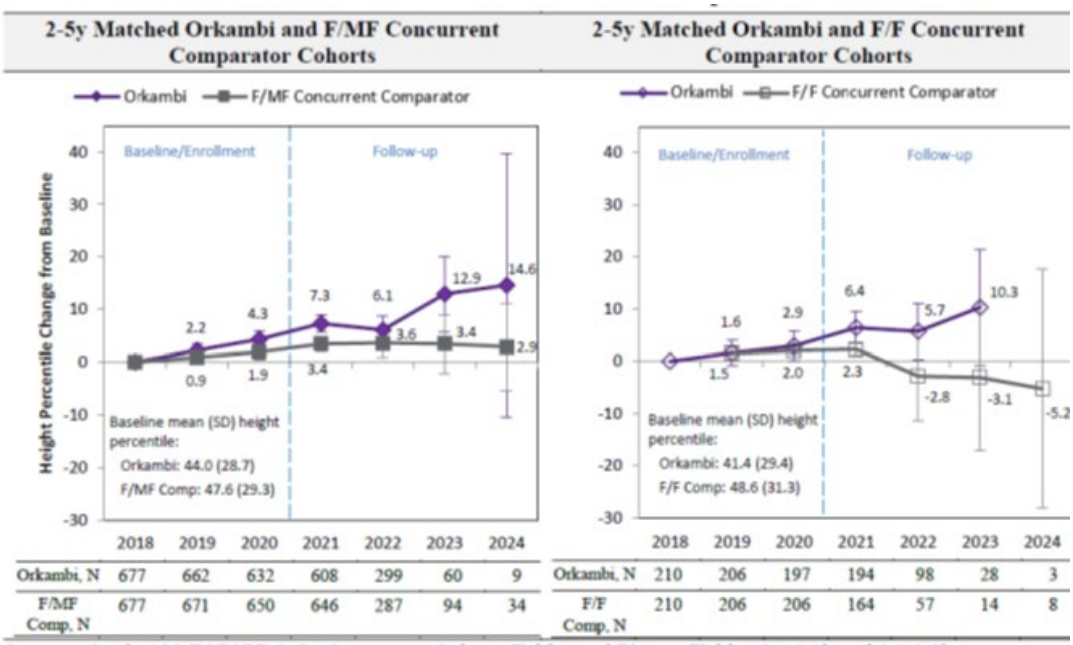


Sources: Study 128 ECFSPR 2-5y Concurrent Cohorts Tables and Figures/Tables 3.2.1.1b, and 3.2.1.2b

BMI: body mass index; CF: cystic fibrosis; Comp: comparator; ECFSPR: European CF Society Patient Registry; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a second mutation that results in minimal *CFTR* function; N: number of subjects in the analysis set

Notes: The vertical dotted line delineates the baseline/enrollment and post-enrollment follow-up periods. The horizontal solid line delineates the change of 0 from baseline. Results for 2-5y Matched Orkambi Cohort in 2024 are not shown due to insufficient sample size (N<5).

Figure 5: Height Percentile Change from Baseline in the ECFSPR 2-5y Matched Orkambi and F/MF and F/F Concurrent Comparator Cohorts

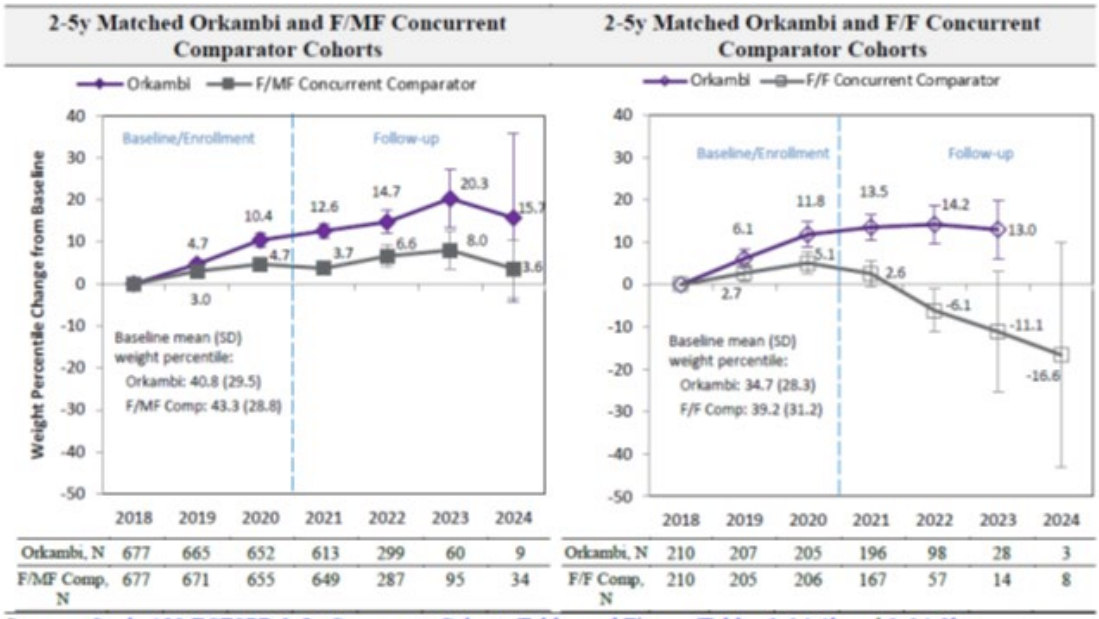


Sources: Study 128 ECFSPR 2-5y Concurrent Cohorts Tables and Figures/Tables 3.4.1.1b and 3.4.1.2b

BMI: body mass index; CF: cystic fibrosis; Comp: comparator; ECFSPR: European CF Society Patient Registry; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a second mutation that results in minimal *CFTR* function; N: number of subjects in the analysis set

Notes: The vertical dotted line delineates the baseline/enrollment and post-enrollment follow-up periods. The horizontal solid line delineates the change of 0 from baseline. Results for 2-5y Matched Orkambi Cohort in 2024 are not shown due to insufficient sample size (N<5).

Figure 6: Weight Percentile Change from Baseline in the ECFSPR 2-5y Matched Orkambi and F/MF and F/F Concurrent Comparator Cohorts



Sources: Study 128 ECFSPR 2-5y Concurrent Cohorts Tables and Figures/Tables 3.6.1.1b and 3.6.1.2b

BMI: body mass index; CF: cystic fibrosis; Comp: comparator; ECFSPR: European CF Society Patient Registry; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a second mutation that results in minimal *CFTR* function; N: number of subjects in the analysis set

Notes: The vertical dotted line delineates the baseline/enrollment and post-enrollment follow-up periods. The horizontal solid line delineates the change of 0 from baseline. Results for 2-5y Matched Orkambi Cohort in 2024 are not shown due to insufficient sample size (N<5).

BMI percentile, height percentile, and weight percentile generally increased from baseline over time in the Orkambi Cohorts whereas they generally decreased or remained stable in the Matched Concurrent Comparator Cohorts (data post-2022 should be interpreted with caution due to attrition).

The results observed in the Orkambi Cohorts were also favourable in the context of patterns observed across the additional comparator cohorts:

• In the F/F Historical Cohort, BMI percentile, height percentile, and weight percentile generally decreased over time

• In the Kalydeco PAES UK F/F Comparator Cohort, BMI percentile, height percentile, and weight percentile also generally decreased over time

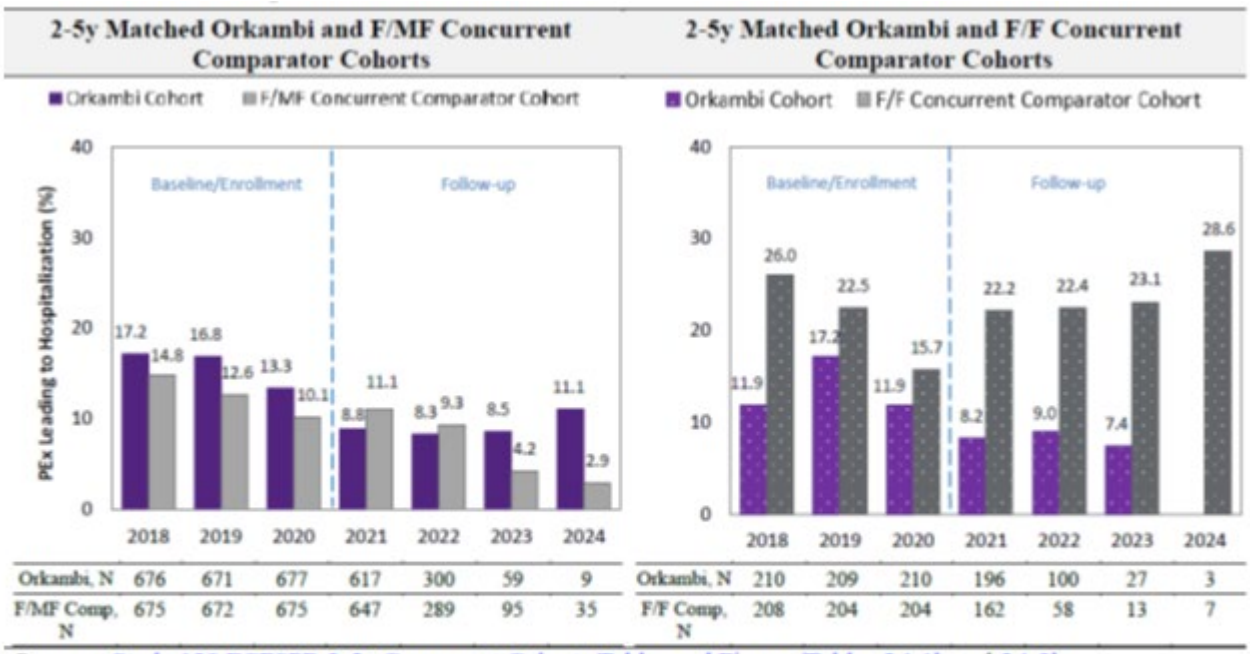
• In Study 110, although older children treated with Orkambi also had improvements in growth parameters following treatment initiation, children who initiated treatment earlier achieved better nutritional status at a younger age. For example, children in the 2-5y Orkambi F/MF Concurrent Comparator Cohort achieved a BMI percentile of 55.2 after approximately 2 years of follow-up, while children in the 6-11y cohort of Study 110 achieved a BMI percentile of 53.8 after a similar duration of follow-up.

The results of analyses of z-scores were consistent with the results of analyses of percentiles.

Pulmonary Exacerbations

The proportion of patients who experienced PEx leading to hospitalization in the ECFSPR 2-5y Matched Orkambi and F/MF and F/F Concurrent Comparator Cohorts is presented in Figure below.

Figure 7: Proportion of Patients Who Experienced ⩾1 PEx Leading to Hospitalization in the ECFSPR 2-5y Matched Orkambi and F/MF and F/F Concurrent Comparator Cohorts



Sources: Study 128 ECFSPR 2-5y Concurrent Cohorts Tables and Figures/Tables 5.1.1b and 5.1.2b

BMI: body mass index; CF: cystic fibrosis; Comp: comparator; ECFSPR: European CF Society Patient Registry; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a second mutation that results in minimal *CFTR* function; N: number of subjects in the analysis set; PEx: pulmonary exacerbation

Note: The vertical dotted line delineates the baseline/enrollment and post-enrollment follow-up periods. Results for 2-5y Matched Orkambi Cohort in 2024 are not shown due to insufficient sample size (N<5).

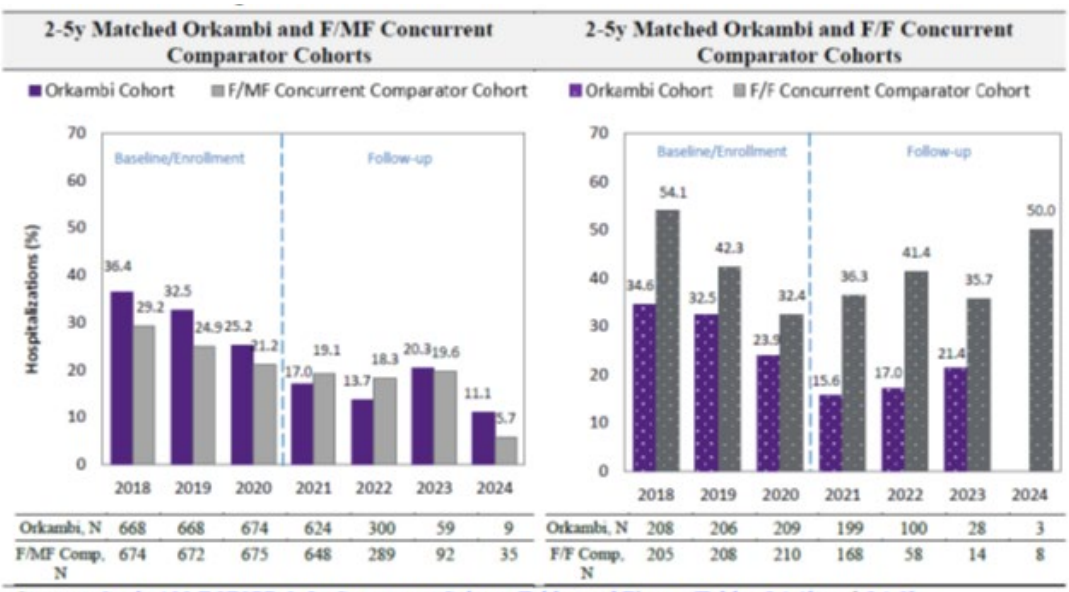
Following treatment initiation and prior to significant cohort attrition in 2022, the annual risk of PEx leading to hospitalization declined in the 2-5y Matched Orkambi cohorts to <10% annually. Although this pattern in PEx in Orkambi-treated children was not notably different in context of the F/MF Matched Concurrent Comparator Cohort, it was favourable in context of the F/F Concurrent Comparator Cohort in which PEx did not decline during follow-up.

The PEx pattern in Orkambi-treated children also was favourable in context of the Kalydeco PAES UK/F/F Comparator Cohort, where PEx frequency in untreated F/F children remained >20% throughout follow-up prior to attrition.

Hospitalizations

Figure below presents the data for the proportion of patients who experienced any hospitalizations for the ECFSPR 2-5y Matched Orkambi and F/MF and F/F Concurrent Comparator Cohorts.

Figure 8: Proportion of Patients Who Experienced ⩾1 Hospitalization in the ECFSPR 2-5y Matched Orkambi and F/MF and F/F Concurrent Comparator Cohorts



Sources: Study 128 ECFSPR 2-5y Concurrent Cohorts Tables and Figures/Tables 5.1.1b and 5.1.2b

BMI: body mass index; CF: cystic fibrosis; Comp: comparator; ECFSPR: European CF Society Patient Registry; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a minimal function mutation; N: number of subjects in the analysis set

Notes: The vertical dotted lines delineate the baseline/enrollment and post-enrollment follow-up periods. Results for 2-5y Matched Orkambi Cohort in 2024 are not shown due to insufficient sample size (N<5).

Following treatment initiation and prior to the significant cohort attritions in 2022, the annual risk of hospitalizations declined in the Orkambi Cohorts to <20% annually. This pattern in hospitalizations in Orkambi-treated children was not notably different in context of the F/MF Concurrent Comparator Cohort but was favourable in context of the F/F Concurrent Comparator Cohort.

Lung Function

The availability of percent predicted forced expiratory volume in 1 second (ppFEV1) data in young children is limited and variable due to the challenge of performing spirometry at young age. As expected, there were no patients with spirometry data at baseline since all patients were aged <6 years at baseline. Only a subset of patients had spirometry performed and ppFEV1 measurements reported during the follow-up period, and thus the data should be interpreted with caution.

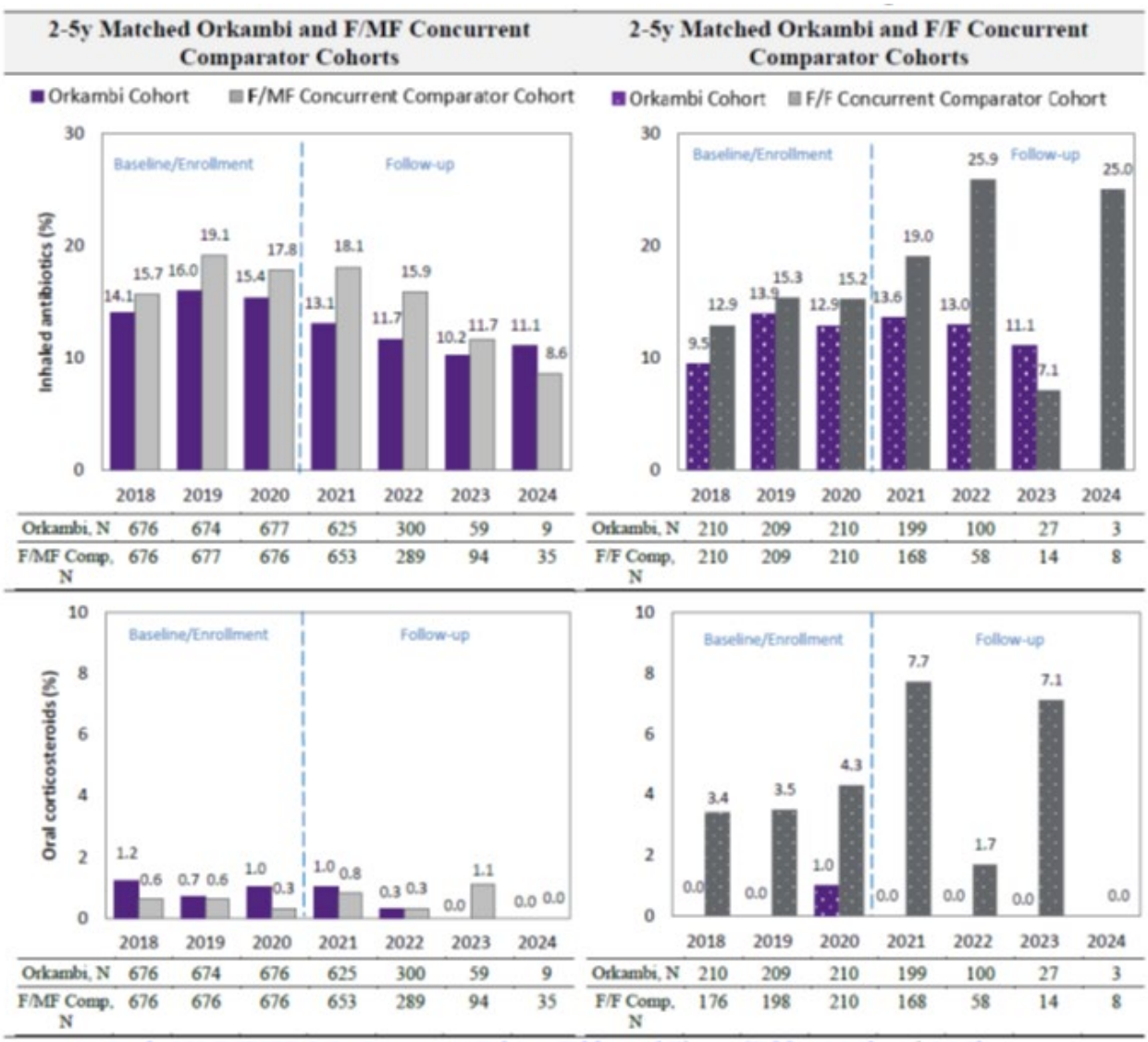
During follow-up and prior to the significant cohort attrition, mean ppFEV1 consistently remained above 95 in the subsets of 2-5y Matched Orkambi Cohort children with lung function available.

Lung function in Orkambi-treated children with available data was not notably different in context of the concurrent comparator children with available data, but was better preserved in context of the Kalydeco PAES UK F/F Comparator Cohort (mean ppFEV1 83.5 to 91.8) and the Study 110 L/I-L/I group (mean ppFEV1 89.7 at baseline and 92.3 at Week 96).

Use of CF Medications

Use of CF medications over time in the 2-5y matched concurrent cohorts is summarized in Figure below.

Figure 9: Proportion of Patients Using CF Medications in the ECFSPR 2-5y Matched Orkambi and F/MF and F/F Concurrent Comparator Cohorts



Sources: Study 128 ECFSPR 2-5y Concurrent Cohorts Tables and Figures/Tables 6.1.1b and 6.1.2b

BMI: body mass index; CF: cystic fibrosis; Comp: comparator; ECFSPR: European CF Society Patient Registry; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a second mutation that results in minimal *CFTR* function; N: number of subjects in the analysis set

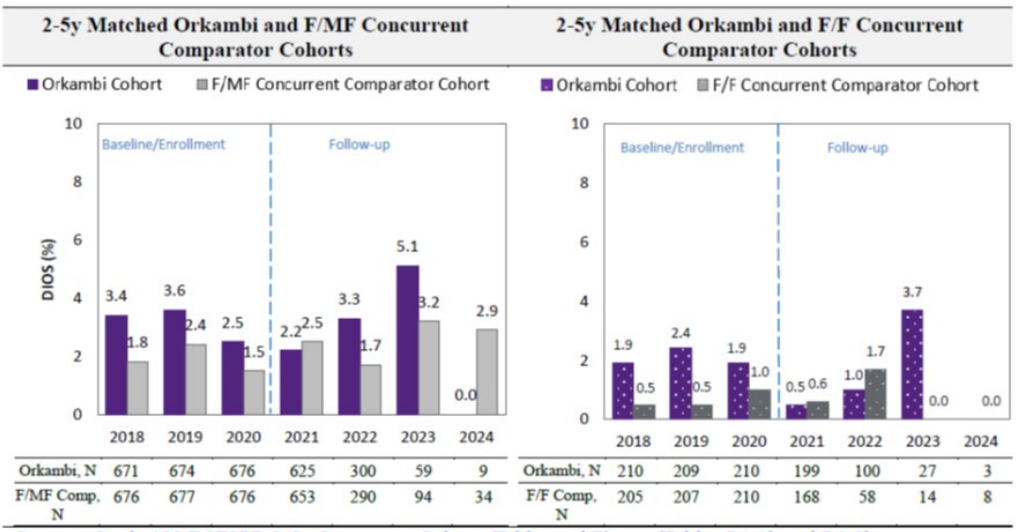
Notes: The vertical dotted line delineates the baseline/enrollment and post-enrollment follow-up periods. Results for 2-5y Matched Orkambi Cohort in 2024 are not shown due to insufficient sample size (N<5).

Prior to the significant attritions in 2022, the proportion of patients using inhaled antibiotics in the Orkambi Cohorts was consistently lower than the Concurrent Comparator Cohorts. Use of oral corticosteroids in the Orkambi Cohorts was very low and was either lower than or comparable to the Concurrent Comparator Cohorts (F/F and F/MF, respectively).

CF Complications (DIOS and CFRD)

Figure below presents the proportion of patients with DIOS in the ECFSPR 2-5y Matched Orkambi and F/MF and F/F Concurrent Comparator Cohorts.

Figure 10: Proportion of Patients with DIOS in the ECFSPR 2-5y Matched Orkambi and F/MF and F/F Concurrent Comparator Cohorts



	2018	2019	2020	2021	2022	2023	2024
Orkambi, N	671	674	676	625	300	59	9
F/MF Comp. N	676	677	676	653	290	94	34

	2018	2019	2020	2021	2022	2023	2024
Orkambi, N	210	209	210	199	100	27	3
F/F Comp. N	205	207	210	168	58	14	8

Sources: Study 128 ECFSPR 2-5y Concurrent Cohorts Tables and Figures/Tables 7.1.1b and 7.1.2b

BMI: body mass index; CF: cystic fibrosis; DIOS: distal intestinal obstruction syndrome; ECFSPR: European CF Society Patient Registry; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a second mutation that results in minimal *CFTR* function; N: number of subjects in the analysis set

Notes: The vertical dotted line delineates the baseline/enrollment and post-enrollment follow-up periods. Results for 2-5y Matched Orkambi Cohort in 2024 are not shown due to insufficient sample size (N<5).

The proportion of patients with DIOS was consistently low across all cohorts (generally <5%), with no discernible trends observed in either of the matched cohorts prior to cohort attrition in 2022; similarly, no clear trend was observed in the Kalydeco PAES UK F/F Comparator Cohort. CFRD was also very rare across all cohorts with no apparent trend (0% to 2.0% in the 2-5y Matched Orkambi Cohorts and 0% to 3.0% in the Concurrent Comparator Cohorts), consistent with the patterns also observed in the Kalydeco PAES UK F/F Comparator Cohort.

Pulmonary Microbiology

Figure below summarizes pulmonary microbiology data for the evaluated bacterial pathogens in the ECFSPR 2-5y Matched Orkambi and F/MF and F/F Concurrent Comparator Cohorts.

Figure 11: Prevalence of Bacterial Pathogens in the ECFSPR 2-5y Matched Orkambi and F/MF and F/F Concurrent Comparator Cohorts

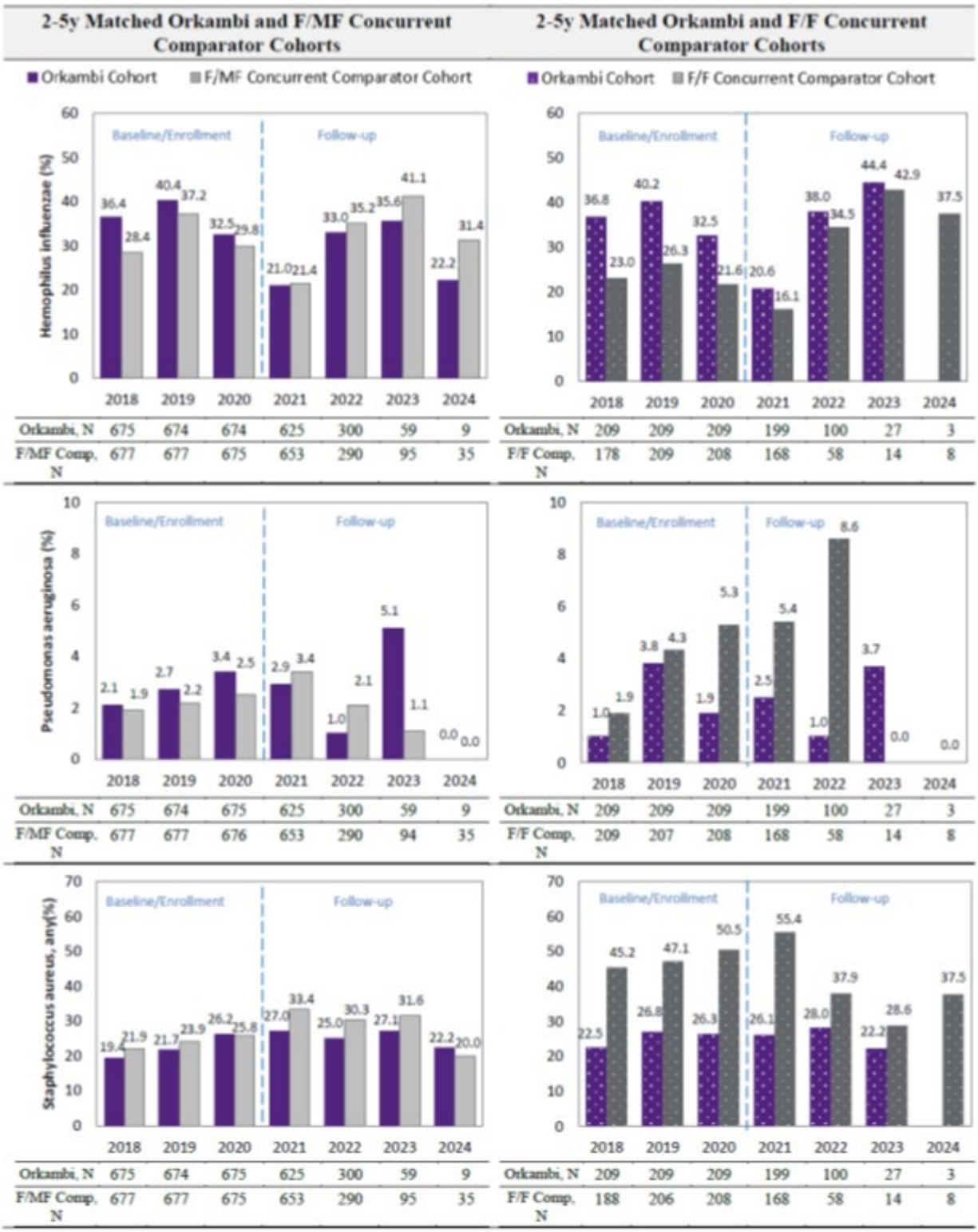
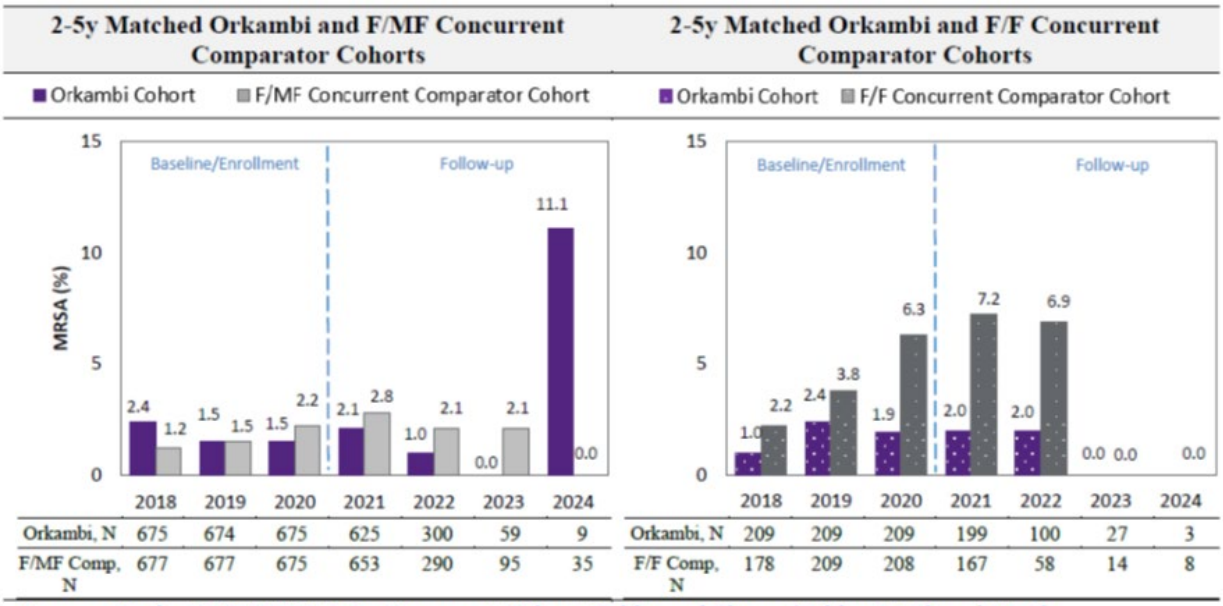


Figure 12: Prevalence of Bacterial Pathogens in the ECFSPR 2-5y Matched Orkambi and F/MF and F/F Concurrent Comparator Cohorts



Sources: Study 128 ECFSPR 2-5y Concurrent Cohorts Tables and Figures/Tables 8.1.1b and 8.1.2b

BMI: body mass index; CF: cystic fibrosis; Comp: comparator; ECFSPR: European CF Society Patient Registry; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a second mutation that results in minimal *CFTR* function; MRSA: methicillin-resistant *Staphylococcus aureus*; N: number of subjects in the analysis set

Notes: The vertical dotted line delineates the baseline/enrollment and post-enrollment follow-up periods. Results for 2-5y Matched Orkambi Cohort in 2024 are not shown due to insufficient sample size (N<5).

Overall, no discernible trends in *P. aeruginosa*, *S. aureus*, and *MRSA* were observed across the matched concurrent cohorts. The prevalence of *H. influenzae* declined prior to the cohort attrition (2022) in all matched cohorts.

ECFSPR Safety Endpoints (Deaths and Transplantations)

Overall, there were no deaths or organ transplantations in the Orkambi Cohort and F/F Concurrent Comparator Cohort, and 1 death and 3 patients with organ transplantations in the F/MF Concurrent Comparator Cohort.

In the ECFSPR 2-5y F/F Longitudinal Historical Cohort, there was 1 death and 15 transplantations over 6 years (2012 to 2017).

ECFSPR 1-<2y Orkambi and Concurrent Comparator Cohorts

As of the end of the ECFSPR 1-<2y cohort entry period (31 December 2023), there were 187 patients who initiated Orkambi and were aged 1-<2 years at treatment initiation. During the same period, there were 181 patients eligible for inclusion in the 1-<2y F/MF Concurrent Comparator Cohort and 99 patients eligible for inclusion in the 1-<2y F/F Concurrent Comparator Cohort.

Following individual 1:1 matching on age, sex, and BMI-for-age z-score, 118 matched pairs were formed between the 1-<2y Orkambi Cohort and 1-<2y F/MF Concurrent Comparator Cohort, and 69 matched pairs were formed between the 1-<2y Orkambi Cohort and 1-<2y F/F Concurrent Comparator Cohort.

Pre-treatment baseline demographic and clinical characteristics for the patients prior to matching and those for the matched cohorts are shown in Table below.

Table 10: Baseline Demographic and Clinical Characteristics for the ECFSPR 1 -< 2y Orkambi and Concurrent Comparator Cohorts by Matching Status

	Before Matching ("Unmatched")			Matched to F/MF Comparator		Matched to F/F Comparator	
Characteristic	**1-<2y Orkambi Cohort N = 187**	**1-<2y F/MF Concurrent Comparator Cohort N = 181**	**1-<2y F/F Concurrent Comparator Cohort N = 99**	**1-<2y Orkambi Cohort N = 118**	**1-<2y F/MF Concurrent Comparator Cohort N = 118**	**1-<2y Orkambi Cohort N = 69**	**1-<2y F/F Concurrent Comparator Cohort N = 69**
Age at baseline, months, mean (SD)[a]	9.9 (5.51)	9.8 (5.91)	9.1 (5.47)	10.5 (5.30)	10.7 (5.44)	9.5 (5.06)	9.5 (5.26)
Female sex, n (%)	88 (47.1)	94 (51.9)	51 (51.5)	58 (49.2)	58 (49.2)	38 (55.1)	38 (55.1)
Country, n (%)							
France	32 (17.1)	43 (23.8)	-	27 (22.9)	34 (28.8)	16 (23.2)	-
Germany	43 (23.0)	55 (30.4)	-	28 (23.7)	39 (33.1)	17 (24.6)	-
United Kingdom	84 (44.9)	56 (30.9)	-	43 (36.4)	29 (24.6)	22 (31.9)	-
Rest of Europe[b]	28 (15.0)	27 (15.0)	-	20 (17.0)	16 (13.5)	14 (20.3)	-
Italy	-	-	30 (30.3)	-	-	-	23 (33.3)
Rest of Europe[c]	-	-	69 (69.7)	-	-	-	46 (66.7)
BMI-for-age z-score, mean (SD)	-0.4 (1.26)	-0.5 (1.40)	-0.9 (1.40)	-0.4 (1.29)	-0.5 (1.47)	-0.8 (1.28)	-0.9 (1.41)
BMI percentile, mean (SD)	41.6 (31.04)	40.5 (31.13)	30.3 (28.98)	41.3 (31.40)	41.2 (31.62)	32.2 (28.98)	30.5 (28.94)
PEx leading to hospitalization, n/N1 (%)	18/129 (14.0)	16/132 (12.1)	17/73 (23.3)	17/108 (15.7)	11/111 (9.9)	7/61 (11.5)	14/66 (21.2)
Hospitalizations, n/N1 (%)	54/144 (37.5)	45/141 (31.9)	42/76 (55.3)	47/118 (39.8)	38/116 (32.8)	26/69 (37.7)	38/69 (55.1)
CF medication use, n/N1 (%)							
Inhaled antibiotics	5/115 (4.3)	17/124 (13.7)	5/76 (6.6)	5/96 (5.2)	12/106 (11.3)	1/56 (1.8)	5/69 (7.2)
Oral corticosteroids	0/115 (0.0)	1/124 (0.8)	2/76 (2.6)	0/96 (0.0)	1/106 (0.9)	0/56 (0.0)	2/69 (2.9)

Pulmonary microbiology, n/N1 (%)							
P. aeruginosa	2/113 (1.8)	2/121 (1.7)	2/75 (2.7)	1/95 (1.1)	2/103 (1.9)	1/55 (1.8)	2/69 (2.9)
H. influenzae	19/113 (16.8)	23/121 (19.0)	9/75 (12.0)	16/95 (16.8)	22/103 (21.4)	8/55 (14.5)	8/69 (11.6)
S. aureus (including MRSA)	18/113 (15.9)	20/121 (16.5)	17/74 (23.0)	17/95 (17.9)	18/103 (17.5)	9/55 (16.4)	17/68 (25.0)
DIOS, n/N1 (%)	5/115 (4.3)	3/124 (2.4)	1/76 (1.3)	5/96 (5.2)	1/106 (0.9)	2/56 (3.6)	1/69 (1.4)
CFRD, n/N1 (%)	0/114 (0.0)	0/124 (0.0)	0/75 (0.0)	0/95 (0.0)	0/106 (0.0)	0/55 (0.0)	0/69 (0.0)

Sources: Study 128 ECFSPR 1y Concurrent Cohorts Tables and Figures/Tables 1.0a, 1.1b, and 1.3b

BMI: body mass index; CF: cystic fibrosis; CFRD: CF-related diabetes; DIOS: distal intestinal obstruction syndrome; ECFSPR: European CF Society Patient Registry; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a minimal function mutation; *H. influenzae*: *Haemophilus influenzae*; MRSA: methicillin-resistant *Staphylococcus aureus*; N: total cohort size; n: number of subjects or observations; N1: number of patients with non-missing measurement; *P. aeruginosa*: *Pseudomonas aeruginosa*; PEx: pulmonary exacerbation; *S. aureus*: *Staphylococcus aureus*; SD: standard deviation

Note: Denominators for percentages are the total cohort size (i.e., N) unless shown otherwise, in which case the denominator is N1, the number of patients with a non-missing measurement of the outcome.

[a] Age as of 31 December 2022

[b] Rest of Europe includes Austria, Denmark, Ireland, Norway, and Sweden

[c] Rest of Europe includes Croatia, Czech Republic, Greece, Latvia, Luxemburg, Netherlands, Poland, Portugal, Spain, Slovenia, and Switzerland

After matching, the cohorts were well-balanced on pre-treatment baseline values of age, sex, and BMI-for-age z-score. However, some residual numeric imbalances existed in terms of other baseline characteristics (e.g., risk of PEx and hospitalizations).

All 1-<2y matched concurrent cohorts experienced pronounced attrition in the follow-up year (2024), primarily due to initiation of other CFTR modulators. The proportions of patients remaining in each cohort as of 2024 were as follows:

- Within the 1-<2y Orkambi Cohort matched to the 1-<2y F/MF Concurrent Comparator Cohort, only 15 out of 118 (12.7%) were still being treated with Orkambi (and did not meet any other censoring criteria) while only 21 out of 118 (17.8%) patients in the 1-<2y F/MF Concurrent Comparator Cohort remained untreated with a CFTR modulator (and were not censored due to other reasons).
- Similarly, within the 1-<2y Orkambi Cohort matched to the 1-<2y F/F Concurrent Comparator Cohort, only 11 out of 69 (15.9%) patients were still being treated with Orkambi (and did not meet any other censoring criteria) while 25 out of 69 (36.2%) patients in the 1-<2y F/F Concurrent Comparator Cohort remained untreated with a CFTR modulator and not censored due to other reasons.

To understand the impact of attrition on study result interpretation, baseline characteristics of the initial patient cohorts were compared to baseline characteristics of patients who remained in the cohorts in the follow-up year (2024). These analyses showed that:

- Patients remaining in the 1-<2y Matched Orkambi and F/MF Concurrent Comparator Cohorts in 2024 were slightly younger and had lower baseline BMI-for-age z-score than the initial cohorts.
- Patients remaining in the 1-<2y Orkambi Cohort matched to the F/F Concurrent Comparator Cohort had a lower baseline BMI-for-age z-score than the initial cohort, whereas patients remaining in the 1-<2y F/F Concurrent Comparator Cohort had a consistent baseline BMI-for-age z-score as the initial cohort.

Therefore, due to the significant differential attrition in the 1-<2y concurrent cohorts and the short duration of follow-up, the interpretability of the results from the 1-<2y cohorts analyses is extremely limited.

Distributions of Orkambi exposure duration in the ECFSPR 1-<2y Matched Orkambi Cohorts are summarized in Table below. As of the end of follow-up, the 1-<2y Matched Orkambi Cohorts were exposed to Orkambi for approximately 9 months, with >75% exposed for less than 12 months.

Table 11: Orkambi Exposure Duration in the ECFSPR 1-<2y Matched Orkambi Cohorts

	Orkambi Cohort Matched to F/MF Concurrent Comparator Cohort N = 118		Orkambi Cohort Matched to F/F Concurrent Comparator Cohort N = 69	
Orkambi Exposure Duration (months) as of:	n	Mean (SD)	n	Mean (SD)
31 December 2023	118	3.8 (2.61)	69	3.6 (2.57)
31 December 2024, initial cohort (including patients who were censored during follow-up)	118	9.1 (3.20)	69	9.2 (3.52)
31 December 2024, remaining cohort (subset of patients followed through the end of the study)	15	14.0 (2.18)	11	13.9 (2.26)

Sources: Study 128 ECFSPR 1y Concurrent Cohorts Tables and Figures/Tables 2.1b and 2.2b; Study 128 ECFSPR 1y Orkambi Cohorts Ad Hoc Table/Table 1.0

ECFSPR: European CF Society Patient Registry; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a minimal function mutation; N: number of subjects in the analysis set; n: number of subjects or observations; SD: standard deviation

ECFSPR 1-<2y F/F Longitudinal Historical Cohort

The ECFSPR 1-<2y F/F Longitudinal Historical Cohort included 291 patients in 2016. Baseline demographic and clinical characteristics for the ECFSPR F/F Longitudinal Historical Cohort are presented in Table below.

Table 12: Baseline Demographic and Clinical Characteristics for the ECFSPR 1 -< 2y F/F Longitudinal Historical Cohort

Characteristic	1-<2y F/F Longitudinal Historical Cohort N = 291
Age as of 01 January 2016, years, mean (SD)	1.5 (0.28)
Female sex, n (%)	134 (46.0)
Country, n (%)	
France	71 (24.4)
Germany	58 (19.9)
Ireland	19 (6.5)
UK	122 (41.9)
Rest of Europe[a]	21 (7.3)
BMI-for-age z-score, mean (SD)	0.0 (1.21)
BMI percentile, mean (SD)	50.9 (31.25)

Sources: Study 128 ECFSPR 1y Historical Cohort Tables and Figures/Tables 1.0, 2.1, and 2.2

BMI: body mass index; CF: cystic fibrosis; CFTR: CF transmembrane conductance regulator protein; ECFSPR: European CF Society Patient Registry; F/F: homozygous for *F508del*; n: number of subjects or observations; SD: standard deviation; UK: United Kingdom

Notes: The cohort entry date was 01 January 2016. Attrition from the cohort over time is permitted as subjects become exposed to CFTR modulators, death or first year of loss to follow-up. The cohort was followed through 31 December 2017.

[a] Rest of Europe includes Austria, Denmark, Norway, and Sweden

No patient was censored during follow-up.

ECFSPR Effectiveness Endpoints

Overall, the BMI and weight percentiles increased in the Orkambi Cohorts, but no discernible differences from the concurrent comparator cohorts were identified. However, the results are of limited interpretability due to the significant cohort attritions and short duration of Orkambi exposure.

There were no notable trends or differences across the 1-<2y cohorts for the other effectiveness endpoints

ECFSPR Safety Endpoints (Deaths and Transplantations)

There were no deaths or organ transplantations in the Orkambi Cohort and F/F Concurrent Comparator Cohort, and 1 death and no organ transplantations in the F/MF Concurrent Comparator Cohort. In the ECFSPR 1-<2y F/F Longitudinal Historical Cohort, there were no deaths or organ transplantations over 2 years (2016 to 2017).

US CFFPR

US CFFPR 2-5y Orkambi and Concurrent Comparator Cohorts

As of the end of the US CFFPR 2-5y cohort entry period (31 December 2019), there were a total of 911 patients who initiated Orkambi and were aged 2 through 5 years at treatment initiation. During the same period, there were 918 patients eligible for inclusion in the 2-5y F/MF Concurrent Comparator Cohort.

Following individual 1:1 matching on age, sex, and BMI-for-age z-score, 779 matched pairs were formed between the 2-5y Orkambi Cohort and 2-5y F/MF Concurrent Comparator Cohort.

Pre-treatment baseline demographic and clinical characteristics of the patients prior to matching and those in the matched cohorts are shown in Table below.

Table 13: Baseline Demographic and Clinical Characteristics for the US CFFPR 2-5y Orkambi and F/MF Concurrent Comparator Cohorts by Matching Status

	Before Matching ("Unmatched")		Matched	
Characteristic	2-5y Orkambi Cohort N = 911	2-5y F/MF Concurrent Comparator Cohort N = 918	2-5y Orkambi Cohort N = 779	2-5y F/MF Concurrent Comparator Cohort N = 779
Age, years, mean (SD)[a]	3.2 (1.11)	3.3 (1.59)	3.3 (1.14)	3.3 (1.14)
Female sex, n (%)	429 (47.1)	459 (50.0)	383 (49.2)	383 (49.2)
BMI-for-age z-score, mean (SD)	0.4 (0.85)	0.3 (0.88)	0.4 (0.87)	0.4 (0.86)
BMI percentile, mean (SD)	61.8 (24.89)	60.2 (25.92)	60.8 (25.35)	61.7 (25.30)
PEx, n/N1 (%)				
PEx leading to hospitalization and/or home IV antibiotics	129/911 (14.2)	149/918 (16.2)	109/779 (14.0)	118/779 (15.1)
PEx leading to hospitalization	129/911 (14.2)	147/918 (16.0)	109/779 (14.0)	116/779 (14.9)
PEx based on physician assessment	100/911 (11.0)	106/918 (11.5)	84/779 (10.8)	83/779 (10.7)
Hospitalizations, n/N1 (%)	205/911 (22.5)	243/918 (26.5)	177/779 (22.7)	199/779 (25.5)
CF medication use, n/N1 (%)				
Inhaled tobramycin	185/911 (20.3)	200/918 (21.8)	153/779 (19.6)	160/779 (20.5)
Inhaled colistin	3/911 (0.3)	7/918 (0.8)	3/779 (0.4)	4/779 (0.5)
Inhaled aztreonam	28/911 (3.1)	41/918 (4.5)	26/779 (3.3)	33/779 (4.2)
Oral corticosteroids	26/911 (2.9)	33/918 (3.6)	25/779 (3.2)	33/779 (4.2)
Pulmonary microbiology, n/N1 (%)				
P. aeruginosa	203/911 (22.3)	225/916 (24.6)	170/779 (21.8)	164/777 (21.1)
H. influenzae	282/911 (31.0)	244/916 (26.6)	244/779 (31.3)	218/777 (28.1)
S. aureus (including MRSA)	672/911 (73.8)	675/916 (73.7)	578/779 (74.2)	569/777 (73.2)
History of DIOS, n (%)	85 (9.3)	83 (9.0)	72 (9.2)	70 (9.0)
History of CFRD, n (%)	4 (0.4)	7 (0.8)	4 (0.5)	4 (0.5)

History of clinically significant ALT, n (%)				
>3 to ≤5 × ULN	81/908 (8.9)	83/899 (9.2)	72/777 (9.3)	68/770 (8.8)
>5 to ≤8 × ULN	43/908 (4.7)	36/899 (4.0)	39/777 (5.0)	32/770 (4.2)
>8 × ULN	26/908 (2.9)	28/899 (3.1)	22/777 (2.8)	22/770 (2.9)
History of clinically significant AST, n (%)				
>3 to ≤5 × ULN	16/907 (1.8)	11/895 (1.2)	16/775 (2.1)	10/767 (1.3)
>5 to ≤8 × ULN	5/907 (0.6)	7/895 (0.8)	4/775 (0.5)	7/767 (0.9)
>8 × ULN	8/907 (0.9)	5/895 (0.6)	6/775 (0.8)	5/767 (0.7)

Sources: Study 128 US CFFPR 2-5y Concurrent Cohorts Tables and Figures/Tables 1.1a and 1.1b

ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; CF: cystic fibrosis; CFFPR: CF Foundation Patient Registry; CFRD: CF-related diabetes; DIOS: distal intestinal obstruction syndrome; F/MF: heterozygous for *F508del* and a minimal function mutation; *H. influenzae*: *Haemophilus influenzae*; IV: intravenous; MRSA: methicillin-resistant *Staphylococcus aureus*; n: number of subjects or observations; N1: number of patients with non-missing measurement; *P. aeruginosa*: *Pseudomonas aeruginosa*; PEx: pulmonary exacerbation; *S. aureus*: *Staphylococcus aureus*; SD: standard deviation; ULN: upper limit of normal; US: United States

Notes: Denominators for percentages are the total cohort size (i.e., N) unless shown otherwise, in which case the denominator is the number of patients with a non-missing measurement of the outcome.

[a] Age at Orkambi initiation for the Matched and Unmatched Orkambi Cohorts; age at Orkambi initiation of the Orkambi Cohort patient in the 1:1 matched set for the Matched F/MF Concurrent Comparator Cohort; age as of 31 December 2018 for the Unmatched F/MF Concurrent Comparator Cohort.

While minor imbalances in distributions of age and sex were observed prior to matching, the matched US CFFPR 2-5y Orkambi and F/MF Concurrent Comparator Cohorts were well balanced on pre-treatment baseline values of age, sex, and BMI-for-age z-score and generally comparable in clinical characteristics.

Both concurrent cohorts experienced pronounced attrition starting from 2021, primarily due to patients initiating other CFTR modulators (Symdeko™ therapy became available for Orkambi Cohort patients 6 to 11 years of age in 2019 and Trikafta™ therapy became available for Orkambi and F/F and F/MF Concurrent Comparator Cohorts patients 6 to 11 years of age in 2021 and 2 to 5 years of age in 2023). By the end of study follow-up in 2024 (last year of follow-up), only 1 out of 779 (0.1%) patient in the 2-5y Matched Orkambi Cohort was still being treated with Orkambi (and did not meet any other censoring criteria), while only 28 out of 779 (3.6%) patients in the 2-5y F/MF Concurrent Comparator Cohort remained untreated with a CFTR modulator (and were not censored due to other reasons).

To understand the impact of attrition on study result interpretation, baseline characteristics of the initial patient cohorts were compared to baseline characteristics of patients who remained in the cohorts in each follow-up year. These analyses showed that the cohort attritions were differential, with patients remaining in the cohorts being generally younger and having higher BMI-for-age z-score than the initial cohorts. However, the patients remaining in each cohort as of 2021 and 2022 were still well balanced on age, sex, and BMI-for-age z-score and generally similar with respect to clinical characteristics.

Distributions of Orkambi exposure duration in the US CFFPR 2-5y Matched Orkambi Cohort are summarized in the Table below:

Table 14: Orkambi Exposure Duration in the US CFFPR 2-5y Matched Orkambi Cohort

Orkambi Exposure Duration (months) as of:	n	Mean (SD)
31 December 2018[a]	779	0.9 (1.37)
31 December 2019	779	10.2 (4.46)
31 December 2020	666	21.9 (4.58)
31 December 2021	298	32.7 (4.74)
31 December 2022	125	42.1 (4.12)
31 December 2023	8	54.5 (4.80)
31 December 2024	1	--

Source: Study 128 US CFFPR 2-5y Concurrent Cohorts Tables and Figures/Table 2.0b
CFFPR: CF Foundation Patient Registry; n: number of subjects or observations; SD: standard deviation; US: United States
[a] Exposure duration among all patients, including those who initiated Orkambi in 2019 (i.e., unexposed to Orkambi in 2018).

US CFFPR 2-5y F/F Longitudinal Historical Cohort

The US CFFPR 2-5y F/F Longitudinal Historical Cohort included 1,441 patients in 2012. Baseline demographic and clinical characteristics for the US CFFPR 2-5y F/F Longitudinal Historical Cohort are presented in Table below.

Table 15: Baseline Demographic and Clinical Characteristics for the US CFFPR 2-5y F/F Longitudinal Historical Cohort

Characteristic	F/F Longitudinal Historical Cohort N = 1441
Age as of 01 January 2012, years, mean (SD)	3.5 (1.14)
Female sex, n (%)	707 (49.1)
BMI-for-age z-score, mean (SD)	0.3 (0.84)
BMI percentile, mean (SD)	58.6 (24.27)
Pulmonary exacerbation (PEx), n/N1 (%)	
PEx leading to hospitalization and/or home IV antibiotics	628/1441 (43.6)
PEx leading to hospitalization	624/1441 (43.3)
Hospitalizations, n/N1 (%)	878/1441 (60.9)
CF medication use, n/N1 (%)	
Inhaled tobramycin	655/1412 (46.4)
Inhaled colistin	15/1412 (1.1)
Inhaled aztreonam	34/1411 (2.4)
Oral corticosteroids	131/1412 (9.3)
Pulmonary microbiology, n/N1 (%)	
P. aeruginosa	868/1411 (61.5)
H. influenzae	803/1411 (56.9)
S. aureus (including MRSA)	1214/1411 (86.0)
History of DIOS, n/N1 (%)	95/1412 (6.7)
History of CFRD, n/N1 (%)	5/1413 (0.4)
History of clinically significant ALT, n/N1 (%)	
>3 to ≤5 × ULN	61/1329 (4.6)
>5 to ≤8 × ULN	25/1329 (1.9)
>8 × ULN	20/1329 (1.5)

Sources: Study 128 US CFFPR 2-5y Historical Cohort Tables and Figures/Tables 1.0, 2.1.1, and 2.21

ALT: alanine transaminase; BMI: body mass index; CF: cystic fibrosis; CFFPR: CF Foundation Patient Registry; CFRD: CF-related diabetes; DIOS: distal intestinal obstruction syndrome; F/F: homozygous for *F508del*; *H. influenzae*: *Haemophilus influenzae*; IV: intravenous; MRSA: methicillin-resistant *Staphylococcus aureus*; N: number of subjects in the analysis set; n: number of subjects or observations; N1: number of patients with non-missing measurement; *P. aeruginosa*: *Pseudomonas aeruginosa*; PEx: pulmonary exacerbation; *S. aureus*: *Staphylococcus aureus*; SD: standard deviation; ULN: upper limit of normal; US: United States

Notes: Denominators for percentages are the total cohort size (i.e., N) unless shown otherwise, in which case the denominator is N1, the number of patients with a non-missing measurement of the outcome. The cohort entry date is 01 January 2012. Attrition from the cohort over time is permitted as subjects become exposed to CFTR modulators, death, or first year of loss to follow-up. The cohort was followed through 31 December 2017. Sex, history of clinically significant ALT, history of CFRD/DIOS, use of CF medications, pulmonary microorganisms, and patients with PEx/hospitalization categories will be identified at any point prior to cohort entry. Data on history of clinically significant AST was not available prior to 2015.

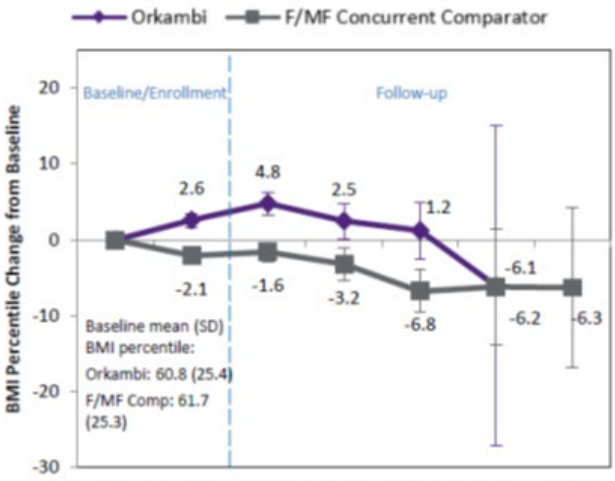
A total of 964 (66.9%) patients were censored over the 6 years of follow-up, 15 due to death, 67 due to loss to follow-up, and 882 due to a record of CFTR modulator use (primarily due to patients initiating Orkambi following commercial availability for patients 6 years of age and older in 2016 and patients 2 years of age and older in 2018). Overall, the patients who remained in the cohort and those who were censored were generally similar with respect to their baseline demographic and clinical characteristics.

US CFFPR Effectiveness Endpoints

Growth Parameters

BMI percentile change from baseline in the matched concurrent cohorts, height percentile change from baseline in the matched concurrent cohorts and weight percentile change from baseline in the matched concurrent cohorts are presented in the Figures below.

Figure 13: BMI Percentile Change from Baseline in the US CFFPR 2-5y Matched Orkambi and F/MF Concurrent Comparator Cohorts



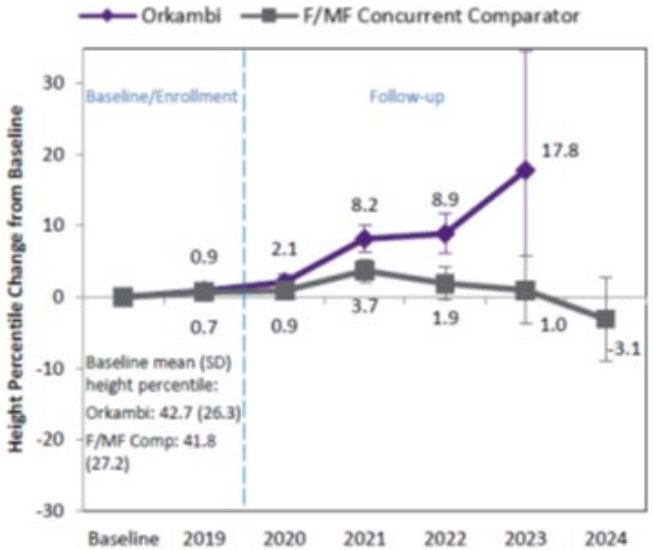
	Baseline	2019	2020	2021	2022	2023	2024
Orkambi, N	779	779	658	298	125	8	1
F/MF Comp, N	779	776	746	399	199	48	28

Source: Study 128 US CFFPR 2-5y Concurrent Cohorts Tables and Figures/Table 3.2.1b

BMI: body mass index; CF: cystic fibrosis; CFFPR: CF Foundation Patient Registry; Comp: comparator; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a second mutation that results in minimal CFTR function; N: number of subjects in the analysis set

Notes: The vertical dotted line delineates the baseline/enrollment and post-enrollment follow-up periods. The horizontal solid line delineates the change of 0 from baseline. Results for 2-5y Matched Orkambi Cohort in 2024 are not shown due to insufficient sample size (N<5).

Figure 14: Height Percentile Change from Baseline in the US CFFPR 2-5y Matched Orkambi and F/MF Concurrent Comparator Cohorts



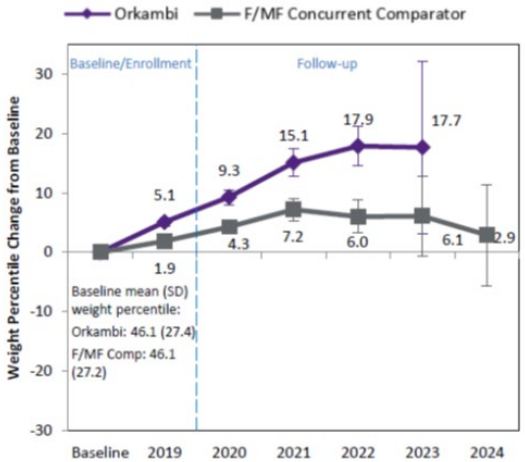
	Baseline	2019	2020	2021	2022	2023	2024
Orkambi, N	779	779	658	298	125	8	1
F/MF Comp, N	779	776	746	399	199	48	28

Source: Study 128 US CFFPR 2-5y Concurrent Cohorts Tables and Figures/Table 3.4.1b

CF: cystic fibrosis; CFFPR: CF Foundation Patient Registry; Comp: comparator; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a second mutation that results in minimal CFTR function; N: number of subjects in the analysis set

Notes: The vertical dotted line delineates the baseline/enrollment and post-enrollment follow-up periods. The horizontal solid line delineates the change of 0 from baseline. Results for 2-5y Matched Orkambi Cohort in 2024 are not shown due to insufficient sample size (N<5).

Figure 15: Weight Percentile Change from Baseline in the US CFFPR 2-5y Matched Orkambi and F/MF Concurrent Comparator Cohorts



	Baseline	2019	2020	2021	2022	2023	2024
Orkambi, N	779	779	661	298	125	8	1
F/MF Comp, N	779	776	751	399	199	48	28

Source: Study 128 US CFFPR 2-5y Concurrent Cohorts Tables and Figures/Table 3.6.1b

CF: cystic fibrosis; CFFPR: CF Foundation Patient Registry; Comp: comparator; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a second mutation that results in minimal CFTR function; N: number of subjects in the analysis set

Notes: The vertical dotted line delineates the baseline/enrollment and post-enrollment follow-up periods. The horizontal solid line delineates the change of 0 from baseline. Results for 2-5y Matched Orkambi Cohort in 2024 are not shown due to insufficient sample size (N<5).

The figures show that BMI percentile, height percentile, and weight percentile generally increased from baseline over time in the Orkambi Cohort whereas they decreased or remained stable in the F/MF Concurrent Comparator Cohort (data post-2022 should be interpreted with caution due to attrition).

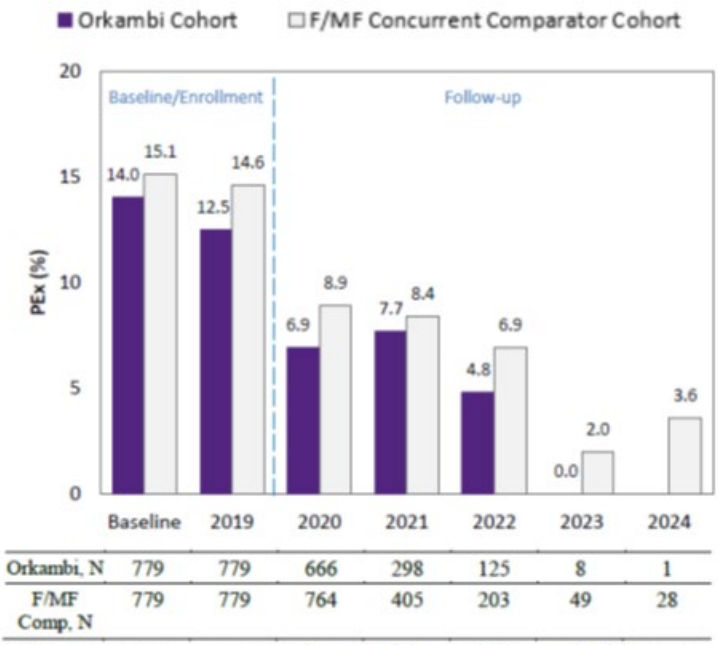
The results observed in the Orkambi Cohort were also favourable in the context of the patterns observed across the additional comparator cohorts:

- In the F/F Historical Cohort, BMI percentile, height percentile, and weight percentile generally decreased over time
- In Study 110, although older children treated with Orkambi also had improvements in growth parameters following treatment initiation, children in this study who initiated treatment earlier achieved better nutritional status at a younger age. For example, children in the Orkambi 2-5y Cohort achieved a BMI percentile of 65.9 after approximately 2 years of follow-up, while children in the 6-11y cohort of Study 110 achieved a BMI percentile of 53.8 after a similar duration of follow-up.

Pulmonary Exacerbations

Figure below presents the proportion of patients who experienced PEx leading to hospitalization and/or home intravenous (IV) antibiotics in the US CFFPR 2-5y Matched Orkambi and F/MF Concurrent Comparator Cohorts.

Figure 16: Proportion of Patients Who Experienced ⩾ 1 PEx Leading to Hospitalization and/or Home IV Antibiotics Use in the US CFFPR 2-5y Matched Orkambi and F/MF Concurrent Comparator Cohorts



	Baseline	2019	2020	2021	2022	2023	2024
Orkambi, N	779	779	666	298	125	8	1
F/MF Comp, N	779	779	764	405	203	49	28

Source: Study 128 US CFFPR 2-5y Concurrent Cohorts Tables and Figures/Table 5.1b

CF: cystic fibrosis; CFFPR: CF Foundation Patient Registry; Comp: comparator; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a second mutation that results in minimal CFTR function; IV: intravenous; N: number of subjects in the analysis set; PEx: pulmonary exacerbation

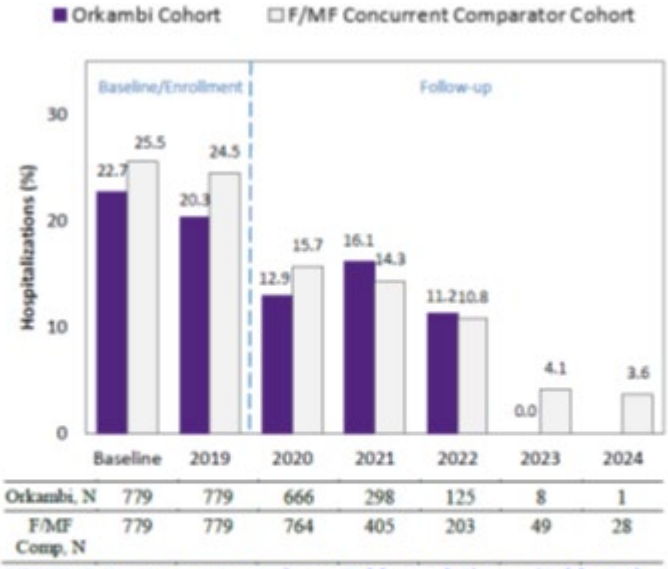
Notes: The vertical dotted line delineates the baseline/enrollment and post-enrollment follow-up periods. Results for 2-5y Matched Orkambi Cohort in 2024 are not shown due to insufficient sample size (N<5).

The proportion of patients who experienced PEx leading to hospitalization and/or home IV antibiotics was consistently lower in the Orkambi Cohort than the F/MF Concurrent Comparator Cohort and declined over time to <10% annually in both concurrent cohorts. This pattern observed in the Orkambi Cohort was favourable in the context of the F/F Historical Cohort, in which the proportion of patients who experienced PEx leading to hospitalization and/or home IV antibiotics increased over time.

Hospitalizations

Figure below shows the proportion of patients who experienced any hospitalization the US CFFPR 2-5y Matched Orkambi and F/MF Concurrent Comparator Cohorts.

Figure 17: Proportion of Patients Who Experienced ⩾1 Hospitalization in the US CFFPR 2-5y Matched Orkambi and F/MF Concurrent Comparator Cohorts



Source: Study 128 US CFFPR 2-5y Concurrent Cohorts Tables and Figures/Table 5.1b

CF: cystic fibrosis; CFFPR: CF Foundation Patient Registry; Comp: comparator; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a second mutation that results in minimal CFTR function; N: number of subjects in the analysis set

Notes: The vertical dotted line delineates the baseline/enrollment and post-enrollment follow-up periods. Results for 2-5y Matched Orkambi Cohort in 2024 are not shown due to insufficient sample size (N<5).

The proportion of patients who experienced hospitalization was lower or comparable in the Orkambi Cohort compared to the F/MF Concurrent Comparator Cohort and declined from baseline in both concurrent cohorts. This pattern observed in the Orkambi Cohort was favourable in the context of the F/F Historical Cohort, in which the proportion of patients who experienced any hospitalization increased over time

Lung Function

Similar to the ECFSPR data, ppFEV1 data were available for only a limited number of relatively older patients in US CFFPR, and there were no patients with spirometry data at baseline since all patients were under the age of 6 years. Only a subset of patients had ppFEV1 measurements reported during the follow-up period, and thus the data should be interpreted with caution.

During follow-up and prior to significant cohort attrition, mean ppFEV1 consistently remained above 95 in the subset of 2-5y Matched Orkambi Cohort children with lung function data available. Lung function in Orkambi-treated children with available data was not notably different in the context of the F/MF Matched Concurrent Comparator Cohort and Historical Cohort (mean 94.9 to 97.0) but better preserved in the context of the Study 110 L/I-L/I group (mean 89.7 at baseline and 92.3 at Week 96).

Use of CF Medications

Use of CF medications over time in the 2-5y US CFFPR matched Orkambi and F/MF Concurrent Comparator Cohorts is summarized in Figure below.

Figure 18: Proportion of Patients Using CF Medications in the US CFFPR 2-5y Matched Orkambi and F/MF Concurrent Comparator Cohorts

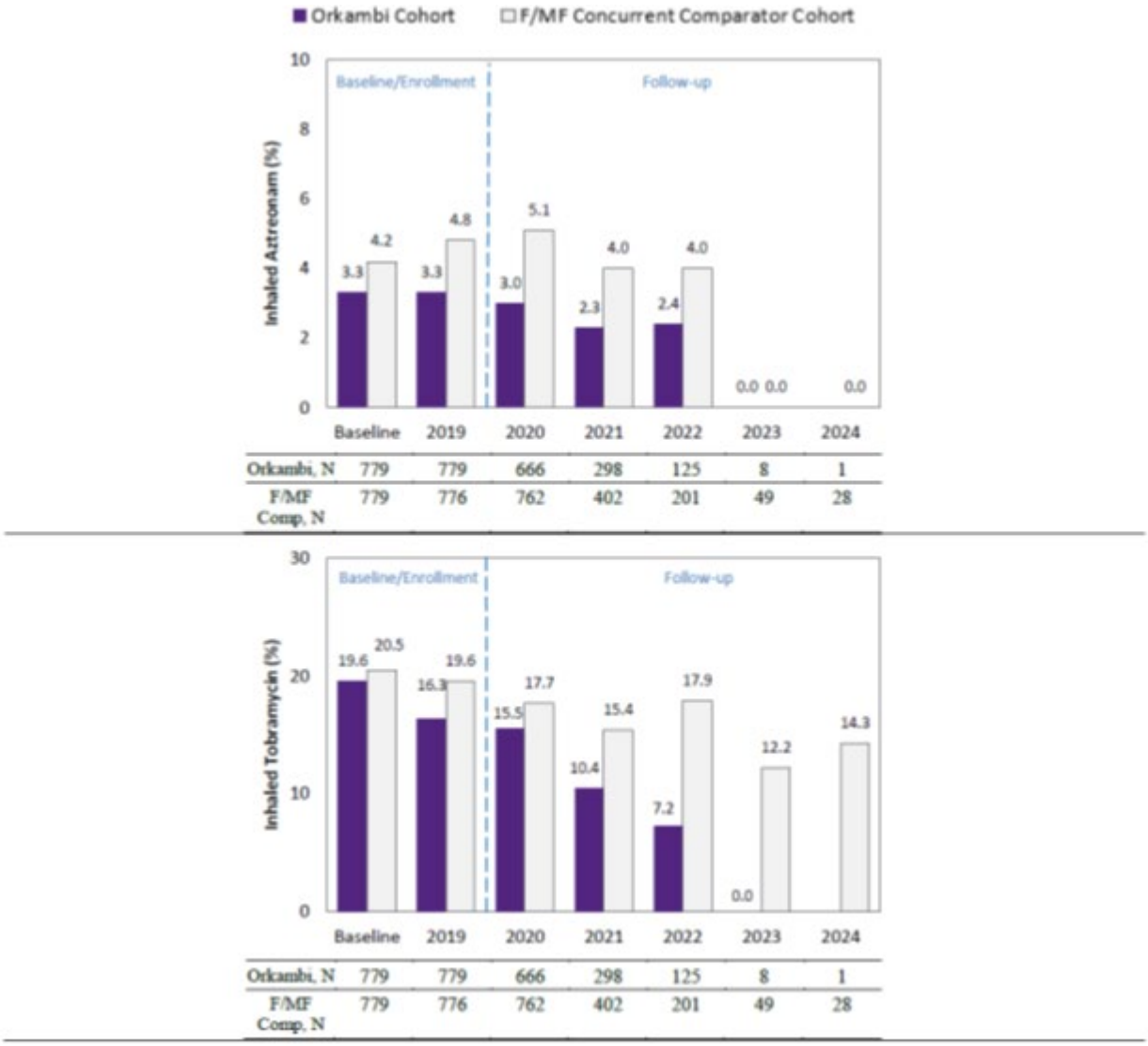
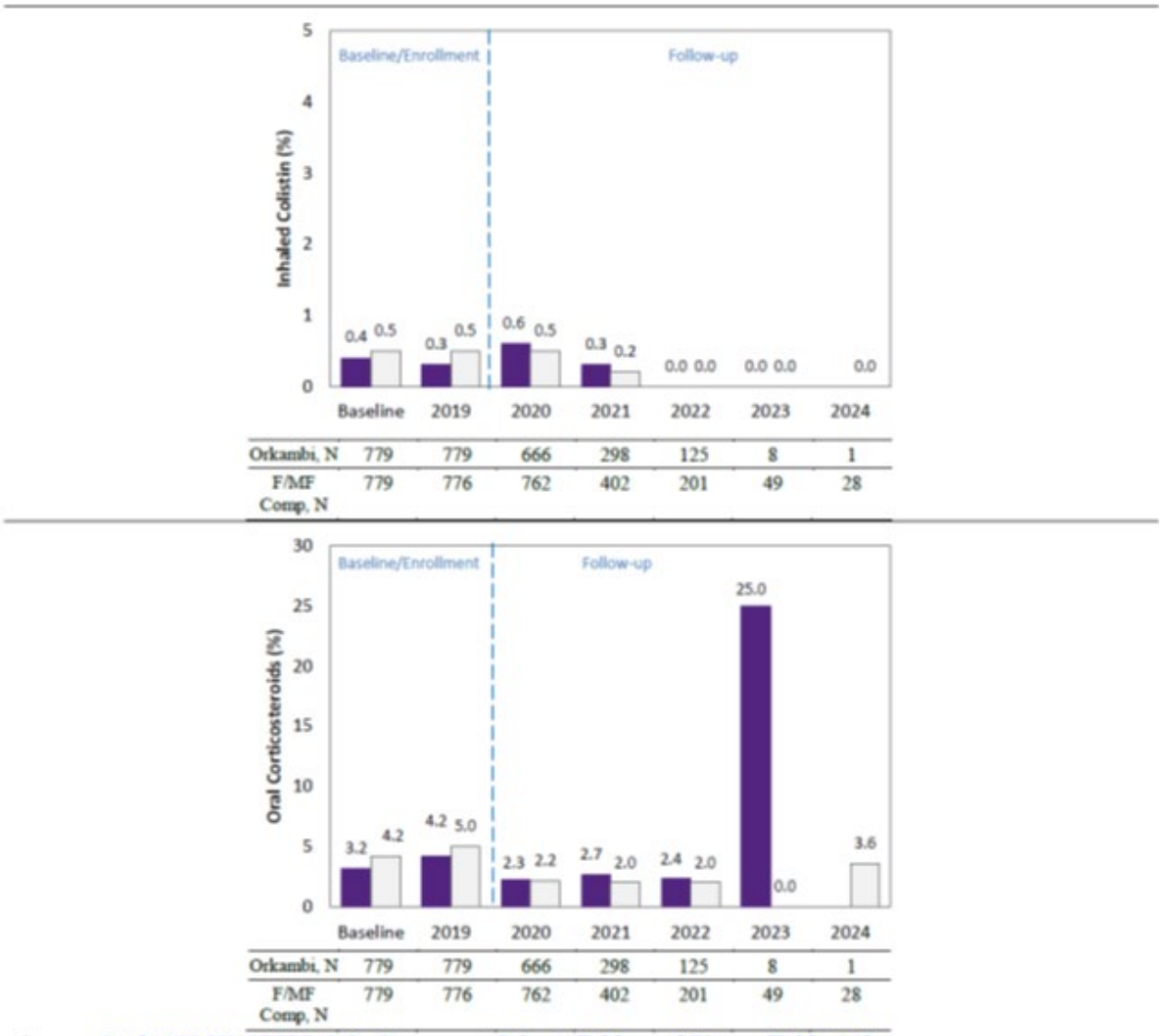


Figure 19: Proportion of Patients Using CF Medications in the US CFFPR 2-5y Matched Orkambi and F/MF Concurrent Comparator Cohorts



Source: Study 128 US CFFPR 2-5y Concurrent Cohorts Tables and Figures/Table 6.1b

CF: cystic fibrosis; CFFPR: CF Foundation Patient Registry; Comp: comparator; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a second mutation that results in minimal CFTR function; N: number of subjects in the analysis set

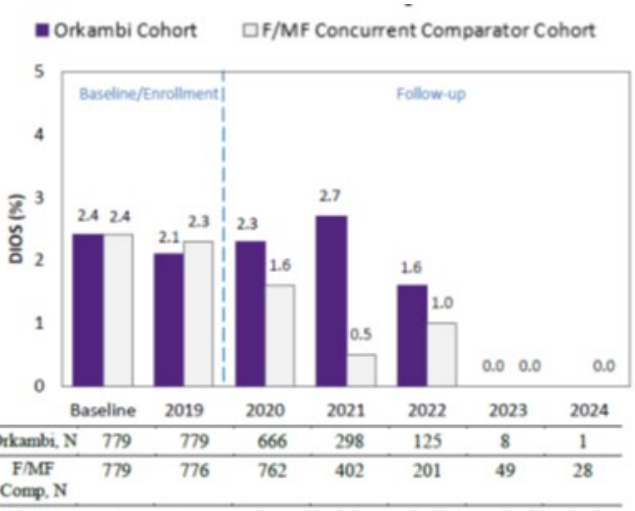
Notes: The vertical dotted line delineates the baseline/enrollment and post-enrollment follow-up periods. Results for 2-5y Matched Orkambi Cohort in 2024 are not shown due to insufficient sample size (N<5).

Use of inhaled aztreonam and use of inhaled colistin in the concurrent cohorts were low and stable over time, in contrast to increasing trends observed in the F/F Historical Cohort. Use of inhaled tobramycin decreased over time in the Orkambi Cohort while remaining generally stable in the F/MF Comparator Cohort and F/F Historical Cohort. Oral corticosteroid use was generally low and stable over time in all 2-5y cohorts prior to cohort attrition post-2022.

CF Complications (DIOS and CFRD)

Figure below presents the proportion of patients with DIOS in the US CFFPR 2-5y Matched Orkambi and F/MF Concurrent Comparator Cohorts.

Figure 20: Proportion of Patients with DIOS in the US CFFPR 2-5y Matched Orkambi and F/MF Concurrent Comparator Cohorts



Source: Study 128 US CFFPR 2-5y Concurrent Cohorts Tables and Figures/Table 7.1b

CF: cystic fibrosis; CFFPR: CF Foundation Patient Registry; Comp: comparator; DIOS: distal intestinal obstruction syndrome; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a second mutation that results in minimal CFTR function; N: number of subjects in the analysis set

Notes: The vertical dotted line delineates the baseline/enrollment and post-enrollment follow-up periods. Results for 2-5y Matched Orkambi Cohort in 2024 are not shown due to insufficient sample size (N<5).

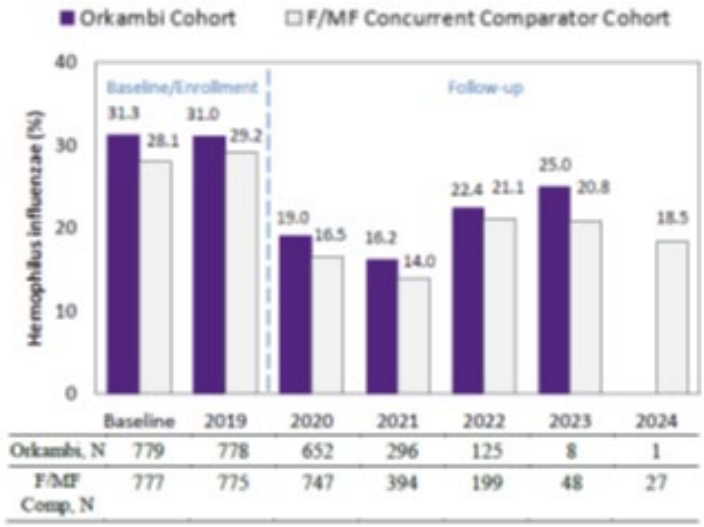
The proportion of patients with DIOS was consistently low (<3%) in the matched concurrent cohorts, with no notable trends observed; similarly, no clear trend was observed in the F/F Historical Cohort.

Similarly, CFRD was very rare across all cohorts, with no apparent trend (0% to 0.8% in the Orkambi Cohort and 0% to 0.5% in the F/MF Concurrent Comparator Cohort), consistent with the F/F Historical Cohort.

Pulmonary Microbiology

Pulmonary microbiology data for the evaluated bacterial pathogens in the US CFFPR 2-5y Matched Orkambi and F/MF Concurrent Comparator Cohorts are summarized in Figure below.

Figure 21: Prevalence of Bacterial Pathogens in the US CFFPR 2-5y Matched Orkambi and F/MF Concurrent Comparator Cohorts



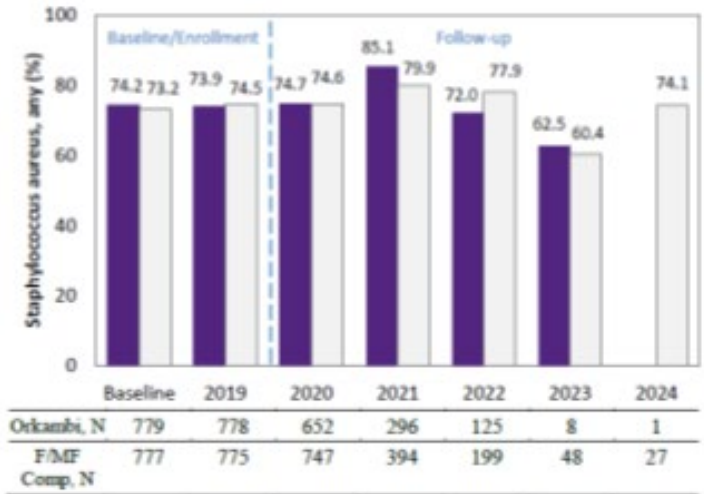


Figure 22: Prevalence of Bacterial Pathogens in the US CFFPR 2-5y Matched Orkambi and F/MF Concurrent Comparator Cohorts

	Baseline	2019	2020	2021	2022	2023	2024
Orkambi, N	779	778	652	296	125	8	1
F/MF Comp, N	777	775	747	394	199	48	27

Source: Study 128 US CFFPR 2-5y Concurrent Cohorts Tables and Figures/Table 8.1b
CF: cystic fibrosis; CFFPR: CF Foundation Patient Registry; Comp: comparator; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a second mutation that results in minimal CFTR function; MRSA: methicillin-resistant *Staphylococcus aureus*; N: number of subjects in the analysis set
Notes: The vertical dotted line delineates the baseline/enrollment and post-enrollment follow-up periods. Results for 2-5y Matched Orkambi Cohort in 2024 are not shown due to insufficient sample size (N<5).

Prevalence of H. influenzae generally decreased over time prior to the major cohort attritions, which was consistent with the pattern observed in the F/F Historical Cohort. Prevalence of P. aeruginosa decreased over time in both concurrent cohorts. In the F/F Historical Cohort, on the other hand, prevalence of P. aeruginosa was generally higher than in the concurrent cohorts and increased over time.

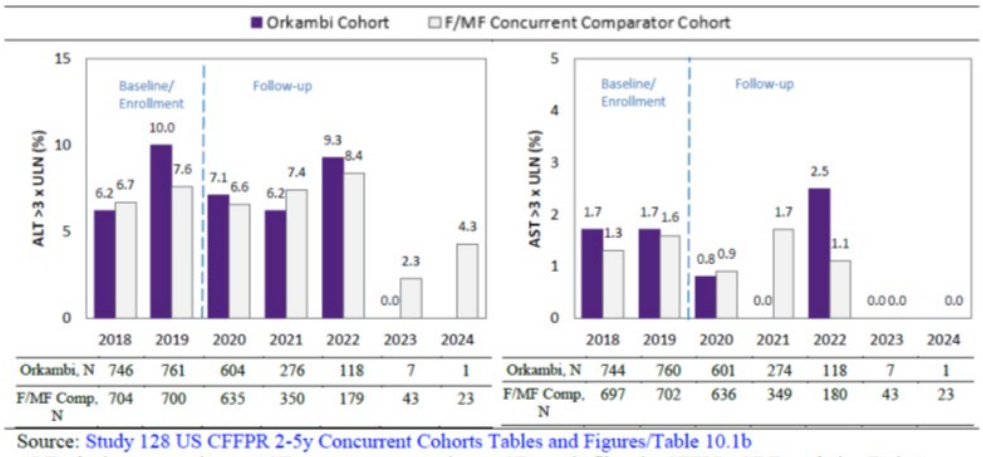
There were no discernible patterns for the prevalence of S. aureus and MRSA in the matched concurrent cohorts, whereas general increases over time were observed in the F/F Historical Cohort.

US CFFPR Safety Endpoints

LFT Elevations

Overall, there were no notable trends or differences in the prevalence of elevations in ALT or AST >3× upper limit of normal (ULN) between the US CFFPR 2-5y Matched Orkambi and F/MF Concurrent Comparator Cohorts prior to pronounced attrition post-2022 (see figure below).

Figure 23: Proportion of Patients with Liver Function Test Abnormalities in the US CFFPR 2-5y Matched Orkambi and F/MF Concurrent Comparator Cohorts



	2018	2019	2020	2021	2022	2023	2024
Orkambi, N	746	761	604	276	118	7	1
F/MF Comp, N	704	700	635	350	179	43	23

	2018	2019	2020	2021	2022	2023	2024
Orkambi, N	744	760	601	274	118	7	1
F/MF Comp, N	697	702	636	349	180	43	23

Source: Study 128 US CFFPR 2-5y Concurrent Cohorts Tables and Figures/Table 10.1b
ALT: alanine transaminase; AST: aspartate transaminase; CF: cystic fibrosis; CFFPR: CF Foundation Patient Registry; Comp: comparator; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a second mutation that results in minimal CFTR function; N: number of subjects in the analysis set
Notes: The vertical dotted line delineates the baseline/enrollment and post-enrollment follow-up periods. Results for 2-5y Matched Orkambi Cohort in 2024 are not shown due to insufficient sample size (N<5).

Similarly, there were no trends in ALT or AST >5 or >8 x ULN in the concurrent cohorts and no trends in the prevalence of LFT elevations in the F/F Historical Cohort.

US CFFPR 1-<2y Orkambi and Concurrent Comparator Cohorts

As of the end of the US CFFPR 1-<2y cohort entry period (31 December 2023), there were a total of 310 children who initiated Orkambi and were aged 1-<2 years at treatment initiation. During the same period, there were 190 children eligible for inclusion in the 1-<2y F/MF Concurrent Comparator Cohort.

Following individual 1:1 matching on age, sex, and BMI-for-age z-score, 161 matched pairs were formed between the 1-<2y Orkambi Cohort and 1-<2y F/MF Concurrent Comparator Cohort.

Pre-treatment baseline demographic and clinical characteristics of the patients prior to matching and those in the matched cohorts are shown in Table below.

Table 16: Baseline Demographic and Clinical Characteristics for the US CFFPR 1 -< 2y Orkambi and F/MF Concurrent Comparator Cohorts by Matching Status

	Before Matching ("Unmatched")		Matched	
Characteristic	1-<2y Orkambi Cohort N = 310	1-<2y F/MF Concurrent Comparator Cohort N = 190	1-<2y Orkambi Cohort N = 161	1-<2y F/MF Concurrent Comparator Cohort N = 161
Age, months, mean (SD)[a]	16.8 (3.56)	10.1 (7.47)	16.4 (3.60)	14.8 (3.33)
Female sex, n (%)	143 (46.1)	95 (50.0)	76 (47.2)	76 (47.2)
BMI-for-age z-score, mean (SD)	0.2 (0.91)	-0.2 (1.02)	0.1 (0.86)	0.1 (0.95)
BMI percentile, mean (SD)	56.1 (27.61)	45.6 (28.81)	51.9 (26.42)	52.6 (27.44)
PEx, n/N1 (%)				
PEx leading to hospitalization and/or home IV antibiotics	60/310 (19.4)	9/190 (4.7)	34/161 (21.1)	17/161 (10.6)
PEx leading to hospitalization	60/310 (19.4)	9/190 (4.7)	34/161 (21.1)	17/161 (10.6)
PEx based on physician assessment	37/310 (11.9)	7/190 (3.7)	20/161 (12.4)	10/161 (6.2)
Hospitalizations, n/N1 (%)	111/310 (35.8)	35/190 (18.4)	69/161 (42.9)	50/161 (31.1)
CF medication use, n/N1 (%)				
Inhaled tobramycin	54/310 (17.4)	20/139 (14.4)	36/161 (22.4)	26/161 (16.1)
Inhaled colistin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Inhaled aztreonam	3/310 (1.0)	2/139 (1.4)	2/161 (1.2)	5/161 (3.1)
Oral corticosteroids	24/310 (7.7)	6/139 (4.3)	14/161 (8.7)	8/161 (5.0)
Pulmonary microbiology, n/N1 (%)				
P. aeruginosa	71/310 (22.9)	29/137 (21.2)	40/161 (24.8)	40/160 (25.0)
H. influenzae	70/310 (22.6)	18/137 (13.1)	37/161 (23.0)	32/160 (20.0)
S. aureus (including MRSA)	212/310 (68.4)	80/137 (58.4)	108/161 (67.1)	107/160 (66.9)
History of DIOS, n (%)	17 (5.5)	5 (3.6)	11 (6.8)	5 (3.1)
History of CFRD, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Sources: Study 128 US CFFPR 1y Concurrent Cohorts Tables and Figures/Tables 1.0a and 1.0b

BMI: body mass index; CF: cystic fibrosis; CFFPR: CF Foundation Patient Registry; CFRD: CF-related diabetes; DIOS: distal intestinal obstruction syndrome; F/MF: heterozygous for F508del and a minimal function mutation; H. influenzae: Haemophilus influenzae; IV: intravenous; MRSA: methicillin-resistant Staphylococcus aureus; N: number of subjects in the analysis set; n: number of subjects or observations; N1: number of patients with non-missing measurement; P. aeruginosa: Pseudomonas aeruginosa; PEx: pulmonary exacerbation; S. aureus: Staphylococcus aureus; SD: standard deviation; US: United States

Note: Denominators for percentages are the total cohort size (i.e., N) unless shown otherwise, in which case the denominator is the number of patients with a non-missing measurement of the outcome.

[a] Age at Orkambi initiation for the Matched and Unmatched Orkambi Cohorts; age at Orkambi initiation of the Orkambi Cohort patient in the 1:1 matched set for the Matched F/MF Concurrent Comparator Cohort; age as of 31 December 2018 for the Unmatched F/MF Concurrent Comparator Cohort.

After matching, the cohorts were well-balanced on pre-treatment baseline values of age, sex, and BMI-for-age z-score. However, some residual numeric imbalances existed in terms of other baseline characteristics (e.g., risk of PEx and hospitalizations).

Both cohorts experienced pronounced patient attrition in the follow-up year (2024), primarily due to initiation of other CFTR modulators. In 2024, only 16 out of 161 (9.9%) patients in the 1-<2y Matched Orkambi Cohort remained being treated with Orkambi (and did not meet any other censoring criteria) while only 59 out of 161 (36.6%) patients in the 1-<2y Matched F/MF Concurrent Comparator Cohort remained untreated with a CFTR modulator (and were not censored due to other reasons).

To understand the impact of attrition on study result interpretation, baseline characteristics of the initial patient cohorts were compared to baseline characteristics of patients who remained at the end of follow-up. These analyses showed that the cohort attritions were differential, such that patients remaining in the Orkambi Cohort had lower BMI-for-age z-score compared to the initial cohort while patients remaining in the F/MF Concurrent Comparator Cohort had slightly higher BMI-for-age z-score than the

initial cohort.

Therefore, due to the significant differential attrition in the 1-<2y concurrent cohorts and the short duration of follow-up, the interpretability of the results from the 1-<2y cohorts analyses is extremely limited.

Distributions of Orkambi exposure duration in the US CFFPR 1-<2y Matched Orkambi Cohort are summarized in Table below. As of the end of follow-up, the 1-<2y Matched Orkambi Cohort was exposed to Orkambi for an average of only 7.5 months, with 84% exposed for less than 12 months.

Table 17: Orkambi Exposure Duration in the US CFFPR 1 -< 2y Matched Orkambi Cohort

Orkambi Exposure Duration (months) as of:	n	Mean (SD)
31 December 2023	161	6.3 (3.81)
31 December 2024, initial cohort (including patients who were censored during follow-up)	161	7.5 (4.60)
31 December 2024, remaining cohort (subset of patients followed through the end of the study)	16	15.5 (4.08)

Sources: Study 128 US CFFPR 1y Concurrent Cohorts Tables and Figures/Table 2.0b; Study 128 US CFFPR 1y Orkambi Cohorts Ad Hoc Table/Table 1.0

CFFPR: CF Foundation Patient Registry; n: number of subjects or observations; SD: standard deviation; US: United States

US CFFPR 1-<2y F/F Longitudinal Historical Cohort

The US CFFPR 1-<2y F/F Longitudinal Historical Cohort included 305 patients in 2016. Baseline demographic and clinical characteristics for the US CFFPR 1-<2y F/F Longitudinal Historical Cohort are presented in Table below.

Table 18: Baseline Demographic and Clinical Characteristics for the US CFFPR 1-<2y F/F Longitudinal Historical Cohort

Characteristic	F/F Longitudinal Historical Cohort N = 305
Age as of 01 January 2016, years, mean (SD)	1.5 (0.28)
Female sex, n (%)	153 (50.2)
BMI-for-age z-score, mean (SD)	0.7 (0.84)
BMI percentile, mean (SD)	69.2 (21.98)
Pulmonary exacerbation (PEx), n/N1 (%)	
PEx leading to hospitalization and/or home IV antibiotics	81/305 (26.6)
PEx leading to hospitalization	80/305 (26.2)
Hospitalizations, n/N1 (%)	136/305 (44.6)
History of CF medication use, n/N1 (%)	
Inhaled tobramycin	57/296 (19.3)
Inhaled aztreonam	6/296 (2.0)
Oral corticosteroids	6/296 (2.0)
Pulmonary microbiology, n/N1 (%)	
P. aeruginosa	102/296 (34.5)
H. influenzae	107/296 (36.1)
S. aureus (including MRSA)	217/296 (73.3)
History of DIOS, n/N1 (%)	19/296 (6.4)
History of CFRD, n/N1 (%)	0/296 (0.0)
History of clinically significant ALT, n/N1 (%)	
>3 to ≤5 × ULN	25/278 (9.0)
>5 to ≤8 × ULN	4/278 (1.4)
>8 × ULN	3/278 (1.1)
History of clinically significant AST, n/N1 (%)	
>3 to ≤5 × ULN	0/190 (0.0)
>5 to ≤8 × ULN	0/190 (0.0)
>8 × ULN	0/190 (0.0)

Sources: Study 128 US CFFPR 1y Historical Cohort Tables and Figures/Tables 1.0, 2.1, and 2.2

ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; CF: cystic fibrosis; CFFPR: CF Foundation Patient Registry; CFRD: CF-related diabetes; DIOS: distal intestinal obstruction syndrome; F/F: homozygous for *F508del*; *H. influenzae*: *Haemophilus influenzae*; IV: intravenous; MRSA: methicillin-resistant *Staphylococcus aureus*; N: number of subjects in the analysis set; n: number of subjects or observations; N1: number of patients with non-missing measurement; *P. aeruginosa*: *Pseudomonas aeruginosa*; PEx: pulmonary exacerbation; *S. aureus*: *Staphylococcus aureus*; SD: standard deviation; ULN: upper limit of normal; US: United States

Notes: Denominators for percentages are the total cohort size (i.e., N) unless shown otherwise, in which case the denominator is N1, the number of patients with a non-missing measurement of the outcome. The cohort entry date is 01 January 2016. Attrition from the cohort over time is permitted as subjects become exposed to CFTR modulators, death, or first year of loss to follow-up. The cohort was followed through 31 December 2017. Sex, history of clinically significant ALT/AST, history of CFRD/DIOS, use of CF medications, pulmonary microorganisms, and patients with PEx/hospitalization categories will be identified at any point prior to cohort entry.

During follow-up, 7 patients were lost to follow-up and 1 patient was censored due to CFTR modulator use.

US CFFPR Effectiveness Endpoints

Overall, the BMI and weight percentiles increased in the Orkambi Cohort, but no discernible differences from the comparator were identified. However, the results are of limited interpretability due to the significant cohort attritions and short duration of Orkambi exposure.

There were no notable trends or differences observed across the 1-<2y cohorts for the other effectiveness endpoints.

US CFFPR Safety Endpoints

LFT Elevations

There were no notable trends or differences observed across the 1-<2y cohorts. However, the results are of limited interpretability due to the significant cohort attritions and short duration of Orkambi exposure.

Deaths and Transplantations

There were no deaths or organ transplantations in the US CFFPR 1-<2y concurrent cohorts and 1 death and no organ transplantations in the 1-<2y F/F Longitudinal Historical Cohort.

5.3. Discussion

Study **VX18809128** is a six-year, observational, registry-based PAES designed to characterise disease progression and safety in children with cystic fibrosis (CF) homozygous for *F508del* (F/F) who initiated lumacaftor/ivacaftor (Orkambi) at 1 through <2 years or 2 through 5 years of age in routine care.

The main research question is whether children treated earlier in life develop a less advanced disease as they grow older, compared with children who either never received a CFTR modulator or initiated Orkambi later in their life.

The study leverages two independent, mature data sources - the European Cystic Fibrosis Society Patient Registry (ECFSPR) and the US Cystic Fibrosis Foundation Patient Registry (CFFPR) - and contextualises findings against an F/F historical cohort, the UK Kalydeco PAES F/F comparator cohort, and Study 110 (including older, 6–11year old Orkambi-treated children from a clinical trial programme).

Matching for concurrent cohort comparisons was 1:1 on age, sex, and BMI-forage z-score; analyses were predominantly descriptive by protocol.

Cohorts, entry windows, and follow-up: For the **2–5y cohorts**, Orkambi and matched F/MF (and, in ECFSPR only, matched F/F) comparators had cohort entry aligned with each region's market availability (US CFFPR: 2018–2019; ECFSPR: 2019–2020) with follow-up to 31 Dec 2024. The 1–<2y cohorts had entry in 2022–2023 (US) and 2023 (EU) with follow-up planned through 2024, yielding necessarily short observation time.

Exposure was tracked longitudinally until treatment switch/discontinuation; censoring occurred at loss to follow-up, death, or initiation of another CFTR modulator. Substantial post 2021/2022 attrition occurred in all concurrent cohorts, particularly among Orkambi-treated children, driven largely by transitions to newer CFTR modulators (e.g., elexacaftor/tezacaftor/ivacaftor). By 2024, <2–5% of matched cohort members generally remained under their original assignment, so post2022 estimates require cautious interpretation.

Endpoints: Effectiveness endpoints included growth parameters (BMI/height/weight z-scores and percentiles; weight-for-length for 1–<2y), pulmonary exacerbations (definitions registry-specific), all-cause hospitalisations, ppFEV$_1$ (when available), CF medication use (inhaled antibiotics, oral corticosteroids), CF complications (distal intestinal obstruction syndrome - DIOS, CF-related diabetes - CFRD), and pulmonary microbiology (*H. influenzae, P. aeruginosa, S. aureus*/MRSA).

Safety endpoints included liver function test (LFT) elevations (ALT/AST; US CFFPR only), organ transplantation, and death.

Effectiveness - children who started at 2–5 years: Across both registries, growth outcomes improved meaningfully after Orkambi initiation, with BMI, weight, and height percentiles generally rising from baseline while remaining stable or declining in matched comparators and historical cohorts. In ECFSPR, the magnitude of improvement was apparent over the first two post-baseline years; in CFFPR, growth gains were also observed though attenuated later by differential attrition. When contextualised against Study 110, younger initiators achieved comparable or better nutritional status at earlier ages, supporting the premise that earlier CFTR modulation may favour growth trajectories.

For **pulmonary exacerbations (PEx)**, patterns diverged by comparator and registry definitions but were directionally favourable for Orkambi. In ECFSPR, the risk of PEx leading to hospitalisation declined in Orkambi-treated children to single digit percentages before extensive attrition and was lower than the matched F/F comparator; with respect to the matched F/MF comparator, differences were modest and influenced by the narrower ECFSPR PEx definition. In US CFFPR, where PEx encompassed hospitalisation and/or home IV antibiotics, the annual risk declined to <10% and with a trend to lower in Orkambi than in F/MF comparators; by contrast, the F/F historical cohort exhibited higher and increasing PEx proportions over time, consistent with progressive disease in the pre-modulator era.

Hospitalisations followed a similar pattern: in ECFSPR, the proportion with ≥1 hospitalisation decreased after Orkambi initiation and was lower than the matched F/F comparator in the first follow-up year; in US CFFPR, declines were also seen in both cohorts, with no consistency between cohort differences beyond early follow-up. These hospitalisation data should be interpreted considering COVID19-related healthcare utilisation changes and heterogeneity in hospital admission thresholds across systems.

Lung function data were necessarily sparse because spirometry is infrequently feasible <6 years; where available, ppFEV$_1$ remained well preserved (generally >90–95%) in Orkambi-treated subsets and comparable to concurrent comparators, while appearing more favourable than in older Orkambi-treated children from Study 110 and the UK Kalydeco comparator, though cross-study comparisons are limited.

For **pulmonary microbiology**, the prevalence of *H. influenzae* decreased across cohorts, with Orkambi groups generally moving from the mid 30% range toward ~20%. *P. aeruginosa* was low in ECFSPR and declined in US CFFPR Orkambi cohorts compared with F/MF comparators and historical F/F cohorts; *S. aureus*/MRSA showed no consistent directional trends in either registry.

Patterns in **CF medication use** were broadly favourable or neutral for Orkambi (e.g., similar or lower inhaled antibiotic use), though therapeutic choices can be confounded by evolving local practice and CFTR modulator uptake.

The proportion of patients with **DIOS** was consistently low across all cohorts, with no discernible trends observed in either of the matched cohorts prior to cohort attrition in 2022; similarly **CFRD** was also rare across all cohorts with no apparent trend.

Effectiveness - children who started at 1–<2 years: Analyses in this very young cohort are severely constrained by short follow-up (only 9 months) and rapid switches to other modulators. The limited available data suggested improvements in growth after Orkambi initiation and no obvious safety concerns, but no robust inference can be made on pulmonary endpoints or longer-term outcomes at this time.

Safety: No new safety signals emerged. In US CFFPR, ALT/AST elevations >3×, >5×, or >8× ULN were uncommon and broadly similar between Orkambi and F/MF comparators; ECFSPR did not collect transaminases. There were no organ transplants reported in Orkambi cohorts in either registry, and one death (trauma, unrelated) in the US Orkambi cohort. Overall, the observed safety profile is consistent with product labelling.

While the above narrative reflects the study's favourable signals, some **limitations and risks of bias** could be identified:

1. **Comparator suitability and residual confounding.** The routine use of an F/MF concurrent comparator is not genotype-matched to the F/F Orkambi cohort and is "phenotypically similar only," making it suboptimal for causal inference; the preferred F/F concurrent comparator in ECFSPR is small and geographically concentrated, which restricts power and generalisability. Historical F/F cohorts, while informative, embed temporal and treatment-era biases (e.g., earlier access to modulators and evolving standards of care) and suffered substantial attrition due to later modulator uptake.

2. **Baseline imbalances and regional heterogeneity.** Even after matching, numerical imbalances persisted for clinically relevant characteristics (e.g., prior hospitalisations; differences in height/weight percentiles), and country mix differed across cohorts (e.g., Orkambi cohorts weighted to the UK/Germany/France vs comparators enriched in Italy/Poland), potentially reflecting system level differences in access patterns and clinical practice. These differences can confound outcomes such as hospitalisation rates and antibiotic use.

3. **Short effective follow-up at the interim cut and COVID19 effects.** In the interim review window, exposure was only ~1 year for many children. In addition, COVID19 (2020–2021) materially altered infection exposure, healthcare utilisation, and measurement frequency (spirometry, LFTs), biasing PEx and hospitalisation metrics downward irrespective of therapy. Although the final analysis extends to 2024, post 2022 attrition compromises later period interpretability.

4. **Cohort attrition and informative censoring.** The US cohorts in particular experienced major, differential attrition - largely children switching to newer CFTR modulators - which breaks matching balance over time (remaining Orkambi patients tended to be younger and with different baseline BMI). Such informative censoring risks over- or under-estimating treatment differences in later years and limits the robustness of 2022–2024.

5. **Endpoint definition heterogeneity and clinical relevance.** Definitions of PEx differ by registry - ECFSPR restricts to hospitalisation requiring PEx, whereas US CFFPR includes

hospitalisation and/or home IV antibiotics - and hospitalisation is captured as "any cause," making cross registry comparisons and clinical interpretation nonuniform.

6. **Missing or limited key paediatric endpoints.** Measures that may be more sensitive in early childhood - LCI2.5, CFQ-R, and sweat chloride - were not collected in routine practice for <6-year-olds and thus were absent from the PAES. Spirometry/ppFEV$_1$ was sparse and absent at baseline (as expected at these ages), further reducing sensitivity to lung function.

7. **Safety.** Transaminases were available in US CFFPR only; ECFSPR did not capture LFTs, leading to incomplete safety ascertainment for hepatotoxicity signals in the EU data cut, although no concerns emerged where measured.

In conclusion, despite methodological constraints inherent to observational registry research and pronounced post 2021/2022 attrition - chiefly due to transitions to newer CFTR modulators - the convergent patterns across two independent registries support that initiating Orkambi at ages 2–5 years is associated with better growth, reduced PEx and hospitalisations, stable lung function, and no new safety concerns versus matched comparators and historical experience. Growth outcomes are considered of potential relevance to prescribers, and a brief summary has been reported in Section 5.1 of the SmPC, including BMI, weight, and height percentiles (see the annexed SmPC for details).

Evidence in the 1–<2 year old cohorts remain preliminary because of limited follow-up and extensive censoring because of treatment switch. Overall, the limited available data can still be considered suggestive of improvements in growth after Orkambi initiation, and no obvious safety concerns were observed in younger children. However, no robust inference can be made on pulmonary endpoints or longer-term outcomes, and changes in clinical practice make the possibility to collect additional prospective data in this population unrealistic.

The submitted data can be considered supportive of the clinical benefit of earlier initiation of CFTR modulation with Orkambi while acknowledging the limits on precision and durability of estimates late in follow-up. The available real-word data are considered overall consistent with the established overall benefit-risk profile of Orkambi.

5.4. Direct Healthcare Professional Communication

N/A

6. PRAC advice

N/A

7. Risk management plan

The MAH submitted an updated RMP version 12, dated 16 Dec 2025 with this application. The (main) proposed RMP changes are the following:

- Updates to reflect the completion of Study 128
- Inclusion of the updated depression-related adverse event safety information collection form in Annex 4
- The LUM/IVA exposure sections were also updated.

Clinical trial exposure

The tables of exposure in lumacaftor development program have been updated to reflect increased PYs of clinical trial exposure

Post-authorisation experience

The tables of exposure to Orkambi from marketing experience are updated to reflect increased PYs of exposure.

Summary of the safety concerns

Table 19: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Respiratory events
Important potential risks	Cataracts
Missing information	Use in pregnant and lactating women Use in patients with organ transplant

PART IV Plans for Post-authorisation Efficacy Studies

The RMP has been updated to remove study 128 from the Plans for Post authorisation Efficacy Studies. The study is also removed from the list of studies which are conditions of the marketing authorisation in section II.C Post-authorisation development plan of the Part VI Summary of the RMP. Additionally, Study 128 has been included within the Table of Completed Studies within Annex II of the RMP.

Part VI Summary of the RMP

Minor updates have been proposed to the Summary of the RMP, in line with changes made to Part IV

Elements for a public summary of the RMP

The summary of the RMP has been amended to reflect the changes throughout the RMP.

Annexes

Annexes 2, 5 and 8 were updated to reflect the completion of study 128.

In addition, updates were made to Specific adverse event follow up forms (depression-related adverse events) in Annex 4. While the applicant has not provided a justification of the updates within this variation, nor a summary of the updates, the PRAC notes the main updates are to expand the question on prior history of depression to seek information on any prior history of anxiety, sleep disturbances behaviour events and/or family history of same. In addition, new queries are added in terms of whether or not there were any concurrent illnesses around the time of the event, and whether the patient underwent mental health evaluation in the past of for this event (along with pre and post Orkambi PHQ9 and or GAD-7 scores if available).

These updates are considered acceptable in the context of the labelled risk of depression and in the context of PI updates relating to anxiety and insomnia as possible comorbidities/symptoms of depression made under PSUSA/00010455/202505.

8. Changes to the Product Information

Changes are made to the SmPC section 5.1, as well as to the PI Annex II conditions as detailed in the recommendations section above.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

9. Attachments

1. Product Information (changes highlighted) for Orkambi, as adopted by CHMP on 26 March 2026.