15 October 2020
EMA/611137/2020
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Orkambi

lumacaftor / ivacaftor

Procedure no: EMEA/H/C/003954/P46/014.3

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

Abbreviation	Definition
AE	Adverse event
BMI	Body mass index
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CI	Confidence interval
CRO	Contract Research Organization
eCRF	Electronic case report form
EDC	Electronic data capture
F508del CFTR	Deletion of phenylalanine at position 508 in the wild-type CFTR protein
FEF	Forced expiratory flow
FEV1	Forced expiratory volume in one second
F/F	Homozygous for F508del-CFTR
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
GPP	Good Pharmacoepidemiology Practices
HRU	Healthcare resource utilization
HIPAA	Health Insurance Portability and Accountability Act
ICSR	Individual case safety report
IQR	Interquartile range
IRB	Institutional review board
IV	Intravenous
IVA	Ivacaftor
LABA	Long-acting beta agonist
LUM	Lumacaftor
PEx	Pulmonary exacerbation
ppFEV1	Percent predicted forced expiratory volume in 1 second
SABA	Short-acting beta agonist
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
US	United States
USPI	United States prescribing information

1. Introduction

On 19 November 2019, the MAH submitted a completed study for Orkambi, that included a subgroup of 30 paediatric patients, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study 117 is a stand-alone study.

The MAH states that According to Article 46 of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006, Vertex Pharmaceuticals is submitting information on a paediatric study **completed on 20 October 2017**. Study Title: "A Multicenter, Retrospective, Real-World, Observational Study on Orkambi Use".

CHMP comment

The submission was received on 19 November 2019, thus **not** within 6 months of study completion, **this is not in accordance with the regulation.**

2.2. Information on the pharmaceutical formulation used in the study

Orkambi was not supplied by Vertex during this study; Orkambi was prescribed by a patient's physician in accordance with the US prescribing information (USPI) and as part of the patient's overall therapeutic strategy.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for: Study VX16 809 117, A Multicenter, Retrospective, Real-world, Observational Study on ORKAMBI Use**.**

2.3.2. Clinical study

Study VX16 809 117, A Multicenter, Retrospective, Real-world, Observational Study on Orkambi Use.

Description

Methods

Objective(s)

To evaluate ORKAMBI treatment patterns, effectiveness, and initiation experience in patients aged 12 and older with CF F/F who initiated ORKAMBI between July 2015 and September 2015 (early initiators) or October 2015 and December 2015 (late initiators).

The outcomes of interest included whether the patient was an early or late initiator (months 1–3 vs. months 3–6 post- ORKAMBI market uptake), treatment patterns (e.g., ORKAMBI discontinuation),

effectiveness, and site characteristics (e.g., availability of ORKAMBI treatment protocol). Early and late initiators of ORKAMBI were distinguished because the difference in the degree of disease severity—being greater in the early initiators—might influence the effectiveness of ORKAMBI.

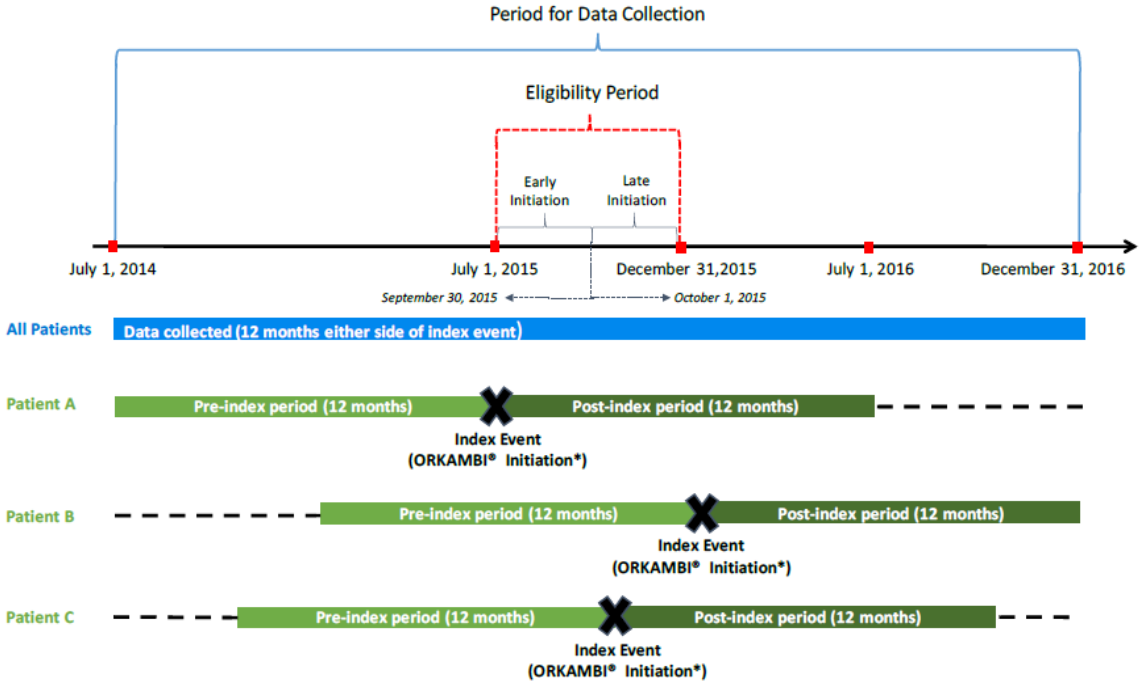
Study design

This was a multicenter, retrospective, observational study to explore real-world use and effectiveness of ORKAMBI in CF F/F patients in the US who were 12 years of age or older. The study was conducted at 8 US academic centers.

Up to 300 cases (approximately 150 early and 150 late initiators) were to be randomly selected by the contract research organization (CRO) for inclusion in the study; selected patients had de-identified, retrospective data abstracted from their patient medical records entered into an eCRF.

A schematic of the study design is provided in Figure 1.

Figure 1: Overview of study design



*Index Event = Rx fill date between July 1, 2015 and December 31, 2015

*Initiation of ORKAMBI® was based on the fill date of the prescription where possible. For patients for whom this data was unavailable, initiation of ORKAMBI® was based on the date on which it was documented that the patient would initiate ORKAMBI® (prescription date).

* September 30, 2015 reflects the end of the early-patient initiation cohort; October 1, 2015 reflects the beginning of the late-phase initiation cohort.

Case Ascertainment Period and Index Date

The case ascertainment period was from July 1, 2015 through December 31, 2015. Patients whose ORKAMBI index date occurred between July 2015 and September 2015 were considered to be "early initiators" and patients whose ORKAMBI index date occurred between October 2015 and December 2015 were defined as late initiators. For patients for whom fill date was unavailable, initiation of ORKAMBI (i.e., index date) was based on the prescription date.

Analysis Period

The analysis period was unique to each patient and comprised two main periods anchored to the index date:

• Pre-index date period: from 12 months before the first day of the case ascertainment period (i.e., July 1, 2014) to one day before the case-specific index event date. A minimum of 12 months (maximum of 18 months) of pre-index data from each case was available.

• Post-index date period: from the case-specific index date to:

• Six months (June 30, 2016) after the last day (December 31, 2015) of the case ascertainment period for the first data abstraction; a minimum of six months (maximum of 12 months) of post-index data from each case was available

• Twelve months (December 31, 2016) after the last day (December 31, 2015) of the case ascertainment period for the second data abstraction; a minimum of 12 months (maximum of 18 months) of post-index data from each case was available

Data Abstraction Period

Patient medical charts were reviewed by local site staff for relevant study data. The two data abstractions for each case were:

• First data abstraction: occurred after June 30, 2016; data was collected from July 1, 2014 through June 30, 2016 (up to 24 months of data from each case)

• Second data abstraction: occurred after December 31, 2016; data was collected from July 1, 2016 through December 31, 2016 (six months of additional data to the first data abstraction; up to 30 months of total data from each case)

Study population /Sample size

Inclusion and Exclusion Criteria

Patients who met all inclusion criteria were eligible for enrolment into the study:

- have a confirmed diagnosis of CF,
- being homozygous for F508del (as documented in the patient's medical record),
- being 12 years or older on the index date (i.e., first filled ORKAMBI prescription or issue date of the prescription);
- have an index date within the case ascertainment period (July 1, 2015 to December 31, 2015).

Patients who participated in any clinical study evaluating ORKAMBI as an investigational study drug within 12 months before the first day of the case-ascertainment period (i.e., between July 1, 2014 and July 1, 2015) were excluded from the study.

Sample Size Considerations

This study was not powered for statistical comparisons, as the objectives were descriptive in nature. A target sample size of up to 300 cases was decided, stratified by timing of initiation of ORKAMBI:

• Early-patient initiation cohort (index date between July 1, 2015 and September 30, 2015)

• Late-patient initiation cohort (index date between October 1, 2015 and December 31, 2015)

Treatments

Orkambi was prescribed by each patient's physician in accordance with the US Prescribing Information (USPI) and as part of routine clinical care. Per the Orkambi US Product Information, the dosing

regimen for CF patients who are homozygous for F508del and aged 12 years and older is 2 tablets (each containing LUM 200 mg/IVA 125 mg) taken orally every 12 hours (q12h).

Outcomes/endpoints

Data Sources

Data sources were patient medical records.

Site information was collected from a one-time, study-specific survey completed by site investigators (note: This is distinct from the feasibility survey administered during site selection.).

This survey collected general information specific to the site (e.g., size of site and treatment of adult and/or pediatric patients) and to general treatment practice by investigators at the site (e.g., availability and timing of implementation of ORKAMBI treatment protocol [defined as site development and/or implementation of guidance regarding managing patients who initiated on ORKAMBI]).

Table 1: Study-specific site survey summary

	Overall N=8 Sites
Total number of CF-treating physicians per site	
n	8
Mean	5.8
SD	5.26
Median	4.0
IQR	2.5, 6.5
Minimum	2.0
Maximum	18.0
Site treatment population	
Adult population, n(%)	1 (12.5%)
Pediatric population, n(%)	0 (0.0%)
Adult and pediatric population, n(%)	7 (87.5%)
Unknown, n(%)	0 (0.0%)
Practice type	
Academic, n(%)	8 (100.0%)
Community-based, n(%)	0 (0.0%)
Unknown, n(%)	0 (0.0%)
Implementation of ORKAMBI treatment protocol	
No, n(%)	4 (50.0%)
Yes, n(%)	4 (50.0%)
Unknown, n(%)	0 (0.0%)
Practice used to help patients to persist on treatment, within the sites who implemented an ORKAMBI treatment protocol Observed ORKAMBI treatment initiation (in clinic or hospital)	
No, n(%)	6 (75.0%)
Yes, n(%)	2 (25.0%)
Unknown, n(%)	0 (0.0%)
Increased frequency of follow-up with patients after ORKAMBI treatment initiation	
No, n(%)	6 (75.0%)
Yes, n(%)	1 (12.5%)
Unknown, n(%)	1 (12.5%)
Lower than labeled starting dose (or frequency)	
No, n(%)	4 (50.0%)
Yes, n(%)	4 (50.0%)
Unknown, n(%)	0 (0.0%)
Reducing dose	
No, n(%)	8 (100.0%)
Yes, n(%)	0 (0.0%)
Unknown, n(%)	0 (0.0%)
Use of LABA	
No, n(%)	8 (100.0%)
Yes, n(%)	0 (0.0%)
Unknown, n(%)	0 (0.0%)
Use of SABA	
No, n(%)	7 (87.5%)
Yes, n(%)	1 (12.5%)
Unknown, n(%)	0 (0.0%)
Use of an inhaled steroid	
No, n(%)	7 (87.5%)
Yes, n(%)	1 (12.5%)
Unknown, n(%)	0 (0.0%)
Discontinuation	
No, n(%)	7 (87.5%)
Yes, n(%)	1 (12.5%)
Unknown, n(%)	0 (0.0%)

		Overall N=8 Sites
Re-start for those who have discontinued		
	No, n(%)	6 (75.0%)
	Yes, n(%)	2 (25.0%)
	Unknown, n(%)	0 (0.0%)
Any additional support provided to patients beyond standard of care education		
	No, n(%)	7 (87.5%)
	Yes, n(%)	1 (12.5%)
	Unknown, n(%)	0 (0.0%)

Footnotes:
-N: Number of sites in the study; n(%): number and percentage of sites, where the denominator for the percentage is the number of sites with available data.
-Pediatric population: patients 12-17 years of age.
-ORKAMBI treatment protocol was defined as site development and/or implementation of guidance regarding managing patients who initiated on ORKAMBI.
-Percentages are calculated relative to the total number of sites.
Abbreviations: CF = cystic fibrosis; IQR = interquartile range; LABA = long-acting beta-adrenoceptor agonist; SABA = short-acting beta-adrenoceptor agonist; SD = standard deviation

Table 1
Study-specific Site Survey Summary

		Overall N=8 Sites
Total number of CF-treating physicians per site		
	n	8
	Mean	5.8
	SD	5.26
	Median	4.0
	IQR	2.5, 6.5
	Minimum	2.0
	Maximum	18.0
Site treatment population		
	Adult population, n(%)	1 (12.5%)
	Pediatric population, n(%)	0 (0.0%)
	Adult and pediatric population, n(%)	7 (87.5%)
	Unknown, n(%)	0 (0.0%)
Practice type		
	Academic, n(%)	8 (100.0%)
	Community-based, n(%)	0 (0.0%)
	Unknown, n(%)	0 (0.0%)
Implementation of ORKAMBI treatment protocol		
	No, n(%)	4 (50.0%)
	Yes, n(%)	4 (50.0%)
	Unknown, n(%)	0 (0.0%)
Practice used to help patients to persist on treatment, within the sites who implemented an ORKAMBI treatment protocol		
Observed ORKAMBI treatment initiation (in clinic or hospital)		
	No, n(%)	2 (50.0%)
	Yes, n(%)	2 (50.0%)
	Unknown, n(%)	0 (0.0%)
Increased frequency of follow-up with patients after ORKAMBI treatment initiation		
	No, n(%)	2 (50.0%)
	Yes, n(%)	1 (25.0%)
	Unknown, n(%)	1 (25.0%)

	Overall N=8 Sites
Lower than labeled starting dose (or frequency)	
No, n(%)	0 (0.0%)
Yes, n(%)	4 (100.0%)
Unknown, n(%)	0 (0.0%)
Reducing dose	
No, n(%)	4 (100.0%)
Yes, n(%)	0 (0.0%)
Unknown, n(%)	0 (0.0%)
Use of LABA	
No, n(%)	4 (100.0%)
Yes, n(%)	0 (0.0%)
Unknown, n(%)	0 (0.0%)
Use of SABA	
No, n(%)	3 (75.0%)
Yes, n(%)	1 (25.0%)
Unknown, n(%)	0 (0.0%)
Use of an inhaled steroid	
No, n(%)	3 (75.0%)
Yes, n(%)	1 (25.0%)
Unknown, n(%)	0 (0.0%)
Discontinuation	
No, n(%)	3 (75.0%)
Yes, n(%)	1 (25.0%)
Unknown, n(%)	0 (0.0%)
Re-start for those who have discontinued	
No, n(%)	2 (50.0%)
Yes, n(%)	2 (50.0%)
Unknown, n(%)	0 (0.0%)
Any additional support provided to patients beyond standard of care education	
No, n(%)	3 (75.0%)
Yes, n(%)	1 (25.0%)
Unknown, n(%)	0 (0.0%)

Footnotes:
-N: Number of sites in the study; n(%): number and percentage of sites, where the denominator for the percentage is the number of sites with available data.
-Pediatric population: patients 12-17 years of age.
-ORKAMBI treatment protocol was defined as site development and/or implementation of guidance regarding managing patients who initiated on ORKAMBI.
-Percentages are calculated relative to the total number of sites except otherwise specified. For the results on practice used to help patients to persist on treatment, the percentages are calculated relative to the number of sites who implemented an ORKAMBI treatment protocol.
Abbreviations: CF = cystic fibrosis; IQR = interquartile range; LABA = long-acting beta-adrenoceptor agonist; SABA = short-acting beta-adrenoceptor agonist; SD = standard deviation

CHMP comment

It is unclear the reason why in the final-eva-18941-table file there are two Tables 1 reporting Study Specific Site Survey Summary with partially different data. The MAH should clarify.

Study variables

Patient-level Variables

Demographic and Baseline Clinical Characteristics

The following variables were collected during the 12-month pre-index period up to date of ORKAMBI fill.

- Age (in years) on date of ORKAMBI initiation (12 to <18 half age was collected [e.g., 12.5], ≥ 18), Sex, Weight (kg) and height (cm)
- CF comorbidities that occurred or were present during the pre-index period and whether these conditions were ongoing at ORKAMBI treatment initiation
- CF severity (i.e., ppFEV1), Lung function: FEV1 (L), forced vital capacity (FVC) (L), forced expiratory flow (FEF) 25%–75% (L/second) for ppFEV1 (%) calculation
- Any positive results for mucoid or non-mucoid Pseudomonas aeruginosa (P aeruginosa)
- Pulmonary exacerbation (PEx), intravenous (IV) antibiotics, inpatient hospitalizations

Orkambi utilization

- Prescription and fill dates (where known)
- Starting dose and dose changes including reasons for modification
- ORKAMBI discontinuations including reasons
- ORKAMBI re-initiation

Orkambi effectiveness

Clinical outcomes

Change in lung function (measures of ppFEV1)

Nutritional status (body mass index [BMI] and weight)

PEx (Note: PEx were defined as IV antibiotic use at home or in hospital and/or PEx-related hospitalizations). Consecutive courses of IV antibiotics or PEx-related hospitalization with less than seven days from the end of prior event to start of subsequent event were considered one event. Outcomes were reported for all PEx, and separately for those requiring hospitalization, those requiring hospitalization with IV antibiotics, and those associated with outpatient visits requiring IV antibiotic therapy. The number and percentage of patients categorized by number of PEx was reported, as was the total number of PEx per patient per year.

Healthcare resource utilization

Inpatient hospitalizations

Outpatient visits related to CF

Acute antibiotic use including IV antibiotic

Other CF medications use (other than antibiotics)

Other Outcomes

- Microbiology (e.g., Pseudomonas)
- Death. Cause of death was also provided for patients who died during the post-index event period

• Transplantation (overall and by type [i.e., liver, lung, heart, heart-lung, other])

Site-level Variables

• Size of site (number of CF-treating physicians)

• Type of available treatment (adult and/or pediatric patients)

• Type of practice (academic- or community-based)

• Availability and timing of implementation of ORKAMBI treatment protocol

• Implementation of the ORKAMBI treatment protocol

Statistical Methods

Analysis Set

The All Subjects Set, also referred to as the overall population, was defined as all subjects included in this retrospective study, and who met all eligibility criteria. The All Subjects Set was used for all ORKAMBI utilization patterns and effectiveness analyses, unless specified otherwise, and included the following exhaustive, two subpopulations: 1) early-patient initiation population, and 2) late-patient initiation population.

Data Analysis

The final analyses were performed in SAS® v9.4 following database lock All data analyses were descriptive and based on observed trends over time. No hypothesis testing was performed.

Missing Data

Missing data was expected due to the retrospective design of the study. The number and proportion of missing data was reported for each variable. **Incomplete/missing data** will not be imputed except for partially missing dates.

Significance Levels and Multiplicity

As the study was descriptive in nature, no statistical tests or significance levels were calculated. However, mean within-group change from baseline scores for key continuous outcomes (e.g., FEV1 and BMI) were presented with 95% CI estimates to evaluate whether they differed from zero. There were no adjustments for multiplicity.

Safety and Monitoring Reporting

This was a non-interventional study based on the retrospective and secondary use of data, thus, reporting of suspected adverse reactions as individual case safety reports (ICSR) was not required.

Results

Recruitment/ Number analysed

Study Population

Study Sites

Eight sites participated in the study. The location of the sites was well distributed across the US with two each in the Midwest, Southeast, and Southwest, and one each in the Northeast and West.

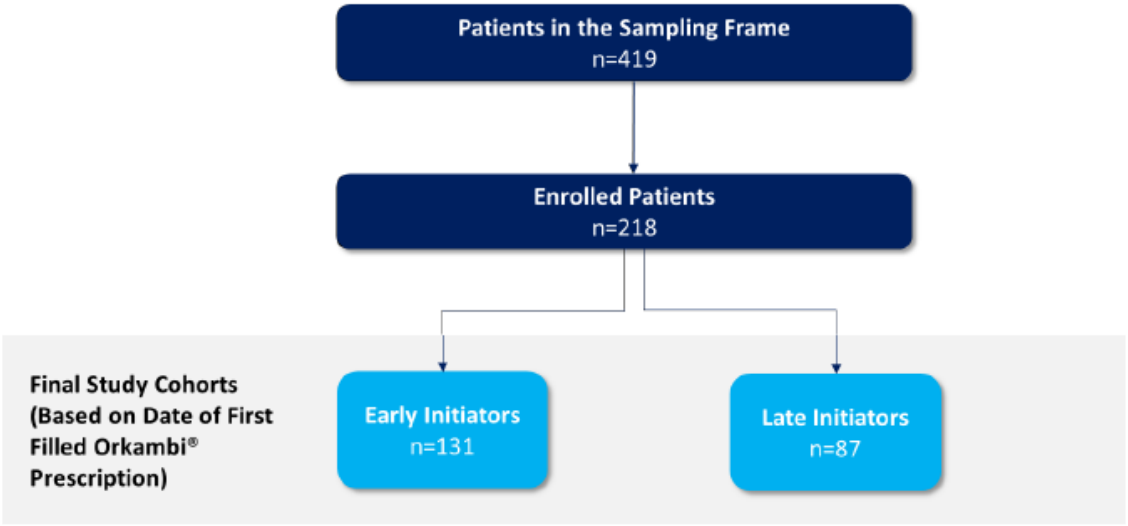
Patient Sampling

Sites identified the medical records of all patients at their site who had been prescribed ORKAMBI and who met the eligibility criteria (i.e., eligible cases). This list of cases constituted the sampling frame from which sampling into the study occurred. For patients for whom fill date was unavailable, initiation of ORKAMBI (i.e., index date) was based on the prescription date. The intent of sampling was to aim for balanced representation of cases in the early- and late-patient initiation cohorts (approximately 150 cases per group) and if feasible, to ensure balanced representation of cases within each group by month of ORKAMBI initiation. Due to the high number of available patients in the early-initiation cohort, a random sample was selected, whereas all eligible late-initiation patients were enrolled. Ensuring balance of representation by month of ORKAMBI initiation was also not possible.

Sites identified an overall sampling frame of 419 potentially eligible patients with CF who initiated treatment with ORKAMBI during the case ascertainment period. Two hundred and one (201) patients (48.0%) were excluded from the study for the following reasons: 121 (28.9%) from the early initiator cohort were not randomly sampled into the study, 29 (6.9%) were selected for inclusion in the study but data abstraction was not completed and 51 (12.2%) were not eligible. Therefore, a total of **218** patients were enrolled and included in the final analysis. In the final enrolled cohort, 131 patients (60.1%) were classified as early-initiators and 87 patients (39.9%) were classified as late-initiators. An overview of patient sampling is included in Figure 2.

Patient Disposition

Figure 2: Patient Inclusion and Cohort Identification



Note: Patients whose first filled ORKAMBI® prescription occurred between July 2015 and September 2015 were considered to be "early initiators" and patients whose first filled ORKAMBI® prescription occurred between October 2015 and December 2015 were defined as late initiators. For patients for whom fill date was unavailable, initiation of ORKAMBI® (i.e., index date) was based on the prescription date.

Table 2: Subject disposition summary, overall and within sites by initiation group (all eligible subjects)

	Initiation Group		
	Early-patient	Late-patient	Overall
Potentially eligible patients on Orkambi identified by study sites for study inclusion			
N	292	127	419
By Site, n(%)			
	34 (11.6%)	12 (9.4%)	46 (11.0%)
	35 (12.0%)	19 (15.0%)	54 (12.9%)
	29 (9.9%)	31 (24.4%)	60 (14.3%)
	103 (35.3%)	25 (19.7%)	128 (30.5%)
	8 (2.7%)	14 (11.0%)	22 (5.3%)
	39 (13.4%)	16 (12.6%)	55 (13.1%)
	4 (1.4%)	3 (2.4%)	7 (1.7%)
	40 (13.7%)	7 (5.5%)	47 (11.2%)
Selected patients as per sampling scheme			
N	159	110	269
By Site, n(%)			
	28 (17.6%)	12 (10.9%)	40 (14.9%)
	27 (17.0%)	19 (17.3%)	46 (17.1%)
	17 (10.7%)	14 (12.7%)	31 (11.5%)
	24 (15.1%)	25 (22.7%)	49 (18.2%)
	8 (5.0%)	14 (12.7%)	22 (8.2%)
	26 (16.4%)	16 (14.5%)	42 (15.6%)
	4 (2.5%)	3 (2.7%)	7 (2.6%)
	25 (15.7%)	7 (6.4%)	32 (11.9%)
Selected patients as per sampling scheme found to be ineligible			
N	20	23	51
By Site, n(%)			
	1 (3.6%)	1 (4.3%)	2 (3.9%)
	0 (0.0%)	0 (0.0%)	0 (0.0%)
	1 (3.6%)	1 (4.3%)	2 (3.9%)
	9 (32.1%)	16 (69.6%)	25 (49.0%)
	0 (0.0%)	2 (8.7%)	2 (3.9%)
	11 (39.3%)	3 (13.0%)	14 (27.5%)
	0 (0.0%)	0 (0.0%)	0 (0.0%)
	6 (21.4%)	0 (0.0%)	6 (11.8%)
Eligible and enrolled patients			
N	131	87	218
By Site, n(%)			
	27 (20.6%)	11 (12.6%)	38 (17.4%)
	27 (20.6%)	19 (21.8%)	46 (21.1%)
	16 (12.2%)	13 (14.9%)	29 (13.3%)
	15 (11.5%)	9 (10.3%)	24 (11.0%)
	8 (6.1%)	12 (13.8%)	20 (9.2%)
	15 (11.5%)	13 (14.9%)	28 (12.8%)
	4 (3.1%)	3 (3.4%)	7 (3.2%)
	19 (14.5%)	7 (8.0%)	26 (11.9%)

Table 2
Subject Disposition Summary, Overall and within Sites, by Initiation Groups (All Eligible Subjects)

	Initiation Group		
	Early-patient	Late-patient	Overall

Footnotes:
-N: Number of subjects; n(%): number and percentage of subjects.
-Percentages are calculated relative to the overall sample size in the relevant sub-population (presented in the first row of each listed event).
-A selected patient as per the sampling scheme may not be enrolled if the full eligibility is not met (e.g. a prescription fill date is outside the eligibility period even though the prescription written date was within the eligibility period).
-Early-patient initiation population was defined as cases with an index date between 01 July 2015 and 30 September 2015, whereas Late-patient initiation population was defined as cases with an index date between 01 October 2015 and 31 December 2015. The index date was defined as the ORKAMBI prescription fill date. If this date was not available, index date was set to the date of ORKAMBI written prescription.

CHMP comment

Out of 419 patients with CF who initiated treatment with Orkambi during the case ascertainment period at the 8 US Sites, only 218 patients were included in the final analysis (131/292 early initiators, 45%; and 87/127 late initiators, 68.5%); therefore, a balanced representation of cases within the two groups was not fully achieved.

Due to the lower than expected number of late initiators, all eligible late-initiation patients were enrolled. Conversely, in the early-initiation cohort, a random sample was selected. Other exclusions were due to the following reasons: patients find to be ineligible (28 early initiators and 23 late initiators), or with incomplete data (29 subjects).

The MAH identified in the market access (most patients received ORKAMBI within the first three months post-market uptake vs. three to six months post-market uptake) the main reason of having a lower number of available late-initiators patients as compared to early-initiators. However, the distribution of enrolled subjects across sites and initiation group appears broad.

The topic of this variation is the submission of paediatric data (i.e. 12-17 years old patients enrolled in the study). The MAH should provide the distribution of paediatric patients (i.e., number eligible and enrolled) across sites.

Baseline data

Demographics

Demographics are summarized in Table 3.

Table 3: Patient demographics overall and by initiation cohorts

	Initiation Cohort		Overall
	Early	Late	N = 218
	N = 131	N = 87	
Age at index date (years)			
Mean (SD)	27.5 (9.44)	25.8 (8.80)	26.8 (9.21)
Pediatric Patients (12–17 years of age) at index date (n, %)	17 (13.0)	13 (14.9)	30 (13.8)
Sex (n, %)			
Female	58 (44.3)	46 (52.9)	104 (47.7)
Male	73 (55.7)	41 (47.1)	114 (52.3)
BMI (kg/m^2)			
Mean (SD)	21.2 (3.41)	21.1 (2.99)	21.1 (3.24)
Unknown (n, %)	6 (4.6%)	1 (1.1%)	7 (3.2%)

Abbreviations: BMI = body mass index; CF = cystic fibrosis; SD = standard deviation

Source Table 3 (main document)

CHMP comment

Out of 218 patients enrolled in Study 117, only **30 (13.8%)** were paediatric patients 12-17 years of age), including 17 (13%) early initiation patients and 13 (14.9%) late initiation patients. The focus of this submission is to provide data on real-world use and effectiveness of ORKAMBI in CF F/F patients in the US who were 12 years or older. For this reason, the assessment of results for the whole study population, as submitted by the MAH, is out of the scope of this AR.

Baseline Clinical Characteristics are summarized in Table 4.

Table 4: Baseline clinical characteristics, overall and by initiation cohorts

	Initiation Cohort		Overall
	Early N = 131	Late N = 87	N = 218
CF comorbid conditions present at any time during pre-index period (n, %)			
Chronic sinusitis	81 (61.8)	48 (55.2)	129 (59.2)
CF-related diabetes	51 (38.9)	30 (34.5)	81 (37.2)
Asthma	21 (16.0)	21 (24.1)	42 (19.3)
Distal intestinal obstruction syndrome	11 (8.4)	6 (6.9)	17 (7.8)

	Initiation Cohort		Overall
	Early N = 131	Late N = 87	N = 218
CF-related arthritis	2 (1.5)	1 (1.1)	3 (1.4)
None	4 (3.1)	7 (8.0)	11 (5.0)
Other	101 (77.1)	67 (77.0)	168 (77.1)
Any positive results for mucoid or non-mucoid pseudomonas aeruginosa during pre-index period (n, %)			
Yes	96 (73.3)	54 (62.1)	150 (68.8)
No	35 (26.7)	33 (37.9)	68 (31.2)
$ppFEV_1$ (%)			
Mean (SD)	58.8 (24.9)	64.8 (26.0)	61.2 (25.5)
Unknown	6 (4.6)	2 (2.3)	8 (3.7)
Any pulmonary exacerbations (PEx) during pre-index period (n, %)			
Yes	51 (38.9)	27 (31.0)	78 (35.8)
No	80 (61.1)	59 (67.8)	139 (63.8)
Unknown	0 (0.0)	1 (1.1)	1 (0.5)
Any IV antibiotics during pre-index period (n, %)			
Yes	34 (26.0)	20 (23.0)	54 (24.8)
No	96 (73.3)	67 (77.0)	163 (74.8)
Unknown	1 (0.8)	0 (0.0)	1 (0.5)
Any inpatient hospitalization for CF or CF pulmonary exacerbations during pre-index period (n, %)			
Yes	27 (20.6)	18 (20.7)	45 (20.6)
No	104 (79.4)	68 (78.2)	172 (78.9)
Unknown	0 (0.0)	1 (1.1)	1 (0.5)

[1] This includes bronchiectasis with obstructive lung disease and with Methicillin-resistant Staphylococcus aureus (MRSA) infection.
[2] Includes CF-related liver disease and liver disease.
Abbreviations: BMI = body mass index; CF = cystic fibrosis; IV = intravenous; GERD = gastroesophageal reflux disease; PEx = pulmonary exacerbation; $ppFEV_1$ = percent predicted forced expiratory volume in one second; SD = standard deviation
Source Table: 3 (main document)

CHMP comment:

Comprehensive baseline clinical characteristics should be provided by the MAH for the paediatric setting, for the overall paediatric population, and by initiation cohort.

ORKAMBI Utilization

In the overall study population, the following results were observed:

• Overall, most patients received a full dose of Orkambi at treatment initiation (86.2%), with few patients receiving a half dose (12.4%) or quarter dose (1.4%)

• Of the total 217 participants with available discontinuation status data, 75 (34.6%) subjects discontinued the study, of which 39 (52.0%) were due to respiratory adverse events (AE). One additional patient had unknown discontinuation status.

• The most common reason for a dose decrease (57.1%) or treatment interruption (50.0%) was respiratory adverse event (AE); the most common reason for a dose increase was "AE resolved" (21.1%)

• A higher discontinuation rate was observed in early initiator (53/131, 40.5%) versus late initiator (22/86, 25.6%) Group.

• A lower discontinuation rate was observed among patients with baseline ppFEV1 ≥40%.

Table 5: Descriptive summary of Orkambi dose at treatment initiation and re-initiation(s) within 12 months post-Orkambi initiation, by age groups, overall all subject set

	Age	
ORKAMBI Dose	12 to < 18 N=30	>=18 N=188
At Treatment Initiation		
Subjects in the All Subjects Set	30	188
Full dose (2 tablets twice a day), n (%)	27 (90.0)	161 (85.6)
Half dose (1 tablet twice a day), n (%)	3 (10.0)	24 (12.8)
Quarterly dose (1 tablet a day), n (%)	0 (0.0)	3 (1.6)
After First Re-initiation		
Subjects who re-initiated after first discontinuation	3	7
Full dose (2 tablets twice a day), n (%)	3 (100.0)	3 (42.9)
Half dose (1 tablet twice a day), n (%)	0 (0.0)	3 (42.9)
Quarterly dose (1 tablet a day), n (%)	0 (0.0)	1 (14.3)

Footnotes:
-All Subjects Set: All the subjects selected to take part in the retrospective study and who meet all eligibility criteria.
-N: Number of subjects in the All Subjects Set; n(%): number and percentage of subjects.
-Percentages are calculated relative to the number of subjects who recorded the event within the relevant sub-population (presented in the first row of each listed event).

Table 6: Descriptive summary of Orkambi dose at treatment initiation and re-initiation(s) within 12 months post-Orkambi initiation, by age groups, within initiation groups all subjects set

ORKAMBI Dose	Initiation Group: Early-patient 12 to <18 N=17	Early-patient >=18 N=114	Late-patient 12 to <18 N=13	Late-patient >=18 N=74
At Treatment Initiation				
Subjects in the All Subjects Set	17	114	13	74
Full dose (2 tablets twice a day), n (%)	15 (88.2)	102 (89.5)	12 (92.3)	59 (79.7)
Half dose (1 tablet twice a day), n (%)	2 (11.8)	12 (10.5)	1 (7.7)	12 (16.2)
Quarterly dose (1 tablet a day), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.1)
After First Re-initiation				
Subjects who re-initiated after first discontinuation	2	2	1	5
Full dose (2 tablets twice a day), n (%)	2 (100.0)	0 (0.0)	1 (100.0)	3 (60.0)
Half dose (1 tablet twice a day), n (%)	0 (0.0)	1 (50.0)	0 (0.0)	2 (40.0)
Quarterly dose (1 tablet a day), n (%)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)

Footnotes:
-All Subjects Set: All the subjects selected to take part in the retrospective study and who meet all eligibility criteria.
-N: Number of subjects in the All Subjects Set; n(%): number and percentage of subjects.
-Percentages are calculated relative to the number of subjects who recorded the event within the relevant sub-population (presented in the first row of each listed event).

CHMP comment

Among the 30 paediatric patients, 27 subjects (90%) received the full dose (2 tablets twice a day) and 3 subjects (10%) received half dose (1 tablet twice a day) within 12–months post Orkambi initiation. All three subjects, who re-initiated after first discontinuation, received the full dose.

ORKAMBI Dose Adjustments

Table 7. ORKAMBI Dose Adjustments within 12 Months Post- ORKAMBI Initiation, Overall, and by Initiation Cohorts

ORKAMBI® Dose Adjustment	Initiation Cohort: Early-patient N=131	Late-patient N=86*	Overall N=217*
Dose adjustment (increase, decrease and/or Interruption), within 12 months post-index			
No adjustment, n (%)	96 (73.3)	71 (82.6)	167 (77.0)
One adjustment, n (%)	13 (9.9)	8 (9.3)	21 (9.7)
Two adjustments, n (%)	15 (11.5)	4 (4.7)	19 (8.8)
At least three adjustments, n (%)	7 (5.3)	3 (3.5)	10 (4.6)
Reason for dose adjustment			
Lack of effectiveness, n (%)	1 (2.9)	0 (0.0)	1 (2.0)
Respiratory AE, n (%)	7 (20.0)	3 (20.0)	10 (20.0)
Gastro-intestinal AE, n (%)	1 (2.9)	0 (0.0)	1 (2.0)
Menstrual AE, n (%)	0 (0.0)	1 (6.7)	1 (2.0)

ORKAMBI® Dose Adjustment	Initiation Cohort		
	Early-patient N=131	Late-patient N=86*	Overall N=217*
Other AE, n (%)	1 (2.9)	1 (6.7)	2 (4.0)
AE resolving, n (%)	4 (11.4)	0 (0.0)	4 (8.0)
AE resolved, n (%)	6 (17.1)	2 (13.3)	8 (16.0)
Other reason, n (%)	12 (34.3)	8 (53.3)	20 (40.0)
Unknown, n (%)	3 (8.6)	0 (0.0)	3 (6.0)
At least one dose increase, within 12 months post-index			
n (%)	25 (19.1)	13 (15.1)	38 (17.5)
Reason for dose increase			
Lack of effectiveness,	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	0 (0.0)	1 (7.7)	1 (2.6)
Gastro-intestinal AE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	0 (0.0)	1 (7.7)	1 (2.6)
Other AE, n (%)	0 (0.0)	1 (7.7)	1 (2.6)
AE resolving, n (%)	5 (20.0)	0 (0.0)	5 (13.2)
AE resolved, n (%)	6 (24.0)	2 (15.4)	8 (21.1)
Other reason, n (%) - Increased to full dose - Holiday drug - Increased to half dose - Increased tolerance - Retrial of ORKAMBI - Pulmonary exacerbation resolution	12 (48.0) 5 (20) 1 (4) 2 (8) 0 (0.0) 1 (4) 1 (4)	8 (61.5) 6 (46.1) 0 (0.0) 0 (0.0) 1 (7.7) 0 (0.0) 0 (0.0)	20 (52.6) 11 (28.9) 1 (2.6) 2 (5.2) 1 (2.6) 1 (2.6) 1 (2.6)
Unknown, n (%)	2 (8.0)	0 (0.0)	2 (5.3)
At least one dose decrease, within 12 months post-index			
n (%)	21 (16.0)	7 (8.1)	28 (12.9)
Reason for dose decrease			
Lack of effectiveness, n (%)	1 (4.8)	0 (0.0)	1 (3.6)
Respiratory AE, n (%)	11 (52.4)	5 (71.4)	16 (57.1)
Gastro-intestinal AE, n (%)	1 (4.8)	1 (14.3)	2 (7.1)
Menstrual AE, n (%)	0 (0.0)	1 (14.3)	1 (3.6)
Other AE, n (%)	2 (9.5)	0 (0.0)	2 (7.1)
AE resolving, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
AE resolved, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Other reason, n (%) - Worsening symptoms - Lung transplant	3 (14.3) 1 (4.8) 2(9.5)	0 (0.0) 0 (0.0) 0 (0.0	3 (10.7) 1 (4.8) 2(9.5)
Unknown, n (%)	3 (14.3)	0 (0.0)	3 (10.7)
At least one dose interruption, within 12 months post-index			

ORKAMBI® Dose Adjustment	Initiation Cohort		
	Early-patient N=131	Late-patient N=86*	Overall N=217*
n (%)	12 (9.2)	2 (2.3)	14 (6.5)
Reason for dose interruption			
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	7 (58.3)	0 (0.0)	7 (50.0)
Gastro-intestinal AE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Other AE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
AE resolving, n (%)	1 (8.3)	0 (0.0)	1 (7.1)
AE resolved, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Other reason, n (%) - Rash - Elevated CK - Severe chest tightness and shortness of breath - Pulmonary exacerbation	4 (33.3) 1 (8.3) 1(8.3) 1(8.3)	2 (100.0) 1 (50)	6 (42.9) 1 (7.2) 1 (7.2) 1 (7.2) 1 (7.2)
Unknown, n (%)	0 (0.0)	0 (0.0)	0 (0.0)

-All Subjects Set: All the subjects selected to take part in the retrospective study and who meet all eligibility criteria
-N: Number of subjects in the All Subjects Set; n (%): number and percentage of subjects
-Percentages are calculated relative to the number of subjects who recorded the event within the relevant sub-population (presented in the first row of each listed event).
- An ORKAMBI® dose adjustment is either an increase, a decrease, or an interruption of the dose.

- Dose adjustment reason counts for the types of adjustments are patient counts i.e. a patient can have more than one adjustment and if the reason is the same then that patient is only counted once in the aggregate section.

*One subject in the late initiation cohort did not have available finalized data on ORKAMBI dose adjustment and was excluded from this table.

Source: Table 13 (main document)

Table 8: Descriptive summary of Orkambi dose adjustments within12 months post-Orkambi initiation, by age groups, overall all subjects set

ORKAMBI Dose Adjustment	Overall 12 to < 18 N=30	Overall >=18 N=188
Patients with an ORKAMBI dose adjustment during the 12-months post-index period (increase, decrease and/or interruption)		
No adjustment, n (%)	26 (86.7)	141 (75.4)
One adjustment, n (%)	0 (0.0)	21 (11.2)
Two adjustments, n (%)	4 (13.3)	15 (8.0)
At least 3 adjustments, n (%)	0 (0.0)	10 (5.3)
Reasons for dose adjustment		
Lack of effectiveness, n (%)	0 (0.0)	1 (2.2)
Respiratory AE, n (%)	0 (0.0)	10 (21.7)
Gastro-intestinal AE, n (%)	0 (0.0)	1 (2.2)
Menstrual AE, n (%)	1 (25.0)	0 (0.0)
Other AE, n (%)	0 (0.0)	2 (4.3)
AE resolving, n (%)	1 (25.0)	3 (6.5)
AE resolved, n (%)	0 (0.0)	8 (17.4)
Other reason, n (%)	1 (25.0)	19 (41.3)
Unknown, n (%)	1 (25.0)	2 (4.3)
Patients with at least one ORKAMBI dose increase during the 12-months post-index period		
n (%)	4 (13.3)	34 (18.2)
Reasons for dose increase		
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	0 (0.0)	1 (2.9)
Gastro-intestinal AE, n (%)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	1 (25.0)	0 (0.0)
Other AE, n (%)	0 (0.0)	1 (2.9)
AE resolving, n (%)	1 (25.0)	4 (11.8)
AE resolved, n (%)	0 (0.0)	8 (23.5)
Other reason, n (%)	1 (25.0)	19 (55.9)
Unknown, n (%)	1 (25.0)	1 (2.9)
Patients with at least one ORKAMBI dose decrease during the 12-months post-index period		
n (%)	2 (6.7)	26 (13.9)
Reasons for dose decrease		
Lack of effectiveness, n (%)	0 (0.0)	1 (3.8)
Respiratory AE, n (%)	0 (0.0)	16 (61.5)
Gastro-intestinal AE, n (%)	0 (0.0)	2 (7.7)
Menstrual AE, n (%)	1 (50.0)	0 (0.0)
Other AE, n (%)	0 (0.0)	2 (7.7)
AE resolving, n (%)	0 (0.0)	0 (0.0)
AE resolved, n (%)	0 (0.0)	0 (0.0)
Other reason, n (%)	0 (0.0)	3 (11.5)
Unknown, n (%)	1 (50.0)	2 (7.7)
Patients with at least one ORKAMBI dose interruption during the 12-months post-index period		
n (%)	2 (6.7)	12 (6.4)
Reasons for dose interruption		
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	0 (0.0)	7 (58.3)
Gastro-intestinal AE, n (%)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)
Other AE, n (%)	0 (0.0)	0 (0.0)
AE resolving, n (%)	0 (0.0)	1 (8.3)
AE resolved, n (%)	0 (0.0)	0 (0.0)
Other reason, n (%)	2 (100.0)	4 (33.3)
Unknown, n (%)	0 (0.0)	0 (0.0)
Number of patients who discontinued after index event, n	8	67

	Overall	
ORKAMBI Dose Adjustment	12 to < 18 N=30	>=18 N=188
Patients with an ORKAMBI dose adjustment from index event to first discontinuation (increase, decrease and/or interruption) within patients who discontinued		
No adjustment, n (%)	7 (87.5)	45 (67.2)
One adjustment, n (%)	0 (0.0)	9 (13.4)
Two adjustments, n (%)	1 (12.5)	9 (13.4)
At least 3 adjustments, n (%)	0 (0.0)	4 (6.0)
Reasons for dose adjustment		
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	0 (0.0)	8 (36.4)
Gastro-intestinal AE, n (%)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)
Other AE, n (%)	0 (0.0)	2 (9.1)
AE resolving, n (%)	0 (0.0)	2 (9.1)
AE resolved, n (%)	0 (0.0)	2 (9.1)
Other reason, n (%)	1 (100.0)	6 (27.3)
Unknown, n (%)	0 (0.0)	2 (9.1)
Patients with at least one ORKAMBI dose increase from index event to first discontinuation within patients who discontinued		
n (%)	1 (12.5)	15 (22.4)
Reasons for dose increase		
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	0 (0.0)	1 (6.7)
Gastro-intestinal AE, n (%)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)
Other AE, n (%)	0 (0.0)	1 (6.7)
AE resolving, n (%)	0 (0.0)	3 (20.0)
AE resolved, n (%)	0 (0.0)	2 (13.3)
Other reason, n (%)	1 (100.0)	7 (46.7)
Unknown, n (%)	0 (0.0)	1 (6.7)
Patients with at least one ORKAMBI dose decrease from index event to first discontinuation within patients who discontinued		
n (%)	0 (0.0)	14 (20.9)
Reasons for dose decrease		
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	0 (0.0)	10 (71.4)
Gastro-intestinal AE, n (%)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)
Other AE, n (%)	0 (0.0)	1 (7.1)
AE resolving, n (%)	0 (0.0)	0 (0.0)
AE resolved, n (%)	0 (0.0)	0 (0.0)
Other reason, n (%)	0 (0.0)	1 (7.1)
Unknown, n (%)	0 (0.0)	2 (14.3)
Patients with at least one ORKAMBI dose interruption from index event to first discontinuation within patients who discontinued		
n (%)	1 (12.5)	7 (10.4)
Reasons for dose interruption		
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	0 (0.0)	3 (42.9)
Gastro-intestinal AE, n (%)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)
Other AE, n (%)	0 (0.0)	0 (0.0)
AE resolving, n (%)	0 (0.0)	1 (14.3)
AE resolved, n (%)	0 (0.0)	0 (0.0)
Other reason, n (%)	1 (100.0)	3 (42.9)

ORKAMBI Dose Adjustment	Overall 12 to < 18 N=30	Overall >=18 N=188
Unknown, n (%)	0 (0.0)	0 (0.0)
Number of patients who discontinued after first re-initiation, n	1	5
Patients with an ORKAMBI dose adjustment from first re-initiation to second discontinuation (increase, decrease and/or interruption) within patients who discontinued after re-initiation		
No adjustment, n (%)	1 (100.0)	4 (80.0)
One adjustment, n (%)	0 (0.0)	1 (20.0)
Two adjustments, n (%)	0 (0.0)	0 (0.0)
At least 3 adjustments, n (%)	0 (0.0)	0 (0.0)
Reasons for dose adjustment		
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	0 (0.0)	1 (100.0)
Gastro-intestinal AE, n (%)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)
Other AE, n (%)	0 (0.0)	0 (0.0)
AE resolving, n (%)	0 (0.0)	0 (0.0)
AE resolved, n (%)	0 (0.0)	0 (0.0)
Other reason, n (%)	0 (0.0)	0 (0.0)
Unknown, n (%)	0 (0.0)	0 (0.0)
Patients with at least one ORKAMBI dose increase from first re-initiation to second discontinuation within patients who discontinued after re-initiation		
n (%)	0 (0.0)	0 (0.0)
Reasons for dose increase		
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	0 (0.0)	0 (0.0)
Gastro-intestinal AE, n (%)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)
Other AE, n (%)	0 (0.0)	0 (0.0)
AE resolving, n (%)	0 (0.0)	0 (0.0)
AE resolved, n (%)	0 (0.0)	0 (0.0)
Other reason, n (%)	0 (0.0)	0 (0.0)
Unknown, n (%)	0 (0.0)	0 (0.0)
Patients with at least one ORKAMBI dose decrease from first re-initiation to second discontinuation within patients who discontinued after re-initiation		
n (%)	0 (0.0)	1 (20.0)
Reasons for dose decrease		
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	0 (0.0)	1 (100.0)
Gastro-intestinal AE, n (%)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)
Other AE, n (%)	0 (0.0)	0 (0.0)
AE resolving, n (%)	0 (0.0)	0 (0.0)
AE resolved, n (%)	0 (0.0)	0 (0.0)
Other reason, n (%)	0 (0.0)	0 (0.0)
Unknown, n (%)	0 (0.0)	0 (0.0)
Patients with at least one ORKAMBI dose interruption from first re-initiation to second discontinuation within patients who discontinued after re-initiation		
n (%)	0 (0.0)	0 (0.0)
Reasons for dose interruption		
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	0 (0.0)	0 (0.0)

	Overall	
ORKAMBI Dose Adjustment	12 to < 18 N=30	>=18 N=188
Gastro-intestinal AE, n (%)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)
Other AE, n (%)	0 (0.0)	0 (0.0)
AE resolving, n (%)	0 (0.0)	0 (0.0)
AE resolved, n (%)	0 (0.0)	0 (0.0)
Other reason, n (%)	0 (0.0)	0 (0.0)
Unknown, n (%)	0 (0.0)	0 (0.0)

Footnotes:
-All Subjects Set: All the subjects selected to take part in the retrospective study and who meet all eligibility criteria.
-N: Number of subjects in the All Subjects Set; n(%): number and percentage of subjects.
-Percentages are first calculated relative to the number of subjects (N) in the relevant population or sub-population, then using for the denominator the total number of subjects who discontinued after first initiation in the relevant population or sub-population, and so on. A subject could contribute to more than one reason for dose adjustments.
-An ORKAMBI dose adjustment is either an increase, a decrease or an interruption of the dose.
-One subject in the >= 18 sub-group did not have available finalized data on ORKAMBI dose adjustment.

Table 9: Descriptive summary of Orkambi dose adjustments within12 months post-Orkambi initiation, by starting dose, by age groups, overall all subjects set

	Overall	
ORKAMBI Dose Adjustment	12 to <18 N=30	>=18 N=188
Patients who started on full dose and had at least one ORKAMBI dose decrease during the 12-months post-index period	1 (3.3)	24 (12.8)
Reasons for dose decrease		
Lack of effectiveness, n (%)	0 (0.0)	1 (4.2)
Respiratory AE, n (%)	0 (0.0)	16 (66.7)
Gastro-intestinal AE, n (%)	0 (0.0)	2 (8.3)
Menstrual AE, n (%)	1 (100.0)	0 (0.0)
Other AE, n (%)	0 (0.0)	1 (4.2)
AE resolving, n (%)	0 (0.0)	0 (0.0)
AE resolved, n (%)	0 (0.0)	0 (0.0)
Other reason, n (%)	0 (0.0)	2 (8.3)
Unknown, n (%)	0 (0.0)	2 (8.3)
Patients who started on reduced dose and had at least one ORKAMBI dose increase during the 12-months post-index period	1 (3.3)	13 (7.0)
Reasons for dose increase		
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	0 (0.0)	0 (0.0)
Gastro-intestinal AE, n (%)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)
Other AE, n (%)	0 (0.0)	1 (7.7)
AE resolving, n (%)	0 (0.0)	1 (7.7)
AE resolved, n (%)	0 (0.0)	1 (7.7)
Other reason, n (%)	0 (0.0)	10 (76.9)
Unknown, n (%)	1 (100.0)	0 (0.0)
Number of patients who discontinued after index event, n	8	67
Patients who started on full dose and had at least one ORKAMBI dose decrease from index event to first discontinuation within patients who discontinued	0 (0.0)	13 (19.4)
Reasons for dose decrease		
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	0 (0.0)	10 (76.9)
Gastro-intestinal AE, n (%)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)
Other AE, n (%)	0 (0.0)	1 (7.7)
AE resolving, n (%)	0 (0.0)	0 (0.0)
AE resolved, n (%)	0 (0.0)	0 (0.0)
Other reason, n (%)	0 (0.0)	0 (0.0)
Unknown, n (%)	0 (0.0)	2 (15.4)
Patients who started on reduced dose and had at least one ORKAMBI dose increase from index event to first discontinuation within patients who discontinued	0 (0.0)	3 (4.5)
Reasons for dose increase		
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	0 (0.0)	0 (0.0)
Gastro-intestinal AE, n (%)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)
Other AE, n (%)	0 (0.0)	1 (33.3)
AE resolving, n (%)	0 (0.0)	1 (33.3)
AE resolved, n (%)	0 (0.0)	0 (0.0)
Other reason, n (%)	0 (0.0)	1 (33.3)
Unknown, n (%)	0 (0.0)	0 (0.0)
Number of patients who discontinued after first re-initiation, n	1	5

ORKAMBI Dose Adjustment	Overall 12 to <18 N=30	Overall >=18 N=188
Patients who re-initiated on full dose and had at least one ORKAMBI dose decrease from first re-initiation to second discontinuation within patients who discontinued after re-initiation	0 (0.0)	1 (20.0)
Reasons for dose decrease		
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	0 (0.0)	1 (100.0)
Gastro-intestinal AE, n (%)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)
Other AE, n (%)	0 (0.0)	0 (0.0)
AE resolving, n (%)	0 (0.0)	0 (0.0)
AE resolved, n (%)	0 (0.0)	0 (0.0)
Other reason, n (%)	0 (0.0)	0 (0.0)
Unknown, n (%)	0 (0.0)	0 (0.0)
Patients who re-initiated on reduced dose and had at least one ORKAMBI dose increase from first re-initiation to second discontinuation within patients who discontinued after re-initiation	0 (0.0)	0 (0.0)
Reasons for dose increase		
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	0 (0.0)	0 (0.0)
Gastro-intestinal AE, n (%)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)
Other AE, n (%)	0 (0.0)	0 (0.0)
AE resolving, n (%)	0 (0.0)	0 (0.0)
AE resolved, n (%)	0 (0.0)	0 (0.0)
Other reason, n (%)	0 (0.0)	0 (0.0)
Unknown, n (%)	0 (0.0)	0 (0.0)

Footnotes:
-All Subjects Set: All the subjects selected to take part in the retrospective study and who meet all eligibility criteria.
-N: Number of subjects in the All Subjects Set; n(%): number and percentage of subjects; AE: Adverse event.
-Percentages are first calculated relative to the number of subjects (N) in the relevant population or sub-population, then using for the denominator the total number of subjects who discontinued after first initiation in the relevant population or sub-population, and so on.
-A subject could contribute to more than one reason for dose adjustments.
-An ORKAMBI dose adjustment is either an increase, a decrease or an interruption of the dose.
-One subject in the >=18 sub-group did not have available finalized data on ORKAMBI dose adjustment.

CHMP comment

Among the 30 paediatric subjects enrolled in the Study, 26 experienced no dose adjustment during the 12 months post-index period. 4 subjects experienced two dose adjustments, due to the followings (1 each): menstrual AE, AE resolving, other reason, unknown.

4 paediatric subjects experienced at least one dose increased; 2 subjects experienced at least one dose decreased, and 2 subjects had at least one Orkambi dose interruption.

8/ 30 (26.7%) paediatric subjects discontinued after index event: of these, 7/8 did not experience any Orkambi dose adjustment prior to discontinuation, 1 subject experienced at least 1 dose increase and one subject dose interruption.

One paediatric subject discontinued after first re-initiation.

ORKAMBI Treatment Duration

Table 10: Descriptive summary of Orkambi treatment duration within12 months post-Orkambi initiation, by age groups, overall all subjects set

ORKAMBI Treatment Duration		Overall 12 to <18 N=30	Overall >=18 N=188
Number of Days on Treatment, over the 12-months analysis period			
	n	30	187
	Mean	317.1	278.2
	SD	97.99	137.05
	Median	365.0	365.0
	IQR	335.0, 365.0	182.0, 365.0
	Minimum	58.0	1.0
	Maximum	365.0	365.0
Percentage of Time the Patient was on Treatment, over the 12-months analysis period			
	n	30	187
	Mean	86.9	76.4
	SD	26.85	37.56
	Median	100.0	100.0
	IQR	91.8, 100.0	49.9, 100.0
	Minimum	15.9	0.3
	Maximum	100.0	100.0
Number of Days on Treatment, First Initiation			
	n	30	187
	Mean	298.0	273.8
	SD	119.37	141.51
	Median	365.0	365.0
	IQR	279.0, 365.0	156.0, 365.0
	Minimum	24.0	1.0
	Maximum	365.0	365.0
Number of Days on Treatment, Second Initiation			
	n	3	7
	Mean	191.7	119.3
	SD	158.18	116.11
	Median	253.0	79.0
	IQR	12.0, 310.0	8.0, 232.0
	Minimum	12.0	3.0
	Maximum	310.0	279.0

Footnotes:
-All Subjects Set: All the subjects selected to take part in the retrospective study and who meet all eligibility criteria.
-N: Number of subjects in the All Subjects Set;
Number of days on treatment, over the 12-months analysis period, was calculated regardless of whether patients had dose changes or interruptions.
-Duration of first use was calculated from index date until first discontinuation date or end of follow-up date as applicable i.e. 12 months after subjects's index date, regardless of changes in dose or interruptions.
Duration of second use was calculated from the re-initiation date to second discontinuation date or end of follow-up date as applicable.
-One subject in the >=18 sub-group with unknown discontinuation status was excluded from this table.
Abbreviations: IQR = interquartile range; SD = standard deviation

CHMP comment

Among the 30 paediatric subjects, the mean number of days on treatment, over the 12 months analysis period, was 317.1.

ORKAMBI Treatment Discontinuation and Reinitiation

Table 11. ORKAMBI Treatment Discontinuation and Reinitiation(s) within 12 Months Post--ORKAMBI Initiation, Overall and by Initiation Cohorts

ORKAMBI® Treatment Discontinuation and Reinitiation	Initiation Cohort		
	Early-patient N=131	Late-patient N=86*	Overall N=217*
Patients who discontinued following first initiation			
n (%)	53 (40.5)	22 (25.6)	75 (34.6)
Reasons for discontinuation			
Lack of effectiveness, n (%)	5 (9.4)	0 (0.0)	5 (6.7)
Respiratory AE, n (%)	28 (52.8)	11 (50.0)	39 (52.0)
Gastrointestinal AE, n (%)	1 (1.9)	1 (4.5)	2 (2.7)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Other AE, n (%)	5 (9.4)	4 (18.2)	9 (12.0)
Other reason, n (%)	13 (24.5)	4 (18.2)	17 (22.7)
Unknown, n (%)	1 (1.9)	2 (9.1)	3 (4.0)
Patients who reinitiated following first discontinuation			
n (%)	4 (7.5)	6 (27.3)	10 (13.3)
Reasons for previous (first) discontinuation			
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	2 (50.0)	3 (50.0)	5 (50.0)
Gastrointestinal AE, n (%)	1 (25.0)	0 (0.0)	1 (10.0)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Other AE, n (%)	1 (25.0)	1 (16.7)	2 (20.0)
Other reason, n (%)	0 (0.0)	2 (33.3)	2 (20.0)
Unknown, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Patients who discontinued following second initiation			
n (%)	2 (50.0)	4 (66.7)	6 (60.0)
Reasons for second discontinuation			
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	1 (50.0)	2 (50.0)	3 (50.0)
Gastrointestinal AE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Other AE, n (%)	1 (50.0)	0 (0.0)	1 (16.7)
Other reason, n (%)	0 (0.0)	2 (50.0)	2 (33.3)
Unknown, n (%)	0 (0.0)	0 (0.0)	0 (0.0)

-All Subjects Set: All the subjects selected to take part in the retrospective study and who meet all eligibility criteria
-N: Number of subjects in the All Subjects Set; n(%): number and percentage of subjects
-The percentage of patients who discontinued after first (second, etc.) initiation, listed by reasons, was calculated using for the denominator the number of subjects who discontinued after first (second, etc.) initiation in the relevant population or sub-population.
-The percentage of patients who reinitiated after first (second) discontinuation was calculated using for the denominator the number of subjects who discontinued following first (second, etc.) initiation in the relevant population or sub-population.
*One subject in the Late Patient Initiation Cohort with unknown discontinuation status was excluded from this table.
Abbreviation: AE = adverse event

Source: Table 42 (main document)

Table 12: Descriptive summary of Orkambi treatment discontinuation and re-initiation within 12 months post-Orkambi initiation, by age groups, within initiation groups all subjects set

	Initiation Group			
	Early-patient		Late-patient	
ORKAMBI Treatment Discontinuation and Re-initiation	12 to <18 N=17	>=18 N=114	12 to <18 N=13	>=18 N=74
Patients who discontinued following first initiation, n (%)	4 (23.5)	49 (43.0)	4 (30.8)	18 (24.7)
Reasons for discontinuation				
Lack of effectiveness, n (%)	1 (25.0)	4 (8.2)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	0 (0.0)	28 (57.1)	0 (0.0)	11 (61.1)
Gastro-intestinal AE, n (%)	1 (25.0)	0 (0.0)	0 (0.0)	1 (5.6)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other AE, n (%)	1 (25.0)	4 (8.2)	3 (75.0)	1 (5.6)
Other reason, n (%)	1 (25.0)	12 (24.5)	1 (25.0)	3 (16.7)
Unknown, n (%)	0 (0.0)	1 (2.0)	0 (0.0)	2 (11.1)
Patients who re-initiated following first discontinuation, n (%)	2 (50.0)	2 (4.1)	1 (25.0)	5 (27.8)
Reasons for previous discontinuation				
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	0 (0.0)	2 (100.0)	0 (0.0)	3 (60.0)
Gastro-intestinal AE, n (%)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other AE, n (%)	1 (50.0)	0 (0.0)	1 (100.0)	0 (0.0)
Other reason, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)
Unknown, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients who discontinued following second initiation, n (%)	1 (50.0)	1 (50.0)	0 (0.0)	4 (80.0)
Reasons for discontinuation				
Lack of effectiveness, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory AE, n (%)	0 (0.0)	1 (100.0)	0 (0.0)	2 (50.0)
Gastro-intestinal AE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Menstrual AE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other AE, n (%)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other reason, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)
Unknown, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

-All Subjects Set: All the subjects selected to take part in the retrospective study and who meet all eligibility criteria.
-N: Number of subjects in the All Subjects Set; n(%): number and percentage of subjects; AE: Adverse event.
-The percentage of patients who discontinued after first (second…) initiation, listed by reasons, was calculated using for the denominator the number of subjects who discontinued after first (second…) initiation in the relevant population or sub-population.
-The percentage of patients who re-initiated after first (second) discontinuation was calculated using for the denominator the number of subjects who discontinued following first (second....) initiation in the relevant population or sub-population.
The percentage of patients who re-initiated after first (second) discontinuation, listed by reasons for previous discontinuation, was calculated using for the denominator the number of subjects who re-initiated after first (second) discontinuation in the relevant population or sub-population.
-One subject in the Late Patient Initiation and >=18 sub-group with unknown discontinuation status was excluded from this table.
Abbreviation: Ae = adverse event; $ppFEV_1$ = percent predicted forced expiratory volume in one second

Table 13: Descriptive summary of time to first treatment discontinuation of Orkambi treatment within 12 months post-Orkambi initiation, by age groups, overall all subjects set

All Subjects Set

	Overall	
	12 to <18	>=18
ORKAMBI Treatment First Discontinuation	N=30	N=188
Patients who discontinued treatment due to any reason		
Any time after treatment initiation, n (%)	8 (26.7)	67 (35.8)
In the first month, n (%)	1 (12.5)	25 (37.3)
In the second month, n (%)	1 (12.5)	8 (11.9)
In the third month, n (%)	1 (12.5)	6 (9.0)
In the fourth month, n (%)	3 (37.5)	3 (4.5)
In the fifth month, n (%)	0 (0.0)	3 (4.5)
In the sixth month, n (%)	1 (12.5)	6 (9.0)
In the seventh month, n (%)	0 (0.0)	5 (7.5)
In the eighth month, n (%)	0 (0.0)	1 (1.5)
In the ninth month, n (%)	0 (0.0)	1 (1.5)
In the tenth month, n (%)	1 (12.5)	0 (0.0)
In the eleventh month, n (%)	0 (0.0)	2 (3.0)
In the twelfth month, n (%)	0 (0.0)	7 (10.4)
Cumulative within the first two months, n (%)	2 (25.0)	33 (49.3)
Cumulative within the first three months, n (%)	3 (37.5)	39 (58.2)
Cumulative within the first four months, n (%)	6 (75.0)	42 (62.7)
Cumulative within the first five months, n (%)	6 (75.0)	45 (67.2)
Cumulative within the first six months, n (%)	7 (87.5)	51 (76.1)
Cumulative within the first seven months, n (%)	7 (87.5)	56 (83.6)
Cumulative within the first eight months, n (%)	7 (87.5)	57 (85.1)
Cumulative within the first nine months, n (%)	7 (87.5)	58 (86.6)
Cumulative within the first ten months, n (%)	8 (100.0)	58 (86.6)
Cumulative within the first eleven months, n (%)	8 (100.0)	60 (89.6)
Cumulative within the first twelve months, n (%)	8 (100.0)	67 (100.0)
Time to discontinuation due to any reason, in days		
n	8	67
Mean	113.6	110.4
SD	77.97	119.18
Median	94.5	67.0
IQR	70.0, 138.5	9.0, 182.0
Minimum	24.0	1.0
Maximum	279.0	365.0
Patients who discontinued treatment due to respiratory AEs		
Any time after treatment initiation, n (%)	0 (0.0)	39 (20.9)
In the first month, n (%)	0 (0.0)	20 (51.3)
In the second month, n (%)	0 (0.0)	4 (10.3)
In the third month, n (%)	0 (0.0)	4 (10.3)
In the fourth month, n (%)	0 (0.0)	1 (2.6)
In the fifth month, n (%)	0 (0.0)	3 (7.7)
In the sixth month, n (%)	0 (0.0)	4 (10.3)
In the seventh month, n (%)	0 (0.0)	1 (2.6)
In the eighth month, n (%)	0 (0.0)	0 (0.0)
In the ninth month, n (%)	0 (0.0)	1 (2.6)
In the tenth month, n (%)	0 (0.0)	0 (0.0)
In the eleventh month, n (%)	0 (0.0)	0 (0.0)
In the twelfth month, n (%)	0 (0.0)	1 (2.6)
Cumulative within the first two months, n (%)	0 (0.0)	24 (61.5)
Cumulative within the first three months, n (%)	0 (0.0)	28 (71.8)
Cumulative within the first four months, n (%)	0 (0.0)	29 (74.4)
Cumulative within the first five months, n (%)	0 (0.0)	32 (82.1)
Cumulative within the first six months, n (%)	0 (0.0)	36 (92.3)
Cumulative within the first seven months, n (%)	0 (0.0)	37 (94.9)
Cumulative within the first eight months, n (%)	0 (0.0)	37 (94.9)
Cumulative within the first nine months, n (%)	0 (0.0)	38 (97.4)
Cumulative within the first ten months, n (%)	0 (0.0)	38 (97.4)
Cumulative within the first eleven months, n (%)	0 (0.0)	38 (97.4)
Cumulative within the first twelve months, n (%)	0 (0.0)	39 (100.0)

ORKAMBI Treatment First Discontinuation	Overall 12 to <18 N=30	Overall >=18 N=188
Time to discontinuation due to respiratory AEs, in days		
n	0	39
Mean	NA	69.1
SD	NA	85.37
Median	NA	29.0
IQR	NA	4.0, 127.0
Minimum	NA	1.0
Maximum	NA	365.0
Among the sub-population of patients who discontinued, n	8	67
Patients who discontinued treatment due to respiratory AEs		
Any time after treatment initiation, n (%)	0 (0.0)	39 (58.2)
In the first month, n (%)	0 (0.0)	20 (51.3)
In the second month, n (%)	0 (0.0)	4 (10.3)
In the third month, n (%)	0 (0.0)	4 (10.3)
In the fourth month, n (%)	0 (0.0)	1 (2.6)
In the fifth month, n (%)	0 (0.0)	3 (7.7)
In the sixth month, n (%)	0 (0.0)	4 (10.3)
In the seventh month, n (%)	0 (0.0)	1 (2.6)
In the eighth month, n (%)	0 (0.0)	0 (0.0)
In the ninth month, n (%)	0 (0.0)	1 (2.6)
In the tenth month, n (%)	0 (0.0)	0 (0.0)
In the eleventh month, n (%)	0 (0.0)	0 (0.0)
In the twelfth month, n (%)	0 (0.0)	1 (2.6)
Cumulative within the first two months, n (%)	0 (0.0)	24 (61.5)
Cumulative within the first three months, n (%)	0 (0.0)	28 (71.8)
Cumulative within the first four months, n (%)	0 (0.0)	29 (74.4)
Cumulative within the first five months, n (%)	0 (0.0)	32 (82.1)
Cumulative within the first six months, n (%)	0 (0.0)	36 (92.3)
Cumulative within the first seven months, n (%)	0 (0.0)	37 (94.9)
Cumulative within the first eight months, n (%)	0 (0.0)	37 (94.9)
Cumulative within the first nine months, n (%)	0 (0.0)	38 (97.4)
Cumulative within the first ten months, n (%)	0 (0.0)	38 (97.4)
Cumulative within the first eleven months, n (%)	0 (0.0)	38 (97.4)
Cumulative within the first twelve months, n (%)	0 (0.0)	39 (100.0)

Footnotes:
-All Subjects Set: All the subjects selected to take part in the retrospective study and who meet all eligibility criteria.
-N: Number of subjects in the All Subjects Set; n(%): number and percentage of subjects;
-The percentage of patients who discontinued treatment due to any reason was calculated using for the denominator the total number of subjects (N) in the relevant population or sub-population.
-*The percentage of patients who discontinued treatment due to respiratory AEs was calculated twice, first using for the denominator the total number of subjects (N) in the relevant population or sub-population, then using for the denominator the total number of subjects who discontinued in the relevant population or sub-population.
-Time to discontinuation was based on the subset of subjects who discontinued due to any reason or due to Respiratory AEs, as applicable, within the relevant population or sub-population.
-One subject in the >=18 sub-group with unknown discontinuation status was excluded from this table.
Abbreviations: AE = adverse event; IQR = interquartile range; SD = standard deviation.

Table 14: Descriptive summary of time to first treatment discontinuation of Orkambi treatment within 12 months post-Orkambi initiation, by age groups, within initiation groups all subjects set

	Initiation Group			
	Early-patient		Late-patient	
ORKAMBI Treatment First Discontinuation	12 to <18 N=17	>=18 N=114	12 to <18 N=13	>=18 N=74
'atients who discontinued treatment due to any reason				
Any time after treatment initiation, n (%)	4 (23.5)	49 (43.0)	4 (30.8)	18 (24.7)
In the first month, n (%)	0 (0.0)	14 (28.6)	1 (25.0)	11 (61.1)
In the second month, n (%)	1 (25.0)	7 (14.3)	0 (0.0)	1 (5.6)
In the third month, n (%)	1 (25.0)	5 (10.2)	0 (0.0)	1 (5.6)
In the fourth month, n (%)	2 (50.0)	2 (4.1)	1 (25.0)	1 (5.6)
In the fifth month, n (%)	0 (0.0)	2 (4.1)	0 (0.0)	1 (5.6)
In the sixth month, n (%)	0 (0.0)	6 (12.2)	1 (25.0)	0 (0.0)
In the seventh month, n (%)	0 (0.0)	3 (6.1)	0 (0.0)	2 (11.1)
In the eighth month, n (%)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)
In the ninth month, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)
In the tenth month, n (%)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)
In the eleventh month, n (%)	0 (0.0)	2 (4.1)	0 (0.0)	0 (0.0)
In the twelfth month, n (%)	0 (0.0)	7 (14.3)	0 (0.0)	0 (0.0)
Cumulative within the first two months, n (%)	1 (25.0)	21 (42.9)	1 (25.0)	12 (66.7)
Cumulative within the first three months, n (%)	2 (50.0)	26 (53.1)	1 (25.0)	13 (72.2)
Cumulative within the first four months, n (%)	4 (100.0)	28 (57.1)	2 (50.0)	14 (77.8)
Cumulative within the first five months, n (%)	4 (100.0)	30 (61.2)	2 (50.0)	15 (83.3)
Cumulative within the first six months, n (%)	4 (100.0)	36 (73.5)	3 (75.0)	15 (83.3)
Cumulative within the first seven months, n (%)	4 (100.0)	39 (79.6)	3 (75.0)	17 (94.4)
Cumulative within the first eight months, n (%)	4 (100.0)	40 (81.6)	3 (75.0)	17 (94.4)
Cumulative within the first nine months, n (%)	4 (100.0)	40 (81.6)	3 (75.0)	18 (100.0)
Cumulative within the first ten months, n (%)	4 (100.0)	40 (81.6)	4 (100.0)	18 (100.0)
Cumulative within the first eleven months, n (%)	4 (100.0)	42 (85.7)	4 (100.0)	18 (100.0)
Cumulative within the first twelve months, n (%)	4 (100.0)	49 (100.0)	4 (100.0)	18 (100.0)
Time to discontinuation due to any reason, in days				
n	4	49	4	18
Mean	87.5	128.6	139.8	60.8
SD	23.90	125.53	108.59	84.19
Median	88.5	85.0	128.0	9.5
IQR	70.0, 105.0	28.0, 188.0	59.0, 220.5	3.0, 97.0
Minimum	58.0	1.0	24.0	1.0
Maximum	115.0	365.0	279.0	253.0
'atients who discontinued treatment due to respiratory AEs				
Any time after treatment initiation, n (%)	0 (0.0)	28 (24.6)	0 (0.0)	11 (15.1)
In the first month, n (%)	0 (0.0)	12 (42.9)	0 (0.0)	8 (72.7)
In the second month, n (%)	0 (0.0)	3 (10.7)	0 (0.0)	1 (9.1)
In the third month, n (%)	0 (0.0)	4 (14.3)	0 (0.0)	0 (0.0)
In the fourth month, n (%)	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)
In the fifth month, n (%)	0 (0.0)	2 (7.1)	0 (0.0)	1 (9.1)
In the sixth month, n (%)	0 (0.0)	4 (14.3)	0 (0.0)	0 (0.0)
In the seventh month, n (%)	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)
In the eighth month, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
In the ninth month, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
In the tenth month, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
In the eleventh month, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
In the twelfth month, n (%)	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)
Cumulative within the first two months, n (%)	0 (0.0)	15 (53.6)	0 (0.0)	9 (81.8)
Cumulative within the first three months, n (%)	0 (0.0)	19 (67.9)	0 (0.0)	9 (81.8)
Cumulative within the first four months, n (%)	0 (0.0)	20 (71.4)	0 (0.0)	9 (81.8)
Cumulative within the first five months, n (%)	0 (0.0)	22 (78.6)	0 (0.0)	10 (90.9)
Cumulative within the first six months, n (%)	0 (0.0)	26 (92.9)	0 (0.0)	10 (90.9)
Cumulative within the first seven months, n (%)	0 (0.0)	27 (96.4)	0 (0.0)	10 (90.9)
Cumulative within the first eight months, n (%)	0 (0.0)	27 (96.4)	0 (0.0)	10 (90.9)
Cumulative within the first nine months, n (%)	0 (0.0)	27 (96.4)	0 (0.0)	11 (100.0)
Cumulative within the first ten months, n (%)	0 (0.0)	27 (96.4)	0 (0.0)	11 (100.0)
Cumulative within the first eleven months, n (%)	0 (0.0)	27 (96.4)	0 (0.0)	11 (100.0)
Cumulative within the first twelve months, n (%)	0 (0.0)	28 (100.0)	0 (0.0)	11 (100.0)

ORKAMBI Treatment First Discontinuation	Initiation Group: Early-patient 12 to <18 N=17	Early-patient >=18 N=114	Late-patient 12 to <18 N=13	Late-patient >=18 N=74
Time to discontinuation due to respiratory AEs, in days				
n	0	28	0	11
Mean	NA	78.4	NA	45.2
SD	NA	86.19	NA	82.25
Median	NA	48.0	NA	7.0
IQR	NA	12.5, 132.0	NA	2.0, 51.0
Minimum	NA	1.0	NA	1.0
Maximum	NA	365.0	NA	253.0
mong the sub-population of patients who discontinued, n	4	49	4	18
atients who discontinued treatment due to respiratory AEs				
Any time after treatment initiation, n (%)	0 (0.0)	28 (57.1)	0 (0.0)	11 (61.1)
In the first month, n (%)	0 (0.0)	12 (42.9)	0 (0.0)	8 (72.7)
In the second month, n (%)	0 (0.0)	3 (10.7)	0 (0.0)	1 (9.1)
In the third month, n (%)	0 (0.0)	4 (14.3)	0 (0.0)	0 (0.0)
In the fourth month, n (%)	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)
In the fifth month, n (%)	0 (0.0)	2 (7.1)	0 (0.0)	1 (9.1)
In the sixth month, n (%)	0 (0.0)	4 (14.3)	0 (0.0)	0 (0.0)
In the seventh month, n (%)	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)
In the eighth month, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
In the ninth month, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
In the tenth month, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
In the eleventh month, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
In the twelfth month, n (%)	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)
Cumulative within the first two months, n (%)	0 (0.0)	15 (53.6)	0 (0.0)	9 (81.8)
Cumulative within the first three months, n (%)	0 (0.0)	19 (67.9)	0 (0.0)	9 (81.8)
Cumulative within the first four months, n (%)	0 (0.0)	20 (71.4)	0 (0.0)	9 (81.8)
Cumulative within the first five months, n (%)	0 (0.0)	22 (78.6)	0 (0.0)	10 (90.9)
Cumulative within the first six months, n (%)	0 (0.0)	26 (92.9)	0 (0.0)	10 (90.9)
Cumulative within the first seven months, n (%)	0 (0.0)	27 (96.4)	0 (0.0)	10 (90.9)
Cumulative within the first eight months, n (%)	0 (0.0)	27 (96.4)	0 (0.0)	10 (90.9)
Cumulative within the first nine months, n (%)	0 (0.0)	27 (96.4)	0 (0.0)	11 (100.0)
Cumulative within the first ten months, n (%)	0 (0.0)	27 (96.4)	0 (0.0)	11 (100.0)
Cumulative within the first eleven months, n (%)	0 (0.0)	27 (96.4)	0 (0.0)	11 (100.0)
Cumulative within the first twelve months, n (%)	0 (0.0)	28 (100.0)	0 (0.0)	11 (100.0)

ootnotes:
All Subjects Set: All the subjects selected to take part in the retrospective study and who meet all eligibility criteria.
N: Number of subjects in the All Subjects Set; n(%): number and percentage of subjects;
The percentage of patients who discontinued treatment due to any reason was calculated using for the denominator the total number f subjects (N) in the relevant population or sub-population.
*The percentage of patients who discontinued treatment due to respiratory AEs was calculated twice, first using for the enominator the total number of subjects (N) in the relevant population or sub-population, then using for the denominator the total umber of subjects who discontinued in the relevant population or sub-population.
Time to discontinuation was based on the subset of subjects who discontinued due to any reason or due to Respiratory AEs, as pplicable, within the relevant population or sub-population.
One subject in the Late Patient Initiation and >=18 sub-group with unknown discontinuation status was excluded from this table.
bbreviations: AE = adverse event; IQR = interquartile range; SD = standard deviation.

CHMP comment

Among the 30 paediatrics patients, 4 early initiators and 4 late initiators (8/30, 26.7% overall) discontinued Orkambi following first initiation, due to the following reasons: lack of effectiveness 1 patient, Gastrointestinal AE 1 patient, other AE 4 patients and other reason 2 patients.

Among the 8 paediatric patients that discontinued Orkambi, 3 patients re-initiated Orkambi following the first discontinuation and one patient discontinued following second initiation.

In the majority of cases (6 out of 8, 75%), Orkambi was discontinued within four months of treatment initiation.

Efficacy results

ORKAMBI Effectiveness

In the overall study population, the following results were observed:

• **Spirometry:** The mean (SE) ppFEV1 value was 61.4 (1.77) at baseline. An absolute change of -0.4% (CI: -2.0, 1.3) was observed in ppFEV1 from baseline.

• **BMI:** The mean (SE) BMI was 21.2 (0.23) kg/m2 at baseline. An absolute change of 0.4 kg/m2 (CI: 0.2, 0.6) was observed in BMI from baseline.
• **PEx:** The annualized rate of PEx was reduced from 2.1 in the 12-month pre-index period to 1.9 in the 12-month post-index period. The percent of patients with at least 1 PEx event was 78.4% in the pre-index period versus 72.5% in the post-index period.

• **Healthcare Resource Utilization:** The percent of patients with at least 1 hospitalization was 61.0% in the pre-index period versus 54.1% in the post-index period. A change of -1.3 (2.8 pre-index vs. 1.6 post-index) was observed in the annualized rate of hospitalizations.
The mean (SD) number of acute antibiotic prescriptions per patient per year was 6.9 (7.2) in the 12-month pre-index period and 7.2 (8.76) in the 12-month post-index period. The percent of patients with at least 1 intravenous acute antibiotic was 61.5% in the pre-index period and 55.5% in the post-index period.

• **Cultures:** In the overall cohort, positive cultures for any mucoid or non-mucoid Pseudomonas Aeruginosa were detected in about two-thirds of patients (66.1%) before ORKAMBI initiation compared to 64.2% after ORKAMBI initiation.

• **Transplants:** Seven patients (3.2%) required at least one transplant after ORKAMBI initiation (all seven were lung transplants), of which 6 patients were early-initiators, compared to no patients requiring transplant prior to Orkambi initiation and 2 patients with unknown prior transplant before Orkambi initiation.

• **Deaths:** There were 2 (0.9%) deaths observed during the post-index period, of which 1 occurred while on ORKAMBI treatment with unknown cause.

CHMP comment:

Effectiveness study results stratified by age (12-<18 and ≥18) have not been provided.

Subgroup analyses in the paediatric patients (12-<18 years old) have been provided only for drug utilization data (frequencies of study discontinuation, re-initiation and dose adjustments).

Among the effectiveness variables collected in the study the following are considered of interest: Clinical outcomes (BMI, ppFEV1, weight, and PEx), Healthcare resource utilization (Inpatient hospitalizations; Outpatient visits, Acute antibiotic use including IV antibiotic, Other CF medications use); Other Outcomes [Microbiology: (e.g., Pseudomonas); Death; Transplantation].

The MAH is requested to submit descriptive data regarding Orkambi effectiveness in the subgroup of paediatric patients.

Assessment of results referred to adult patients is out of the scope of this submission.

Safety results

The aim of Study 117 was to evaluate treatment patterns, effectiveness and initiation experience. No safety data have been provided, apart from frequencies of discontinuations due to AEs (please refer to previous sections.)

2.3.3. Discussion on clinical aspects

The MAH states that According to Article 46 of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006, information on a paediatric study, a Multicenter, Retrospective, Real-World, Observational Study on Orkambi Use, completed on 20 October 2017 is being submitted. The study included 30 paediatric subjects (≥12 to <18 years old) out of 218 total subjects enrolled. The submission was received on 19 November 2019, thus not within 6 months of study completion, and therefore not in accordance with the regulation, that requires submission of study results within 6 months of study completion. Therefore, the PAM is not fulfilled.

The study was conducted at 8 US academic-based centres. Paediatric patients (n=30) were enrolled in four of the participating US sites.

Study 117 was designed to explore retrospective data from patients' medical records to assess real-world Orkambi initiation experience during July 2015 to December 2015 following the approval in CF F/F patients aged 12 years and older in the United States. The outcomes that were evaluated included treatment patterns (e.g., Orkambi discontinuation), demographic characteristics, resource utilization, and descriptive 12-month effectiveness.

Qualified staff at each site identified the medical records of all patients who were prescribed Orkambi at their site and met the eligibility criteria. Eligible patients had the date of their first filled Orkambi prescription (referred to hereafter as the "index date") within the case ascertainment period of 01 July 2015 through 31 December 2015. Within the 6-month case ascertainment period, patients were divided into the following 2 initiation cohorts, solely by Orkambi initiation date:

• Early initiators: index date between 01 July 2015 and 30 September 2015

• Late initiators: index date between 01 October 2015 and 31 December 2015

The analysis period for each patient consists of a pre-index period of at least 12 months and a post-index period of at least 12 months.

A total of 218 patients who met all eligibility criteria were included in the study (N= 131 early and N= 87 late patients initiators), therefore a balanced representation of cases within the two groups was not fully achieved. The MAH identified in the market access (most patients received ORKAMBI within the first three months post-market uptake vs. three to six months post-market uptake) the main reason of having a lower number of available late-initiators patients as compared to early-initiators.

Orkambi was prescribed by each patient's physician in accordance with the US Prescribing Information (USPI) and as part of routine clinical care. Per the Orkambi US and EU Product Information, the dosing regimen for CF patients who are homozygous for F508del and aged 12 years and older is 2 tablets (each containing LUM 200 mg/IVA 125 mg) taken orally every 12 hours (q12h).

The analyses were only descriptive, in line with the study objectives.

Out of 218 patients enrolled in Study 117, only 30 (13.8%) were paediatric patients 12-<18 years of age), including 17 (13%) early initiation patients and 13 (14.9%) late initiation patients. The focus of this submission is providing data on real-world use and effectiveness of ORKAMBI in CF F/F patients in the US who were 12 years or older.

For this reason, an assessment of results for the whole study population, as submitted by the MAH, is out of the scope of this AR. In the initial submission, only data on drug utilization have been provided for the paediatric subgroup (30 subjects): 1) the great majority (27 subjects, 90%) received the full dose (2 tablets twice a day) and 3 subjects (10%) received half dose (1 tablet twice a day) within 12–months post Orkambi initiation. All three subjects who re-initiated after first discontinuation, received the full dose. 2) only a minority of subjects (4 paediatric subjects at least one dose increased; 2 subjects at least one dose decreased and 2 subjects at least one Orkambi dose interruption) experienced dose adjustments Therefore, the great majority of pediatric patients received the full dose.

The MAH was requested to provide baseline clinical characteristics and descriptive results regarding Orkambi effectiveness in the subgroup of paediatric patients.

In the subgroup of paediatric patients, the mean (SD) age at the index date was 14.4 (1.80) years, mean (SD) weight was 47.0 (10.61) kg, mean (SD) height was 156.00 (11.00) cm, mean (SD) BMI was 19.1 (2.67) kg/m2, with no relevant differences between early and late initiators. The proportion of male patients was 43.3% (early initiators: 47.1%; late initiators: 38.5%). The most commonly reported CF comorbid conditions during the pre-index period or ongoing at index date were chronic

sinusitis and asthma, followed by CF related diabetes. However, the interpretation of these data is limited, as most baseline comorbid conditions were categorized as "Others" (16/30, 53%). The mean (SD) ppFEV1 was 89.5 (20.51) percentage points (early initiators: 84.8 [SD: 23.80] percentage points; late initiators: 95.2 [14.42] percentage points). The proportion of paediatric patients with PEx was 16.7% (early initiators: 23.5%; late initiators: 7.7%). The proportion of paediatric patients treated with IV antibiotics was 6.7% (early initiators:11.8%; late initiators: 0.0%) and the proportion of paediatric patients with CF-related inpatient hospitalizations was 6.7% (early initiators: 11.8%; late initiators: 0.0%).

Descriptive results regarding Orkambi effectiveness in the subgroup of paediatric patients 12 through 17 years of age from Study 117 present limitations and should be interpreted with caution due to the low number of paediatric subjects aged 12-17 years enrolled (N=30, among them N=17 'early initiators' and N=13 'late initiators'), the retrospective data collection from patient medical records and the exploratory nature of the study.

A numerical decrease in ppFEV1 was observed in the paediatric subgroup [-2.9 percentage points (95% CI: -9.1, 3.4)] from baseline to the last available assessment within the 12-month post-index period. This rate of decrease is similar to the annualized rate of lung function decline reported in a published analysis of US Cystic Fibrosis Foundation (CFF) registry data in patients homozygous for F508del, aged 13 through 17 years, untreated with a CFTR modulator (-2.66 percentage points per year; Wegener et al, J Cyst Fibros. 2018;17(4):503-10). However, given the small sample size of Study 117 paediatric subgroup and the wide CI that crosses 0, no conclusions can be made regarding the effect of Orkambi treatment on ppFEV1 in this subgroup.

In the larger, ongoing comparator-controlled PASS, a reduction in the rate of lung function decline was observed over 4 years in the subgroup of Orkambi-treated patients 12 through 17 years of age, compared to an untreated cohort.

The paediatric subgroup analysis of 30 patients from Study 117 showed improvements in BMI [mean change from baseline: 1.1 kg/m2 (95% CI: 0.6, 1.6)] and weight [mean change from baseline 4.4 kg (95% CI: 3.3, 5.6)].

No major differences, although with numerical slight decreases, were observed in the paediatric subgroup between pre-index period and post index period for: annualized PEx rate [1.1 (SD 1.52) vs 0.9 (SD1.01)], rate of hospitalizations [1.2 (2.17) vs 0.8 (1.19)], outpatient visits [6.0 (4.62) vs 5.4 (2.81)], acute antibiotic prescriptions [3.4 (4.03) vs 3.1 (5.01)], and the proportion of patients with positive P. aeruginosa after Orkambi initiation (56.7% vs 50%). There were no lung transplants or deaths in the paediatric subgroup.

Furthermore, the MAH was requested to discuss the high frequency of Orkambi discontinuation observed in the subgroup of paediatric subjects (8/30, 26.7%) and to provide further information on the reasons for discontinuation in the 4 subjects where the reported reason was "other AE" and in the 2 subjects classified as "other reason". Of the 8 paediatric patients who discontinued Orkambi after the first initiation of treatment, 3 reinitiated Orkambi: two of these 3 patients remained on treatment through the end of the study; 1 subject discontinued after the second initiation of treatment. Thus, 6/30 paediatric patients (20%) permanently discontinued treatment in Study 117. This frequency of discontinuation is higher than the one observed in the same age range in pivotal clinical trials (1.0%, 3/290 subjects), and in another observational study conducted in France (8.2%) (Burgel et al, 2019). As regards to the types of AEs observed, the events were mostly known ADRs (2 subjects discontinued due to transaminase increase; one subject each discontinued due to headaches and rash). The other two subjects presented exacerbation of reflux symptoms leading to discontinuation and fever one hour after dose and rhinorrhea (1 patient each).

Also, in the overall population enrolled in Study 117, a high frequency of discontinuation (35.8%) was observed. The most frequent reason for study discontinuation was respiratory AEs (39 subjects, 52% of subjects who discontinued). The frequency of discontinuation observed in Study 117 is considerably higher than the frequency of AEs leading to treatment discontinuation observed in the overall population enrolled in the pooled placebo-controlled Phase 3 studies (pivotal Studies 103 and 104) (4.6%), as well as in the long term extension of pivotal studies up to 96 weeks treatment duration (6.8%).

In the observational study conducted in France to evaluate real-world treatment effects of Orkambi over the first year of treatment previously cited (Burgel et al, 2019), the overall study rates of Orkambi discontinuation in adults was 23.5%.

The MAH was requested to discuss the high frequency of discontinuation (35.8%) and to discuss all available data on the reasons for discontinuations observed in the adult population of patients enrolled in Study 117. The reasons for treatment discontinuation were respiratory AEs (39 patients [52.0%]), other reason (17 patients [22.7%]), other AE (9 patients [12.0%]), lack of effectiveness (5 patients [6.7%]), unknown (3 patients [4.0%]), and gastrointestinal AE (2 patients [2.7%]). Among the 17 patients that discontinued due to other reasons, most patients discontinued due to AEs. As regards to the types of AEs leading to discontinuation, the events were mostly known ADRs for Orkambi. Of note, one patients discontinued due to worsened depression and one patient discontinued due to Stevens Johnson's syndrome.

It is acknowledged that the data from the PASS study, given the larger sample size and longer duration, may be considered more representative of the real-world Orkambi experience. In the annual interim analysis results from the larger, registry-based, 5-year post-authorization safety study (PASS) Study 108, the proportion of patients in the Orkambi Safety Cohort who had no record of Orkambi use in the subsequent calendar year suggests a discontinuation rate of 10.1% for the 2016 Orkambi Safety Cohort (N= 5,553) and 12.2% for the 2017 Orkambi Safety Cohort (N = 6,664).

In the overall study population, seven patients (3.2%) required at least one transplant after ORKAMBI initiation (all seven were lung transplants), of which 6 patients were early-initiators, compared to no patients requiring transplant prior to Orkambi initiation and 2 patients with unknown prior transplant before Orkambi initiation. There were 2 (0.9%) deaths observed during the post-index period, 1 of which occurred while on Orkambi treatment with unknown cause. The MAH has been requested to provide all available information (including age) of the 7 subjects requiring lung transplant after Orkambi initiation and of the 2 deaths observed during the post index period.

The age at the time that Orkambi was prescribed for the 7 patients who had a lung transplant ranged from 23 to 56 years of age. The 2 patients who died during the post-index period were aged 20 and 52 years old. The MAH clarified that no further information is available on these patients, given that for death and organ transplant, there was no option in the CRFs for the sites to provide any additional description regarding these events.

In Study 117, a higher proportion of patients (3.2%) required lung transplant after Orkambi initiation in comparison to the proportion of patients with a history of any organ transplant (0.4%) in the Orkambi Safety Cohort in 2018 in PASS Study 108. It is acknowledged that the data from the PASS study, given the larger sample size and longer duration, may be considered more representative of the real-world Orkambi experience. In the third interm analysis of the ongoing PASS, consistently with the previous 2 interim reports, the risk of death and organ transplant was statistically significantly lower in the Orkambi Cohort compared to the Comparator Cohort.

3. CHMP overall conclusion and recommendation

On 19 November 2019, the MAH submitted a completed paediatric study for Orkambi. Study Title: "A Multicenter, Retrospective, Real-World, Observational Study on Orkambi Use". The study included 30 paediatric subjects (≥12 years old). The study was completed on 20 October 2017, thus not within 6 months of study completion. This is not in accordance with the regulation (Article 46 of Regulation (EC) No1901/2006, as amended). Therefore, the PAM is not considered to be fulfilled as it was not submitted within the legal timelines (i.e. within six months of completion of each study).

The focus of this submission is providing data on real-world use and descriptive effectiveness of ORKAMBI in CF F/F patients in the US who were 12 years or older. For this reason, the assessment of results for the whole study population, as submitted by the MAH, is out of the scope of this AR. Data on drug utilization have been provided for the paediatric cohort (30 subjects) indicating that the great majority of subjects (90%) received the full Orkambi dose.

Descriptive results regarding Orkambi effectiveness in the subgroup of paediatric patients 12 through 17 years of age from Study 117 present limitations and should be interpreted with caution due to the low number of paediatric subjects aged 12-17 years enrolled (N=30), the retrospective data collection from patient medical records and the exploratory nature of the study.

A more severe pattern of baseline disease characteristics was observed in early initiators as compared to late initiators.

Results seem not suggesting a positive trend on ppFEV1. However, given the small sample size of Study 117 paediatric subgroup and the wide CI that crosses 0, no conclusions can be made. Of note, supportive results of Orkambi effectiveness on $ppFEV_1$ are coming from the larger, ongoing comparator-controlled PASS.

Increases in weight and BMI were observed in the paediatric subgroup between pre-index period and post index period. There were no major differences for the other variables/outcomes, slight numerical decreases were observed.

A high frequency of discontinuation was observed in Study 117, both in the overall population (35.8%) and in the subgroup of paediatric subjects (8/30, 26.7%).

However, the types of AEs leading to discontinuation were mostly known ADRs for Orkambi.

In order to allow to contextualize the higher frequency of treatment discontinuation observed in Study 117 in adolescents 12 through 17 years of age, compared to the one observed in the same age range in pivotal clinical trials, the MAH was requested to provide baseline disease characteristics of the subgroup of 30 paediatric subjects included in Study 117 in comparison with baseline clinical characteristics of adolescents 12 through 17 years of age, enrolled in the pooled placebo-controlled Phase 3 studies (pivotal Studies 103 and 104). It is of note that ppFEV1 value of patients 12 to 17 years of age enrolled in Study 117 is higher (mean 89.5, SD 20.51) in comparison to patients of the same age range enrolled in pivotal studies 103/104 (mean 67.3, SD 13.0) underlying a quite different lung function as measured by ppFEV1 at baseline surely limiting indirect comparability of study results but possibly not substantially contributing to a higher treatment discontinuation observed in Study 117 study.

7 subjects required lung transplant after Orkambi initiation and two 2 deaths were observed during the post index period. It is noted that a higher proportion of patients (3.2%) required lung transplant after Orkambi initiation in comparison to the proportion of patients with a history of any organ transplant (0.4%) in the Orkambi Safety Cohort in 2018 in PASS Study 108. No details on CRF were available. It

is acknowledged that the data from the PASS study, given the larger sample size and longer duration, may be considered more representative of the real-world Orkambi experience.

☒ Not fulfilled. The submission was received on 19 November 2019, thus not within 6 months of study completion, and therefore not in accordance with the regulation, that requires submission of study results within 6 months of study completion. The MAH is requested to adhere to legal timelines when submitting article 46 paediatric study application(s).

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. The MAH should clarify if Study 117 was a stand-alone study or a study part of a clinical development program.
2. It is unclear the reason why in the final-eva-18941-table file there are two Tables 1 reporting Study Specific Site Survey Summary with partially different data. The Applicant should clarify.
3. Unexpectedly, only data on drug utilization have been provided for the paediatric subgroup (30 subjects). To allow the assessment of study 117 results, the MAH is required to submit
   - i) the distribution of paediatric patients (i.e, number eligible and enrolled) across sites;
   - ii) comprehensive baseline clinical characteristics of the overall paediatric population and by initiation cohort;
   - iii) descriptive results regarding Orkambi effectiveness in the subgroup of paediatric patients for the following variables: Clinical outcomes (BMI, ppFEV1, weight, and PEx), Healthcare resource utilization (Inpatient hospitalizations; Outpatient visits, Acute antibiotic use including IV antibiotic, Other CF medications use); Other Outcomes [Microbiology: (e.g., Pseudomonas); Death; Transplantation].

MAH responses to the 1st Request for supplementary information

Question 1

The MAH should clarify if Study 117 was a stand-alone study or a study part of a clinical development program.

MAH's Response:

Study 117 was a stand-alone exploratory study and was not part of the Orkambi (lumacaftor/ivacaftor) clinical development program.

Assessment of the MAH's Response

The Applicant clarified that Study 117 was a stand-alone exploratory study and was not part of the Orkambi (lumacaftor/ivacaftor) clinical development program.

Issue resolved

Question 2

It is unclear the reason why in the final-eva-18941-table file there are two Tables 1 reporting Study Specific Site Survey Summary with partially different data. The Applicant should clarify.

MAH's Response:

The second Table 1 (starting on page 2 of the FINAL_EVA_18941_Tables file) contains incomplete data from an interim analysis and was inadvertently included.

Assessment of the MAH's Response

The Applicant clarified that the second Table 1 (starting on page 2 of the FINAL_EVA_18941_Tables file) contains incomplete data from an interim analysis and was inadvertently included.

Issue resolved

Question 3

Unexpectedly, only data on drug utilization have been provided for the paediatric subgroup (30 subjects). To allow the assessment of study 117 results, the MAH is required to submit

i) the distribution of paediatric patients (i.e., number eligible and enrolled) across sites;

ii) comprehensive baseline clinical characteristics of the overall paediatric population and by initiation cohort;

iii) descriptive results regarding Orkambi effectiveness in the subgroup of paediatric patients for the following variables: clinical outcomes (BMI, ppFEV1, weight, and PEx), Healthcare resource utilization (Inpatient hospitalizations; Outpatient visit, Acute antibiotic use including IV antibiotic, Other CF medications use); Other Outcomes [Microbiology: (e.g., Pseudomonas); Death; Transplantation].

MAH's Response:

Study 117 was an exploratory, retrospective chart study designed to explore the real-world utilization and treatment patterns in the indicated population for Orkambi in the months following the initial approval in the US. The indicated population, and those enrolled in the study, included cystic fibrosis (CF) patients homozygous for F508del who were 12 through 17 years of age. The study was not designed to evaluate the paediatric subgroup; therefore, subgroup analyses of these patients are not considered informative or appropriate.

Post hoc subgroup analyses of the paediatric population enrolled in Study 117 would not be informative or appropriate because:

1) this was an exploratory study using medical records abstraction;

2) the subgroup is not powered to detect changes in the requested endpoints; and

3) because the study was not designed or powered to assess this paediatric subgroup, there is a high likelihood of confounding from imbalanced baseline characteristics between the even smaller subgroups of early and late initiators.

For these reasons, analyses of the paediatric subgroup would have a high likelihood of not being representative of CF patients 12 through 17 years of age initiating Orkambi and would not be interpretable. In summary, the requested subgroup analyses are not considered appropriate for this study.

Assessment of the MAH's Response

The focus of this study is providing data on real-world use and effectiveness of ORKAMBI in CF F/F patients in the US including adults and patients who were 12-17 years old. Of 218 patients enrolled in Study 117, 30 (13.8%) were paediatric patients 12-<18 years of age), including 17 (13%) early initiation patients and 13 (14.9%) late initiation patients. Only data on drug utilization have been

provided for the paediatric subgroup (30 subjects). Baseline data and post-hoc analyses on pediatric patients (12-17 years old) were required however the MAH did not provide these analyses since were not considered to be informative or appropriate for the following reasons: i) the study design was exploratory and medical records were used, ii) the study is not powered for the subgroup analysis and data from a small subgroup would be not interpretable.

It is acknowledged that the study is exploratory and retrospective and that the main aim was to explore the real-world utilization and treatment patterns of Orkambi in F/F CF patients ≥12 years in the US, however the requested data could have been an opportunity to gain some information on the subgroup, although limited, of pediatric patients included in the study. However, due to the limited number of patients and lack of complete baseline data, it is recognised that the results would not be sufficiently informative to allow inclusion of relevant information in the SmPC.

Not further pursued.

MS comments

Reportedly, the main objective of this retrospective observational study was to «explore real-world use and effectiveness of ORKAMBI in CF F/F patients in the US who were 12 years of age or older». It is agreed that a low number of paediatric subjects aged 12-17 years was enrolled (N=30, among them N=17 'early initiators' and N=13 'late initiators') and that the retrospective data collection and exploratory character of the investigation undoubtedly result in limitations.

However, the analyses presented by the MAH for the paediatric population are scarce, cursory, and mainly limited to drug usage data. It appears that effectiveness and safety data were collected, but not even descriptively analysed, let alone comprehensively evaluated. In the absence of such a descriptive analysis, the MAH's overall conclusion that the «results would not be sufficiently informative [anyway]» is an assumption which is not sufficiently corroborated by facts.

Additional comment in relation with the paediatric drug usage data: based on the tables presented in the AR, it appears that Orkambi treatment was discontinued in 8/30 children (26.7%) following first initiation, and not – as erroneously mentioned in the AR – in 4/30 children (13.3%). In the majority of cases (6 out of 8), Orkambi was discontinued within four months of treatment initiation. Moreover, the underlying reasons were not sufficiently specified or made transparent by the MAH: N=4 other AE, N=2 other reason.

Additional clarification requested (2nd RSI)

Based on the data submitted, the MAH should address the following questions as part of this procedure

1. It is acknowledged that a low number of paediatric subjects aged 12-17 years was enrolled (N=30) and that the retrospective data collection and exploratory character of the investigation undoubtedly result in limitations. However, given that some effectiveness and safety data were collected, in the absence of a descriptive analysis, the MAH's overall conclusion that the «results would not be sufficiently informative [anyway]» is an assumption which is not sufficiently corroborated by facts. To allow the assessment of study 117 results, the MAH is required to submit

   i) the distribution of paediatric patients (i.e, number eligible and enrolled) across sites;

   ii) comprehensive baseline clinical characteristics of the overall paediatric population and by initiation cohort;

iii) descriptive results regarding Orkambi effectiveness in the subgroup of paediatric patients for the following variables: Clinical outcomes (BMI, ppFEV1, weight, and PEx), Healthcare resource utilization (Inpatient hospitalizations; Outpatient visits, Acute antibiotic use including IV antibiotic, Other CF medications use); Other Outcomes [Microbiology: (e.g., Pseudomonas); Death; Transplantation].

2. Orkambi treatment was discontinued in 8/30 children (26.7%) following first initiation. In the majority of cases (6 out of 8), Orkambi was discontinued within four months of treatment initiation. The underlying reasons were the following: N=4 other AE, N=2 other reason, lack of effectiveness 1 patient, Gastrointestinal AE 1 patient. The Applicant should provide further information on the reasons for discontinuation in the 4 subjects where the reported reason was "other AE" and in the 2 subjects classified as "other reason". The Applicant should discuss the high frequency of Orkambi discontinuation observed in this study.

MAH responses to 2nd Request for supplementary information

Question 1

2. It is acknowledged that a low number of paediatric subjects aged 12-17 years was enrolled (N=30) and that the retrospective data collection and exploratory character of the investigation undoubtedly result in limitations. However, given that some effectiveness and safety data were collected, in the absence of a descriptive analysis, the MAH's overall conclusion that the «results would not be sufficiently informative [anyway]» is an assumption which is not sufficiently corroborated by facts. To allow the assessment of study 117 results, the MAH is required to submit

   iv) the distribution of paediatric patients (i.e, number eligible and enrolled) across sites;

   v) comprehensive baseline clinical characteristics of the overall paediatric population and by initiation cohort;

   vi) descriptive results regarding Orkambi effectiveness in the subgroup of paediatric patients for the following variables: Clinical outcomes (BMI, ppFEV1, weight, and PEx), Healthcare resource utilization (Inpatient hospitalizations; Outpatient visits, Acute antibiotic use including IV antibiotic, Other CF medications use); Other Outcomes [Microbiology: (e.g., Pseudomonas); Death; Transplantation].

MAH's Response:

In line with EMA guidance, the outcome of an Article 46 procedure assessed by the EMA is to determine whether an update to the SmPC is warranted or not. Vertex is in agreement with the Rapporteur's assessment that "due to the limited number of patients and lack of complete baseline data, it is recognised that the results would not be sufficiently informative to allow inclusion of relevant information in the SmPC."

Vertex acknowledges the request for additional analyses, but respectfully declines this request for the following reasons. Study 117 was an exploratory retrospective study that was not designed or powered to assess the paediatric subgroup for the requested endpoints. While some data relating to the utilization patterns of Orkambi were collected, the data were very limited.

Limitations for the requested subgroup analyses include:

• this was an exploratory, retrospective chart study using medical records abstraction

• the paediatric subgroup is not powered to detect changes in the requested endpoints

• the small paediatric subgroup would have a high likelihood of not being representative of CF patients 12 through 17 years of age

• due to the small size of the paediatric subgroup, there is a high likelihood of imbalanced baseline characteristics between the early and late initiator groups. As a result, the requested analyses for baseline characteristics by initiation cohort would not provide representative data for this age group.

• the large number of variables that would be analyzed for the requested subgroup analyses would lead to a high chance of misleading findings

For these reasons, the requested subgroup analyses would not be representative of CF patients 12 through 17 years of age and are not considered appropriate for this study.

Study 117 was an exploratory study designed to explore the early treatment patterns following the initial US approval. In the Orkambi clinical development program, Vertex has evaluated Orkambi in paediatric patients in larger and more comprehensive studies, such as placebo-controlled Phase 3 studies (Studies VX12-809-103, VX12-809-104, and VX14-809-109), open-label long-term safety studies (Study VX12-809-105 and Study VX15-809-110 [Study 110]), and an observational post-authorization study (Study VX14-809-108); the data from these studies better represent the paediatric experience with Orkambi. The analysis of this small subgroup would not be likely to change the positive benefit:risk profile in CF patients12 through 17 years of age.

Assessment of the MAH's Response:

Despite the repeated requests to provide descriptive results regarding Orkambi effectiveness in the subgroup of 30 paediatric patients included in Study 117 (first request by e-mail prior to first assessment report, second request through 1st RSI, third request following DE comments through 2nd RSI) the MAH has not provided the requested data on the basis of the argumentation that Study 117 was an exploratory retrospective study, that was not designed or powered to assess the paediatric subgroup for the requested endpoints. While some data relating to the utilization patterns of Orkambi were collected, the data were very limited and the MAH's opinion is that the analysis of this small subgroup would not be likely to change the positive benefit/risk profile in CF patients 12 through 17 years of age.

The MAH refusal to provide the requested data is difficult to understand.

Even though it is acknowledged that a low number of paediatric subjects aged 12 - 17 years was enrolled (N=30) and that the retrospective data collection and exploratory character of the investigation undoubtedly result in limitations, as previously commented by DE, given that some effectiveness data were collected, in the absence of a descriptive analysis, the MAH's overall conclusion that "the analysis of this small subgroup would not be likely to change the positive benefit:risk profile in CF patients 12 through 17 years of age" is an assumption which is not sufficiently corroborated by data.

Thus, the request to provide the following data is reiterated:

i) the distribution of paediatric patients (i.e, number eligible and enrolled) across sites;

ii) comprehensive baseline clinical characteristics of the overall paediatric population and by initiation cohort;

iii) descriptive results regarding Orkambi effectiveness in the subgroup of paediatric patients for the following variables: Clinical outcomes (BMI, ppFEV1, weight, and PEx), Healthcare resource utilization (Inpatient hospitalizations; Outpatient visits, Acute antibiotic use including IV antibiotic,

Other CF medications use); Other Outcomes [Microbiology: (e.g., Pseudomonas); Death; Transplantation]

Question 2

Orkambi treatment was discontinued in 8/30 children (26.7%) following first initiation. In the majority of cases (6 out of 8), Orkambi was discontinued within four months of treatment initiation. The underlying reasons were the following: N=4 other AE, N=2 other reason, lack of effectiveness 1 patient, Gastrointestinal AE 1 patient. The Applicant should provide further information on the reasons for discontinuation in the 4 subjects where the reported reason was "other AE" and in the 2 subjects classified as "other reason". The Applicant should discuss the high frequency of Orkambi discontinuation observed in this study.

MAH's Response:

As requested, additional information is provided in Table 1 for the 8 paediatric patients who discontinued after first initiation, including the patients where the reported reason for discontinuation was "other AE" (n = 4) or "other reason" (n = 2). The case report forms (CRFs) included an option for the sites to enter free text to specify the reasons for discontinuation; the free text is provided verbatim from the CRF in Table 15.

Table 15: Reason for discontinuation for pediatric patients

Patient[a]	Primary Reason for Discontinuation (Category)	Reason for Discontinuation Specified by Free Text (Verbatim)
1	Lack of effectiveness	--
2	Gastrointestinal AE	Exacerbation of reflux symptoms
3	Other reason	Inability to swallow tablets
4	Other reason	lack of perceived therapeutic effect
5[b]	Other AE	Headaches
	Other AE	increase in transaminases
6	Other AE	increase in transaminases
7	Other AE	Rash
8	Other AE	Fevers up to 102 one hour after dose; rhinorrhea

AE: adverse event
Source: Data on file
[a] The listed patient numbers do not reflect individual study identification numbers.
[b] This patient discontinued after the first initiation of treatment due to "other AE" (verbatim free text: "Headaches"). Then, the patient subsequently discontinued after reinitiation of treatment due to "other AE" (verbatim free text: "increases in transaminases").

With respect to the frequency of discontinuation, Vertex would like to clarify that of the 8 paediatric patients who discontinued Orkambi after the first initiation of treatment, 3 reinitiated Orkambi (Study 117 CSR/Table 44). Two of these 3 patients remained on treatment through the end of the study; 1 subject discontinued after the second initiation of treatment (see Patient 5 from Table 1). Thus, only 6 paediatric patients discontinued treatment in Study 117.

Furthermore, as discussed in the response to Question 1, Study 117 was conducted early in the Orkambi lifecycle. In the last 5 years, other larger studies have shown lower discontinuation rates in paediatric patients than that observed in Study 117. In an observational study conducted in France to evaluate real-world treatment effects of Orkambi, the overall discontinuation rate for adolescents 12 through 17 years of age was 8.2% (n = 292).[1] In addition, several Vertex clinical studies in paediatric subjects have shown that Orkambi is well tolerated with lower rates of discontinuation. For example, the overall discontinuation rate in paediatric subjects who initiated Orkambi treatment between 6 through 11 years of age (Study 110) was 10.0% (n = 239), with AEs leading to treatment

discontinuation in only 3.8% of subjects. Taken together, these studies indicate that the discontinuation rate observed in Study 117 is not representative of real-world or clinical experience with Orkambi to date.

[1] Burgel PR. Real-Life Safety and Effectiveness of Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis. AJRCCM [Internet]. 2019 October [cited 201(2):[about 36 p.]]. Available from: https://www.atsjournals.org/doi/pdf/10.1164/rccm.201906-1227OC.

Assessment of the MAH's Response:

The MAH provided the requested data for the 8/30 paediatric patients who discontinued Orkambi after first initiation.

Two subjects (2/30, 6.7%) discontinued due to lack of effectiveness/lack of perceived therapeutic effect; one subject (1/30, 3.3%) discontinued due to inability to swallow the tablets, and 6/30 subjects (20%) discontinued due to AEs. Among the 6 subjects discontinuing due to AEs, the AEs leading to discontinuation were the following (verbatim text): increase in transaminase (2 patients), exacerbation of reflux symptoms, headaches, rash, fevers one hour after dose and rhinorrhea (1 patient each).

Of the 8 paediatric patients who discontinued Orkambi after the first initiation of treatment, 3 reinitiated Orkambi: two of these 3 patients remained on treatment through the end of the study; 1 subject discontinued after the second initiation of treatment (this patient discontinued after the first initiation of treatment due to: "Headaches". Then, the patient subsequently discontinued after reinitiation of treatment due to "increases in transaminases"). Thus, 6/30 paediatric patients (20%) permanently discontinued treatment in Study 117.

The MAH states other larger studies have shown lower discontinuation rates in paediatric patients than that observed in Study 117: in an observational study conducted in France to evaluate real-world treatment effects of Orkambi over the first year of treatment, the overall discontinuation rate for adolescents 12 through 17 years of age was 8.2% (n = 292); conversely in this study rates of Orkambi discontinuation were significantly higher in adults than in adolescents (23.5% vs 8.2%, p< 0.0001) (Burgel et al, 2019). Thus, in the MAH's opinion, the discontinuation rate observed in Study 117 is not representative of real-world or clinical experience with Orkambi to date.

Of the 1108 subjects who received study drug in the pooled placebo-controlled Phase 3 studies (pivotal Studies 103 and 104), 290 subjects were aged ≥12 to <18 years of age. Among subjects ≥12 to <18 years of age, 3 subjects (1.0%) discontinued due to an adverse event during the 6 months study duration: 2 subjects on placebo (acne, n =1; haemoptysis, n = 1) and 1 subject in the LUM 400 mg q12h/IVA 250 mg q12h group (forced expiratory volume decrease).

In the overall pooled placebo-controlled Phase 3 studies, the incidence of adverse events leading to study drug discontinuation was higher in the total LUM/IVA group (4.2%) compared with the placebo group (1.6%).

In study 105 A, the long-term extension of pivotal studies up to 96 weeks treatment duration, a total of 70 (6.8%) subjects had AEs that led to treatment discontinuation.

In the adult population enrolled in Study 117, 67/188 subjects (35.8%) discontinued due to any reason. The most frequent reason for study discontinuation was respiratory AEs (39 subjects, 58.2% of subjects who discontinued).

Conclusion:

6/30 adolescents 12 through 17 years of age (20%) permanently discontinued treatment in Study 117. This frequency of discontinuation is higher than the one observed in the same age range in pivotal

clinical trials (1.0%, 3/290 subjects), and in another observational study conducted in France (8.2%) (Burgel et la, 2019).

As regards to the types of AEs observed, the events were mostly known ADRs (2 subjects discontinued due to transaminase increase; one subject each discontinued due to headaches and rash). The other two subjects presented exacerbation of reflux symptoms leading to discontinuation and fevers one hour after dose and rhinorrhea (1 patient each).

In order to better contextualize the higher frequency of treatment discontinuation (20%) observed in Study 117 in adolescents 12 through 17 years of age, compared to the one observed in the same age range in pivotal clinical trials (1.0%, 3/290 subjects), baseline clinical characteristics of the subgroup of 30 pediatric subjects included in Study 117 are needed (please refer to assessment of question 2 for further aspects on this issue). Baseline clinical characteristics of the subgroup of 30 paediatric subjects included in Study 117 should be discussed by the MAH in comparison with baseline clinical characteristics of adolescents 12 through 17 years of age, enrolled in the pooled placebo-controlled Phase 3 studies (pivotal Studies 103 and 104).

The MAH is requested to discuss the high frequency of discontinuation (35.8%) and to discuss all available data on the reasons for discontinuations observed in the adult population of patients enrolled in Study 117.

In the overall study population, seven patients (3.2%) required at least one transplant after ORKAMBI initiation (all seven were lung transplants), of which 6 patients were early-initiators, compared to no patients requiring transplant prior to Orkambi initiation and 2 patients with unknown prior transplant before Orkambi initiation. There were 2 (0.9%) deaths observed during the post-index period, 1 of which occurred while on Orkambi treatment with unknown cause. The MAH has been requested to provide all available information (including age) of the 7 subjects requiring lung transplant after Orkambi initiation and of the 2 deaths observed during the post index period.

The higher proportion of patients requiring at least one organ transplantation after Orkambi initiation in Study 117 (3.2%) in comparison to the proportion of patients with a history of any organ transplant (0.4%) in the Orkambi Safety Cohort in 2018 in PASS Study 108 should be discussed.

Additional clarification requested (3rd RSI)

The argumentations provided by the MAH are not agreed.

Based on the data submitted, the MAH should address the following questions as part of this procedure

1. It is acknowledged that a low number of paediatric subjects aged 12 - 17 years was enrolled (N=30) and that the retrospective data collection and exploratory character of the investigation undoubtedly result in limitations. However, given that some effectiveness and safety data were collected, in the absence of a descriptive analysis, the MAH's overall conclusion that the "the analysis of this small subgroup would not be likely to change the positive benefit:risk profile in CF patients 12 through 17 years of age" is an assumption which is not sufficiently corroborated by data. To allow the assessment of study 117 results, the MAH is required to submit

   vii) the distribution of paediatric patients (i.e., number eligible and enrolled) across sites;

   viii) comprehensive baseline clinical characteristics of the overall paediatric population and by initiation cohort;

ix) descriptive results regarding Orkambi effectiveness in the subgroup of paediatric patients for the following variables: Clinical outcomes (BMI, ppFEV1, weight, and PEx), Healthcare resource utilization (Inpatient hospitalizations; Outpatient visits, Acute antibiotic use including IV antibiotic, Other CF medications use); Other Outcomes [Microbiology: (e.g., Pseudomonas); Death; Transplantation].

2. In order to allow to contextualize the higher frequency of treatment discontinuation (20%) observed in Study 117 in adolescents 12 through 17 years of age, compared to the one observed in the same age range in pivotal clinical trials (1.0%, 3/290 subjects), baseline clinical characteristics of the subgroup of 30 paediatric subjects included in Study 117 are needed. Baseline clinical characteristics of the subgroup of 30 paediatric subjects included in Study 117 should be discussed by the MAH in comparison with baseline clinical characteristics of adolescents 12 through 17 years of age, enrolled in the pooled placebo-controlled Phase 3 studies (pivotal Studies 103 and 104).
3. The MAH is requested to discuss the high frequency of discontinuation (35.8%) and to discuss available data on the reasons for discontinuations observed in the adult population of patients enrolled in Study 117.
4. The MAH is requested to provide all available information (including age) of the 7 subjects requiring lung transplant after Orkambi initiation and of the 2 deaths observed during the post index period. The higher proportion of patients requiring at least one organ transplantation after Orkambi initiation in Study 117 (3.2%) in comparison to the proportion of patients with a history of any organ transplant (0.4%) in the Orkambi Safety Cohort in 2018 in PASS Study 108 should be discussed.

MAH responses to 3rd Request for supplementary information

Question 1

It is acknowledged that a low number of paediatric subjects aged 12 -17 years was enrolled (N=30) and that the retrospective data collection and exploratory character of the investigation undoubtedly result in limitations. However, given that some effectiveness and safety data were collected, in the absence of a descriptive analysis, the MAH's overall conclusion that the "the analysis of this small subgroup would not be likely to change the positive benefit:risk profile in CF patients 12 through 17 years of age" is an assumption which is not sufficiently corroborated by data. To allow the assessment of study 117 results, the MAH is required to submit

vii) the distribution of paediatric patients (i.e, number eligible and enrolled) across sites;

viii) comprehensive baseline clinical characteristics of the overall paediatric population and by initiation cohort;

x) descriptive results regarding Orkambi effectiveness in the subgroup of paediatric patients for the following variables: Clinical outcomes (BMI, ppFEV1, weight, and PEx), Healthcare resource utilization (Inpatient hospitalizations; Outpatient visits, Acute antibiotic use including IV antibiotic, Other CF medications use); Other Outcomes [Microbiology: (e.g., Pseudomonas); Death; Transplantation].

Summary of the MAH's Responses

After establishing the positive benefit-risk balance of Orkambi in F/F patients 12 years and older and receiving marketing approval for the adolescent and adult F/F population, Vertex conducted Study 117 to explore the real-world utilization and treatment patterns over 12 months after Orkambi initiation in the indicated population who initiated treatment shortly after approval of Orkambi in the US. Data

were extracted from medical records of US CF subjects only and are subject to the limitations of uncontrolled observational real-world data, especially those of short duration. The subgroup analysis of paediatric subjects was not planned, as the number of subjects 12 through 17 years of age was small with significant limitations to interpretation of effectiveness outcomes.

As requested, Vertex has conducted post-hoc subgroup analyses of the paediatric patients 12 through 17 years of age from Study 117. The results from the paediatric subgroup analyses are summarized below. A list of the tables summarizing the paediatric subgroup data for the requested endpoints is provided in the Appendix.

These data should be interpreted with caution due to the exploratory nature of this study and the limitations of the data collected via medical record abstraction. The study was conducted in the US only and was not designed or powered to assess the paediatric subgroup for the requested endpoints. Limitations in the retrospective data collection from patient medical records include incomplete/missing data and inconsistencies due to differences in medical chart documentation.

Moreover, given the small sample size of 30 patients, it is not appropriate to infer that the results from the requested subgroup analyses are generalizable to the population of CF patients 12 through 17 years of age or that it would change the established positive benefit-risk of Orkambi.

i. <u>Distribution of Paediatric Patients Enrolled Across Sites</u>

Table 16. Subject Disposition Summary, Overall and within Sites and by Initiation Groups - Paediatric Sub-Population (aged 12–17 years)

		Initiation Group		
		Early-patient	Late-patient	Overall
Potentially eligible patients (aged 12-17 years) on Orkambi identified by study sites for study inclusion	N	48	18	66
By Site, n(%)	[redacted]	5 (10.4%)	2 (11.1%)	7 (10.6%)
	[redacted]	9 (18.8%)	7 (38.9%)	16 (24.2%)
	[redacted]	0 (0.0%)	0 (0.0%)	0 (0.0%)
	[redacted]	34 (70.8%)	7 (38.9%)	41 (62.1%)
	[redacted]	0 (0.0%)	0 (0.0%)	0 (0.0%)
	[redacted]	0 (0.0%)	0 (0.0%)	0 (0.0%)
	[redacted]	0 (0.0%)	2 (11.1%)	2 (3.0%)
	[redacted]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Selected patients as per sampling scheme	N	18	18	36
By Site, n(%)	[redacted]	4 (22.2%)	2 (11.1%)	6 (16.7%)
	[redacted]	6 (33.3%)	7 (38.9%)	13 (36.1%)
	[redacted]	0 (0.0%)	0 (0.0%)	0 (0.0%)
	[redacted]	8 (44.4%)	7 (38.9%)	15 (41.7%)
	[redacted]	0 (0.0%)	0 (0.0%)	0 (0.0%)
	[redacted]	0 (0.0%)	0 (0.0%)	0 (0.0%)
	[redacted]	0 (0.0%)	2 (11.1%)	2 (5.6%)
	[redacted]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Selected patients as per sampling scheme found to be ineligible	N	1	5	6
By Site, n(%)	[redacted]	0 (0.0%)	0 (0.0%)	0 (0.0%)
	[redacted]	0 (0.0%)	0 (0.0%)	0 (0.0%)
	[redacted]	0 (0.0%)	0 (0.0%)	0 (0.0%)
	[redacted]	1 (100.0%)	5 (100.0%)	6 (100.0%)
	[redacted]	0 (0.0%)	0 (0.0%)	0 (0.0%)
	[redacted]	0 (0.0%)	0 (0.0%)	0 (0.0%)
	[redacted]	0 (0.0%)	0 (0.0%)	0 (0.0%)
	[redacted]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eligible and enrolled patients	N	17	13	30
By Site, n(%)	[redacted]	4 (23.5%)	2 (15.4%)	6 (20.0%)
	[redacted]	6 (35.3%)	7 (53.8%)	13 (43.3%)
	[redacted]	0 (0.0%)	0 (0.0%)	0 (0.0%)
	[redacted]	7 (41.2%)	2 (15.4%)	9 (30.0%)
	[redacted]	0 (0.0%)	0 (0.0%)	0 (0.0%)
	[redacted]	0 (0.0%)	0 (0.0%)	0 (0.0%)

	Initiation Group		
	Early-patient	Late-patient	Overall
[redacted]	0 (0.0%)	2 (15.4%)	2 (6.7%)
	0 (0.0%)	0 (0.0%)	0 (0.0%)

Footnotes:

N: Number of subjects; n(%): number and percentage of subjects.

Percentages are calculated relative to the overall sample size in the relevant sub-population (presented in the first row of each listed event).

A selected patient as per the sampling scheme may not be enrolled if the full eligibility is not met (e.g. a prescription fill date is outside the eligibility period even though the prescription written date was within the eligibility period).

Early-patient initiation population was defined as cases with an index date between 01 July 2015 and 30 September 2015, whereas Late-patient initiation population was defined as cases with an index date between 01 October 2015 and 31 December 2015. The index date was defined as the ORKAMBI prescription fill date. If this date was not available, index date was set to the date of ORKAMBI written prescription.

ii. Demographics and Baseline Characteristics

Table 17. Summary Statistics for Demographics and Baseline Characteristics, Overall and by Initiation Groups - Paediatric Sub-Population (aged 12–17 years)

		Initiation Group		
		Early-patient N=17	Late-patient N=13	Overall N=30
Baseline demographics				
Age at index date (years)				
	n	17	13	30
	Mean	14.7	14.0	14.4
	SD	1.87	1.68	1.80
	Median	14.1	13.5	14.0
	IQR	13.5, 16.6	12.6, 15.6	12.6, 16.0
	Minimum	12.1	12.0	12.0
	Maximum	17.6	16.6	17.6
Pediatric Patients (12-17 years of age) at index date				
	n(%)	17 (100.0)	13 (100.0)	30 (100.0)
Sex (Male)				
	n(%)	8 (47.1)	5 (38.5)	13 (43.3)
Baseline General Characteristics				
Weight (kg)				
	n	16	13	29
	Mean	46.5	47.6	47.0
	SD	10.83	10.74	10.61
	Median	46.8	45.6	45.6
	IQR	36.4, 50.8	36.7, 58.2	36.7, 53.3
	Minimum	33.9	33.8	33.8
	Maximum	72.8	64.0	72.8
Height (cm)				
	n	16	13	29
	Mean	155.1	157.3	156.0
	SD	9.16	13.21	11.00
	Median	157.5	154.9	156.0
	IQR	145.1, 161.0	146.7, 162.6	145.6, 161.5
	Minimum	142.3	141.0	141.0
	Maximum	170.2	179.7	179.7
BMI (kg/m^2)				
	n	16	13	29
	Mean	19.1	19.1	19.1
	SD	2.85	2.54	2.67
	Median	18.4	18.7	18.7
	IQR	17.1, 20.3	17.7, 19.5	17.4, 20.0
	Minimum	16.2	16.3	16.2
	Maximum	27.2	26.3	27.2
Baseline Clinical Characteristics				
CF comorbid conditions present at any time during pre-index period				
	None, n (%)	1 (5.9)	3 (23.1)	4 (13.3)
	CF-related diabetes, n (%)	3 (17.6)	2 (15.4)	5 (16.7)
	Distal intestinal obstruction syndrome, n (%)	1 (5.9)	1 (7.7)	2 (6.7)
	CF-related arthritis, n (%)	0 (0.0)	1 (7.7)	1 (3.3)
	Asthma, n (%)	6 (35.3)	5 (38.5)	11 (36.7)

	Initiation Group		
	Early-patient N=17	Late-patient N=13	Overall N=30
Chronic sinusitis, n (%)	9 (52.9)	4 (30.8)	13 (43.3)
Other, n (%)	10 (58.8)	6 (46.2)	16 (53.3)
CF comorbid conditions still ongoing at index date			
CF-related diabetes, n (%)	2 (11.8)	2 (15.4)	4 (13.3)
Distal intestinal obstruction syndrome, n (%)	0 (0.0)	1 (7.7)	1 (3.3)
CF-related arthritis, n (%)	0 (0.0)	1 (7.7)	1 (3.3)
Asthma, n (%)	6 (35.3)	5 (38.5)	11 (36.7)
Chronic sinusitis, n (%)	9 (52.9)	4 (30.8)	13 (43.3)
Other, n (%)	10 (58.8)	6 (46.2)	16 (53.3)
Any positive results for mucoid or non-mucoid pseudomonas aeruginosa during pre-index period			
No, n(%)	6 (35.3%)	7 (53.8%)	13 (43.3%)
Yes, n(%)	11 (64.7%)	6 (46.2%)	17 (56.7%)
Unknown, n(%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lung Function			
FEV_1 (L)			
n	17	13	30
Mean	2.4	2.7	2.5
SD	0.69	0.78	0.73
Median	2.5	2.4	2.5
IQR	2.0, 2.8	2.2, 3.0	2.0, 2.8
Minimum	1.1	1.8	1.1
Maximum	3.5	4.1	4.1
FVC (L)			
n	17	13	30
Mean	3.0	3.2	3.1
SD	0.81	0.95	0.86
Median	3.2	3.1	3.1
IQR	2.6, 3.3	2.5, 3.5	2.5, 3.5
Minimum	1.3	2.0	1.3
Maximum	4.3	4.9	4.9
FEF 25%-75% (L/second)			
n	17	13	30
Mean	2.4	3.0	2.6
SD	1.07	1.15	1.13
Median	2.5	2.8	2.6
IQR	1.8, 3.2	2.2, 3.4	2.0, 3.3
Minimum	0.4	1.7	0.4
Maximum	4.1	6.0	6.0
$ppFEV_1$ (%)			
n	16	13	29
Mean	84.8	95.2	89.5
SD	23.80	14.42	20.51
Median	90.4	89.7	89.9
IQR	71.4, 100.1	87.3, 95.6	84.8, 95.6
Minimum	38.5	75.9	38.5
Maximum	114.1	128.8	128.8
Baseline CF Disease Status			
Any pulmonary exacerbations			

	Initiation Group		
	Early-patient N=17	Late-patient N=13	Overall N=30
No, n(%)	13 (76.5%)	12 (92.3%)	25 (83.3%)
Yes, n(%)	4 (23.5%)	1 (7.7%)	5 (16.7%)
Unknown, n(%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any IV antibiotics			
No, n(%)	15 (88.2%)	13 (100.0%)	28 (93.3%)
Yes, n(%)	2 (11.8%)	0 (0.0%)	2 (6.7%)
Unknown, n(%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any inpatient hospitalization for CF or CF pulmonary exacerbations			
No, n(%)	15 (88.2%)	13 (100.0%)	28 (93.3%)
Yes, n(%)	2 (11.8%)	0 (0.0%)	2 (6.7%)
Unknown, n(%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Footnotes:

Pediatric Sub-Population: Subset of the overall patient population (All Subjects Set) aged 12 to 17 years of age.

N: Number of subjects in the Pediatric Sub-Population; n(%): number and percentage of subjects.

Percentages are calculated relative to the Overall sample size in the relevant sub-population.

For baseline continuous patient characteristics, results are at index date and if the information was not available on the index date, information from the closest preceding date prior to the index date was used. For the presence of CF comorbid conditions, the baseline evaluation period was defined as any time during the pre-index period (July 1, 2014 until the index date, inclusively). For the status of CF disease based on the presence of certain infections, events, or treatments, the baseline evaluation period corresponds to one month prior to, and inclusive of, the index date.

PEx could be directly recorded as an event in the patient's chart or indirectly defined as a course of new IV antibiotic therapy and/or PEx related hospitalizations. Courses of IV antibiotics or PEx-related hospitalization occurring within less than seven days from end of first event to start of next one were considered one event.

$ppFEV_1$ derived as per protocol Appendix F.

Abbreviations: BMI = body mass index; CF = cystic fibrosis; FEF = Forced expiratory flow; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; IQR = interquartile range; IV = intravenous; ppFEV1 = percent predicted forced expiratory volume in one second; SD = standard deviation

Source Table: 3

iii. Orkambi Effectiveness Results

Clinical outcomes

ppFEV1 (Ad Hoc Table 3): The mean absolute change in ppFEV1 from baseline to the last available assessment within the 12-month post-index period was -2.9 percentage points (95% CI: -9.1, 3.4). Given the small sample size and the wide CI that crosses 0, no conclusions can be made regarding the effect of Orkambi treatment on ppFEV1 in this subgroup.

Table 18. Descriptive Summary of ppFEV1, Absolute and Relative Change from Baseline in ppFEV1 within 12 Months Post-ORKAMBI Initiation, Overall - Paediatric Sub-Population (aged 12–17 years)

$ppFEV_1$ (%)		Overall N=30
At Index Date (Baseline)		
	n	29
	Mean	89.5
	SD	20.51
	SE	3.81
	95% CI	81.7, 97.3
	Median	89.9
	IQR	84.8, 95.6
	Minimum	38.5
	Maximum	128.8
Last available assessment within the 12-month post-index period		
	n	29
	Mean	86.6
	SD	22.34
	SE	4.15
	95% CI	78.1, 95.1
	Median	89.7
	IQR	77.6, 99.0
	Minimum	32.5
	Maximum	118.5
Absolute change from baseline to the last available assessment within the 12-month post-index period		
	n	29
	Mean	-2.9
	SD	16.42
	SE	3.05
	95% CI	-9.1, 3.4
	Median	0.2
	IQR	-6.0, 6.8
	Minimum	-58.7
	Maximum	19.3
Relative change from baseline to the last available assessment within the 12-month post-index period, (%)		
	n	29
	Mean	-2.0
	SD	18.91
	SE	3.51
	95% CI	-9.2, 5.2
	Median	0.2
	IQR	-10.3, 6.1
	Minimum	-62.9
	Maximum	44.4
Time from baseline to the last available assessment within the 12-month post-index period, (days)		
	n	29
	Mean	307.3
	SD	39.45
	SE	7.33
	95% CI	292.3, 322.3
	Median	317.0
	IQR	293.0, 330.0
	Minimum	201.0

ppFEV$_1$ (%)		Overall N=30
	Maximum	365.0

Footnotes:

Pediatric Sub-Population: Subset of the overall patient population (All Subjects Set) aged 12 to 17 years of age.

N: Number of subjects in the Pediatric Sub-Population.

Baseline value, unless specified otherwise, was defined as the patient characteristic value observed on the index date. If the information was not available on the index date, information from the closest preceding date prior to the index date was used.

Only subjects with an assessment at baseline and within the 12-month post-index period were retained.

Abbreviations: CI = confidence interval; IQR = interquartile range; ppFEV$_1$ = percent predicted forced expiratory volume in one second; SD = standard deviation; SE = standard error

Weight: The mean absolute change in weight from baseline to the last available assessment within the 12-month post-index period was 4.4 kg (95% CI: 3.3, 5.6).

BMI: The mean absolute change in BMI from baseline to the last available assessment within the 12-month post-index period was 1.1 kg/m2 (95% CI: 0.6, 1.6)

PEx: The annualized PEx rate (PEx per patient per year) (SD) in the paediatric subgroup was 1.1 (1.52) in the pre-index period and 0.9 (1.01) in the post-index period.

Table 19. Descriptive Summary of Pulmonary Exacerbations (Overall and by Type), in the 12 Months Pre-index and Post-index Periods, Overall - Paediatric Sub-Population (aged 12–17 years)

Pulmonary Exacerbations (PEx)		Overall N=30
All PEx		
Pre-index Period (Study months -12 to -1)		
	0, n(%)	15 (50.0%)
	1, n(%)	7 (23.3%)
	2, n(%)	2 (6.7%)
	3+, n(%)	6 (20.0%)
Post-index Period (Study months 1 to 12)		
	0, n(%)	14 (46.7%)
	1, n(%)	9 (30.0%)
	2, n(%)	4 (13.3%)
	3+, n(%)	3 (10.0%)
Difference in percentages of patients with at least 1 PEx		
	Post-index - Pre-index, (%)	3.3
Increased number of PEx in post-index period as compared to pre-index period, n (%)		8 (26.7)
Equal number of PEx in both pre- and post-index periods, n (%)		12 (40.0)
Decreased number of PEx in post-index period as compared to pre-index period, n (%)		10 (33.3)
PEx requiring hospitalization (with/without IV antibiotics)		
Pre-index Period (Study months -12 to -1)		
	0, n(%)	19 (63.3%)
	1, n(%)	8 (26.7%)
	2, n(%)	2 (6.7%)
	3+, n(%)	1 (3.3%)
Post-index Period (Study months 1 to 12)		
	0, n(%)	20 (66.7%)
	1, n(%)	9 (30.0%)
	2, n(%)	0 (0.0%)
	3+, n(%)	1 (3.3%)
Difference in percentages of patients with at least 1 PEx requiring hospitalization (with/without IV antibiotics)		
	Post-index - Pre-index, (%)	-3.3
Increased number of PEx requiring hospitalization in post-index period as compared to pre-index period, n (%)		6 (20.0)
Equal number of PEx requiring hospitalization in both pre- and post-index periods, n (%)		16 (53.3)
Decreased number of PEx requiring hospitalization in post-index period as compared to pre-index period, n (%)		8 (26.7)
PEx requiring hospitalization with IV antibiotics		
Pre-index Period (Study months -12 to -1)		
	0, n(%)	19 (63.3%)
	1, n(%)	8 (26.7%)
	2, n(%)	2 (6.7%)
	3+, n(%)	1 (3.3%)

Pulmonary Exacerbations (PEx)		Overall N=30
Post-index Period (Study months 1 to 12)		
	0, n(%)	20 (66.7%)
	1, n(%)	9 (30.0%)
	2, n(%)	0 (0.0%)
	3+, n(%)	1 (3.3%)
Difference in percentages of patients with at least 1 PEx requiring hospitalization with IV antibiotics		
	Post-index - Pre-index, (%)	-3.3
Increased number of PEx requiring hospitalization in post-index period as compared to pre-index period, n (%)		6 (20.0)
Equal number of PEx requiring hospitalization in both pre- and post-index periods, n (%)		16 (53.3)
Decreased number of PEx requiring hospitalization in post-index period as compared to pre-index period, n (%)		8 (26.7)
PEx requiring outpatient visit with IV antibiotics		
Pre-index Period (Study months -12 to -1)		
	0, n(%)	25 (83.3%)
	1, n(%)	4 (13.3%)
	2, n(%)	1 (3.3%)
	3+, n(%)	0 (0.0%)
Post-index Period (Study months 1 to 12)		
	0, n(%)	25 (83.3%)
	1, n(%)	4 (13.3%)
	2, n(%)	1 (3.3%)
	3+, n(%)	0 (0.0%)
Difference in percentages of patients with at least 1 PEx requiring outpatient visit with IV antibiotics		
	Post-index - Pre-index, (%)	0.0
Increased number of PEx requiring outpatient visit with IV antibiotics in post-index period as compared to pre-index period, n (%)		5 (16.7)
Equal number of PEx requiring outpatient visit with IV antibiotics in both pre- and post-index periods, n (%)		21 (70.0)
Decreased number of PEx requiring outpatient visit with IV antibiotics in post-index period as compared to pre-index period, n (%)		4 (13.3)
All PEx		
Total number of PEx per patient per year		
Pre-index Period (Study months -12 to -1)		
	n	30
	Mean	1.1
	SD	1.52
	Median	0.5
	IQR	0.0, 2.0
	Minimum	0.0
	Maximum	6.0
Post-index Period (Study months 1 to 12)		
	n	30
	Mean	0.9
	SD	1.01
	Median	1.0

Pulmonary Exacerbations (PEx)		Overall N=30
	IQR	0.0, 1.0
	Minimum	0.0
	Maximum	3.0
Difference in annualized counts per patient		
	n	30
	Mean	-0.2
	SD	1.38
	Median	0.0
	IQR	-1.0, 1.0
	Minimum	-3.0
	Maximum	3.0
PEx requiring hospitalization (with/without IV antibiotics) Total number of PEx per patient per year		
Pre-index Period (Study months -12 to -1)		
	n	30
	Mean	0.5
	SD	0.78
	Median	0.0
	IQR	0.0, 1.0
	Minimum	0.0
	Maximum	3.0
Post-index Period (Study months 1 to 12)		
	n	30
	Mean	0.4
	SD	0.67
	Median	0.0
	IQR	0.0, 1.0
	Minimum	0.0
	Maximum	3.0
Difference in annualized counts per patient		
	n	30
	Mean	-0.1
	SD	0.92
	Median	0.0
	IQR	-1.0, 0.0
	Minimum	-3.0
	Maximum	2.0
PEx requiring hospitalization with IV antibiotics Total number of PEx per patient per year		
Pre-index Period (Study months -12 to -1)		
	n	30
	Mean	0.5
	SD	0.78
	Median	0.0
	IQR	0.0, 1.0
	Minimum	0.0
	Maximum	3.0
Post-index Period (Study months 1 to 12)		
	n	30
	Mean	0.4
	SD	0.67
	Median	0.0
	IQR	0.0, 1.0

Pulmonary Exacerbations (PEx)		Overall N=30
	Minimum	0.0
	Maximum	3.0
Difference in annualized counts per patient		
	n	30
	Mean	-0.1
	SD	0.92
	Median	0.0
	IQR	-1.0, 0.0
	Minimum	-3.0
	Maximum	2.0
PEx requiring outpatient visit with IV antibiotics		
Total number of PEx per patient per year		
Pre-index Period (Study months -12 to -1)		
	n	30
	Mean	0.2
	SD	0.48
	Median	0.0
	IQR	0.0, 0.0
	Minimum	0.0
	Maximum	2.0
Post-index Period (Study months 1 to 12)		
	n	30
	Mean	0.2
	SD	0.48
	Median	0.0
	IQR	0.0, 0.0
	Minimum	0.0
	Maximum	2.0
Difference in annualized counts per patient		
	n	30
	Mean	0.0
	SD	0.64
	Median	0.0
	IQR	0.0, 0.0
	Minimum	-2.0
	Maximum	1.0

Footnotes:

Pediatric Sub-Population: Subset of the overall patient population (All Subjects Set) aged 12 to 17 years of age.

N: Number of subjects in the Pediatric Sub-Population; n(%): number and percentage of subjects.

Percentages are calculated relative to the Overall sample size in the relevant sub-population.

PEx could be directly recorded as an event in the patient's chart or indirectly defined as a course of new IV antibiotic therapy and/or PEx related hospitalizations. Courses of IV antibiotics or PEx-related hospitalization occurring within less than seven days from end of first event to start of next one were considered one event.

Abbreviations: IQR = interquartile range; IV = intravenous; PEx = pulmonary exacerbation; SD = standard deviation

Source Table: 80

Healthcare Resource Utilization

- **Hospitalizations:** The annualized hospitalization rate (hospitalizations per patient per year) (SD) was 1.2 (2.17) in the pre-index period and 0.8 (1.19) in the post-index period.

Table 20. Descriptive Summary of Hospitalizations (Overall and by Primary Reasons for Hospitalizations), in the 12 Months Pre-index and Post-index Periods, Overall - Paediatric Sub-Population (aged 12–17 years)

Hospitalizations	Overall N=30
Primary reason for hospitalizations	
Pre-index Period (Study months -12 to -1)	
Pulmonary exacerbation, n (%)	11 (36.7)
Pulmonary complication other than exacerbation, n (%)	1 (3.3)
CF complication, n (%)	1 (3.3)
Transplant-related, n (%)	0 (0.0)
Sinus infection, n (%)	0 (0.0)
Non-transplant surgery, n (%)	0 (0.0)
Other, n (%)	1 (3.3)
Unknown, n (%)	0 (0.0)
Post-index Period (Study months 1 to 12)	
Pulmonary exacerbation, n (%)	11 (36.7)
Pulmonary complication other than exacerbation, n (%)	0 (0.0)
CF complication, n (%)	0 (0.0)
Transplant-related, n (%)	0 (0.0)
Sinus infection, n (%)	0 (0.0)
Non-transplant surgery, n (%)	0 (0.0)
Other, n (%)	4 (13.3)
Unknown, n (%)	0 (0.0)
Difference in percentages of patients with at least one hospitalization	
Post-index - Pre-index, (%)	
Pulmonary exacerbation	0.0
Pulmonary complication other than exacerbation	-3.3
CF complication	-3.3
Transplant-related	0.0
Sinus infection	0.0
Non-transplant surgery	0.0
Other	10.0
Unknown	0.0
All Hospitalizations	
Pre-index Period (Study months -12 to -1)	
0, n(%)	18 (60.0%)
1, n(%)	6 (20.0%)
2, n(%)	1 (3.3%)
3+, n(%)	5 (16.7%)
Post-index Period (Study months 1 to 12)	
0, n(%)	17 (56.7%)
1, n(%)	6 (20.0%)
2, n(%)	5 (16.7%)
3+, n(%)	2 (6.7%)
Difference in percentages of patients with at least one hospitalization	
Post-index - Pre-index (Study months -12 to -1), (%)	3.3
Increased number of hospitalizations in post-index period as compared to pre-index period, n (%)	7 (23.3)
Equal number of hospitalizations in both pre- and post-index periods, n (%)	11 (36.7)

Hospitalizations		Overall N=30
Decreased number of hospitalizations in post-index period as compared to pre-index period, n (%)		12 (40.0)
Pulmonary Exacerbation as Primary Reason		
Pre-index Period (Study months -12 to -1)		
	0, n(%)	19 (63.3%)
	1, n(%)	5 (16.7%)
	2, n(%)	1 (3.3%)
	3+, n(%)	5 (16.7%)
Post-index Period (Study months 1 to 12)		
	0, n(%)	19 (63.3%)
	1, n(%)	4 (13.3%)
	2, n(%)	5 (16.7%)
	3+, n(%)	2 (6.7%)
Difference in percentages of patients with at least one hospitalization for pulmonary exacerbation Post-index - Pre-index (Study months -12 to -1), (%)		0.0
Increased number of hospitalizations for pulmonary exacerbation in post-index period as compared to pre-index period, n (%)		5 (16.7)
Equal number of hospitalizations for pulmonary exacerbation in both pre- and post-index periods, n (%)		14 (46.7)
Decreased number of hospitalizations for pulmonary exacerbation in post-index period as compared to pre-index period, n (%)		11 (36.7)
Primary Reasons Other Than Pulmonary Exacerbations		
Pre-index Period (Study months -12 to -1)		
	0, n(%)	27 (90.0%)
	1, n(%)	1 (3.3%)
	2, n(%)	1 (3.3%)
	3+, n(%)	1 (3.3%)
Post-index Period (Study months 1 to 12)		
	0, n(%)	26 (86.7%)
	1, n(%)	4 (13.3%)
	2, n(%)	0 (0.0%)
	3+, n(%)	0 (0.0%)
Difference in percentages of patients with at least one hospitalization for reason other than pulmonary exacerbation Post-index - Pre-index (Study months -12 to -1), (%)		3.3
Increased number of hospitalizations for other reasons in post-index period as compared to pre-index period, n (%)		4 (13.3)
Equal number of hospitalizations requiring for other reasons in both pre- and post-index periods, n (%)		23 (76.7)
Decreased number of hospitalizations for other reasons in post-index period as compared to pre-index period, n (%)		3 (10.0)
All Hospitalizations Total number of hospitalizations per patient per year		
Pre-index Period (Study months -12 to -1)		
	n	30
	Mean	1.2
	SD	2.17
	Median	0.0

Hospitalizations		Overall N=30
	IQR	0.0, 1.0
	Minimum	0.0
	Maximum	9.0
Post-index Period (Study months 1 to 12)		
	n	30
	Mean	0.8
	SD	1.19
	Median	0.0
	IQR	0.0, 1.0
	Minimum	0.0
	Maximum	5.0
Difference in annualized counts per patient		
	Post-index - Pre-index	
	n	30
	Mean	-0.4
	SD	1.47
	Median	0.0
	IQR	-1.0, 0.0
	Minimum	-4.0
	Maximum	2.0
Pulmonary Exacerbation as Primary Reason Total number of hospitalizations per patient per year		
Pre-index Period (Study months -12 to -1)		
	n	30
	Mean	1.1
	SD	2.18
	Median	0.0
	IQR	0.0, 1.0
	Minimum	0.0
	Maximum	9.0
Post-index Period (Study months 1 to 12)		
	n	30
	Mean	0.7
	SD	1.20
	Median	0.0
	IQR	0.0, 1.0
	Minimum	0.0
	Maximum	5.0
Difference in annualized counts per patient		
	Post-index - Pre-index	
	n	30
	Mean	-0.4
	SD	1.43
	Median	0.0
	IQR	-1.0, 0.0
	Minimum	-4.0
	Maximum	2.0
Primary Reasons Other Than Pulmonary Exacerbations Total number of hospitalizations per patient per year		
Pre-index Period (Study months -12 to -1)		
	n	30

Hospitalizations		Overall N=30
	Mean	0.2
	SD	0.66
	Median	0.0
	IQR	0.0, 0.0
	Minimum	0.0
	Maximum	3.0
Post-index Period (Study months 1 to 12)		
	n	30
	Mean	0.1
	SD	0.35
	Median	0.0
	IQR	0.0, 0.0
	Minimum	0.0
	Maximum	1.0
Difference in annualized counts per patient		
	Post-index - Pre-index	
	n	30
	Mean	-0.1
	SD	0.78
	Median	0.0
	IQR	0.0, 0.0
	Minimum	-3.0
	Maximum	1.0
All Hospitalizations		
Total length of stay (days) per patient per year		
	Pre-index Period (Study months -12 to -1)	
	n	6
	Mean	66.5
	SD	43.22
	Median	52.5
	IQR	34.0, 107.0
	Minimum	22.0
	Maximum	131.0
	Post-index Period (Study months 1 to 12)	
	n	6
	Mean	35.2
	SD	26.86
	Median	29.5
	IQR	16.0, 35.0
	Minimum	14.0
	Maximum	87.0
Difference in length of stay per patient		
	Post-index - Pre-index	
	n	6
	Mean	-31.3
	SD	24.43
	Median	-27.0
	IQR	-44.0, -9.0
	Minimum	-73.0
	Maximum	-8.0
Pulmonary Exacerbation as Primary Reason		
Total length of stay (days) per patient per year		

Hospitalizations		Overall N=30
Pre-index Period (Study months -12 to -1)		
	n	6
	Mean	66.5
	SD	43.22
	Median	52.5
	IQR	34.0, 107.0
	Minimum	22.0
	Maximum	131.0
Post-index Period (Study months 1 to 12)		
	n	6
	Mean	35.2
	SD	26.86
	Median	29.5
	IQR	16.0, 35.0
	Minimum	14.0
	Maximum	87.0
Difference in length of stay per patient		
Post-index - Pre-index		
	n	6
	Mean	-31.3
	SD	24.43
	Median	-27.0
	IQR	-44.0, -9.0
	Minimum	-73.0
	Maximum	-8.0
Primary Reasons Other Than Pulmonary Exacerbations Total length of stay (days) per patient per year		
Pre-index Period (Study months -12 to -1)		
	n	0
	Mean	NA
	SD	NA
	Median	NA
	IQR	NA
	Minimum	NA
	Maximum	NA
Post-index Period (Study months 1 to 12)		
	n	0
	Mean	NA
	SD	NA
	Median	NA
	IQR	NA
	Minimum	NA
	Maximum	NA
Difference in length of stay per patient		
Post-index - Pre-index		
	n	0
	Mean	NA
	SD	NA
	Median	NA
	IQR	NA
	Minimum	NA

Hospitalizations		Overall N=30
	Maximum	NA

Footnotes:

Pediatric Sub-Population: Subset of the overall patient population (All Subjects Set) aged 12 to 17 years of age.

N: Number of subjects in the Pediatric Sub-Population; n(%): number and percentage of subjects.

A subject may contribute for more than one reasons for hospitalization.

Percentages are calculated relative to the Overall sample size in the relevant sub-population.

Abbreviations: CF= cystic fibrosis; IQR = interquartile range; SD = standard deviation;

- **Outpatient Visits (Ad Hoc Table 8):** The outpatient visit rate (outpatient visits per patient per year) (SD) in the paediatric subgroup was 6.0 (4.62) in the pre-index period and 5.4 (2.81) in the post-index period.

Table 21. Descriptive Summary of Outpatient Visits in the 12 Months Pre-index and Post-index Periods, Overall - Paediatric Sub-Population (aged 12–17 years)

Outpatient Visits		Overall N=30
Pre-index Period (Study months -12 to -1)		
	0, n(%)	0 (0.0%)
	1, n(%)	1 (3.3%)
	2, n(%)	0 (0.0%)
	3+, n(%)	29 (96.7%)
Post-index Period (Study months 1 to 12)		
	0, n(%)	0 (0.0%)
	1, n(%)	0 (0.0%)
	2, n(%)	1 (3.3%)
	3+, n(%)	29 (96.7%)
Difference in percentages of patients with at least one outpatient visit		
	Post-index - Pre-index, (%)	0.0
Increased number of outpatient visits in post-index period as compared to pre-index period, n (%)		10 (33.3)
Equal number of outpatient visits in both pre- and post-index periods, n (%)		11 (36.7)
Decreased number of outpatient visits in post-index period as compared to pre-index period, n (%)		9 (30.0)
Total number of outpatient visits per patient per year		
Pre-index Period (Study months -12 to -1)		
	n	30
	Mean	6.0
	SD	4.62
	Median	4.0
	IQR	3.0, 7.0
	Minimum	1.0
	Maximum	20.0
Post-index Period (Study months 1 to 12)		
	n	30
	Mean	5.4
	SD	2.81
	Median	4.0
	IQR	3.0, 7.0
	Minimum	2.0
	Maximum	14.0
Difference in annualized counts per patient		
	Post-index - Pre-index	
	n	30
	Mean	-0.6
	SD	3.35
	Median	0.0
	IQR	-1.0, 1.0
	Minimum	-12.0
	Maximum	6.0

Footnotes:

Pediatric Sub-Population: Subset of the overall patient population (All Subjects Set) aged 12 to 17 years of age.

N: Number of subjects in the Pediatric Sub-Population; n(%): number and percentage of subjects.

Percentages are calculated relative to the Overall sample size in the relevant sub-population.

Abbreviations: IQR = interquartile range; SD = standard deviation;

- **Acute Antibiotic Prescriptions:** The acute antibiotic prescription rate (acute antibiotic prescriptions per patient per year) (SD) in the paediatric subgroup was 3.4 (4.03) in the pre-index period and 3.1 (5.01) in the post-index period.

Table 22. Descriptive Summary of Chronic and Acute Antibiotic Use in the 12 Months Pre-index and Post-index Periods, Overall - Paediatric Sub-Population (aged 12–17 years)

Chronic and/or Acute Antibiotic Use		Overall N=30
Pre-index Period (Study months -12 to -1)		
	Chronic antibiotic use	
	Any route, n(%)	11 (36.7)
	Oral, n(%)	3 (10.0)
	IV, n(%)	1 (3.3)
	Other, n(%)	10 (33.3)
	Acute antibiotic use	
	Any route, n(%)	21 (70.0)
	Oral, n(%)	19 (63.3)
	IV, n(%)	12 (40.0)
	Other, n(%)	1 (3.3)
Post-index Period (Study months 1 to 12)		
	Chronic antibiotic use	
	Any route, n(%)	7 (23.3)
	Oral, n(%)	3 (10.0)
	IV, n(%)	0 (0.0)
	Other, n(%)	4 (13.3)
	Acute antibiotic use	
	Any route, n(%)	19 (63.3)
	Oral, n(%)	17 (56.7)
	IV, n(%)	10 (33.3)
	Other, n(%)	2 (6.7)
Difference in percentages of patients requiring chronic antibiotic use		
	Post-index - Pre-index	
	Any route, %	-13.3
	Oral, %	0.0
	IV, %	-3.3
	Other, %	-20.0
Difference in percentages of patients requiring acute antibiotic use		
	Post-index - Pre-index	
	Any route, %	-6.7
	Oral, %	-6.7
	IV, %	-6.7
	Other, %	3.3
Total number of acute antibiotic prescriptions per patient per year		
Pre-index Period (Study months -12 to -1)		
	n	30
	Mean	3.4
	SD	4.03
	Median	2.5
	IQR	0.0, 5.0
	Minimum	0.0
	Maximum	18.0
Post-index Period (Study months 1 to 12)		
	n	30
	Mean	3.1
	SD	5.01
	Median	1.0

Chronic and/or Acute Antibiotic Use		Overall N=30
	IQR	0.0, 4.0
	Minimum	0.0
	Maximum	23.0
Difference in annualized counts per patient		
Post-index - Pre-index		
	n	30
	Mean	-0.3
	SD	3.44
	Median	-1.0
	IQR	-3.0, 1.0
	Minimum	-5.0
	Maximum	8.0
Total number of days on acute antibiotic treatment per patient per year		
Pre-index Period (Study months -12 to -1)		
	n	30
	Mean	28.9
	SD	35.01
	Median	15.0
	IQR	0.0, 41.0
	Minimum	0.0
	Maximum	110.0
Post-index Period (Study months 1 to 12)		
	n	30
	Mean	31.8
	SD	49.21
	Median	13.5
	IQR	0.0, 35.0
	Minimum	0.0
	Maximum	181.0
Difference in annualized counts per patient		
Post-index - Pre-index		
	n	30
	Mean	2.9
	SD	43.26
	Median	0.0
	IQR	-22.0, 15.0
	Minimum	-75.0
	Maximum	166.0

Footnotes:

Pediatric Sub-Population: Subset of the overall patient population (All Subjects Set) aged 12 to 17 years of age.

N: Number of subjects in the Pediatric Sub-Population; n(%): number and percentage of subjects.

The determination of chronic vs. acute antibiotic treatment was based on the research coordinator assessment performed during data abstraction.

Percentages are calculated relative to the Overall sample size in the relevant sub-population.

A patient could contribute data multiple times.

Abbreviations: IQR = interquartile range; IV = intravenous; SD = standard deviation;

Source Table: 92

- **Use of CF Medications Other than Antibiotics (Ad Hoc Table 10):** Generally, the use of CF medications other than antibiotics in the paediatric subgroup was consistent with that observed in the overall population.

Table 23. Descriptive Summary of Cystic Fibrosis Medication Use other than Antibiotics, in the 12 Months Pre-index and Post-index Periods, Overall - Paediatric Sub-Population (aged 12–17 years)

Cystic Fibrosis Medication Use other than Antibiotics	Overall N=30
Pre-index Period (Study months -12 to -1)	
Bronchodilator, n (%)	4 (13.3)
Enzymes, n (%)	1 (3.3)
Inhaled mucous modifiers, n (%)	3 (10.0)
Anti-inflammatory drug, n (%)	8 (26.7)
Gastrointestinal medication, n (%)	10 (33.3)
Pancreatic enzyme replacement therapy, n (%)	5 (16.7)
Pulmozyme, n (%)	1 (3.3)
Hormonal contraception, n (%)	0 (0.0)
IUD, n (%)	0 (0.0)
Diabetes control, n (%)	0 (0.0)
Other, n (%)	18 (60.0)
Post-index Period (Study months 1 to 12)	
Bronchodilator, n (%)	3 (10.0)
Enzymes, n (%)	1 (3.3)
Inhaled mucous modifiers, n (%)	2 (6.7)
Anti-inflammatory drug, n (%)	9 (30.0)
Gastrointestinal medication, n (%)	6 (20.0)
Pancreatic enzyme replacement therapy, n (%)	3 (10.0)
Pulmozyme, n (%)	1 (3.3)
Hormonal contraception, n (%)	0 (0.0)
IUD, n (%)	0 (0.0)
Diabetes control, n (%)	1 (3.3)
Other, n (%)	15 (50.0)
Difference in percentages of patients requiring CF medication use other than antibiotics	
Post-index - Pre-index, (%)	
Bronchodilator	-3.3
Enzymes	0.0
Inhaled mucous modifiers	-3.3
Anti-inflammatory drug	3.3
Gastrointestinal medication	-13.3
Pancreatic enzyme replacement therapy	-6.7
Pulmozyme	0.0
Hormonal contraception	0.0
IUD	0.0
Diabetes control	3.3
Other	-10.0

Footnotes:

Pediatric Sub-Population: Subset of the overall patient population (All Subjects Set) aged 12 to 17 years of age.

N: Number of subjects in the Pediatric Sub-Population; n(%): number and percentage of subjects.

Percentages are calculated relative to the Overall sample size in the relevant sub-population.

A patient could contribute data multiple times or not contribute to any rows due to no relevant medication use.

Abbreviations: CF = cystic fibrosis; IUD = intrauterine device;

Other Outcomes

● **Positive for P. aeruginosa (Ad Hoc Table 11):** The proportion of patients with positive cultures for P. aeruginosa (mucoid or non-mucoid) in the pediatric subgroup was 56.7% before Orkambi initiation and 50% after Orkambi initiation.

● **Lung Transplant (Ad Hoc Table 11):** No patients required a lung transplant after Orkambi initiation in the paediatric subgroup.

● **Death (Ad Hoc Table 11):** There were no deaths in the paediatric subgroup.

MAH's Summary

The paediatric subgroup analysis of 30 patients from Study 117 showed improvements in BMI and weight, as well as a reduction in the annualized PEx rate, the rate of hospitalizations, outpatient visits, acute antibiotic prescriptions, and the proportion of patients with positive P. aeruginosa after Orkambi initiation. The rate of PEx, hospitalizations, outpatient visits, acute antibiotic prescriptions, and positive P. aeruginosa status were all lower in the paediatric subgroup than in the overall population. There were no lung transplants or deaths in the paediatric subgroup.

A numerical decrease in ppFEV1 was observed in the paediatric subgroup, which can be expected of this age group and the natural progression of the disease. These results should be interpreted with caution given that the confidence intervals cross zero, the small sample size, the lack of a comparator control, and other limitations of this exploratory chart review study. In the larger, ongoing comparator-controlled PASS, a reduction in the rate of lung function decline was observed in Orkambi-treated patients (n = 2,287) compared to untreated comparator patients (n = 3,527) across various age strata over a longer observational period. Specifically, in the subgroup of patients 12 through 17 years of age (n = 773), the decline in lung function change from the pre-treatment baseline was -3.84 percentage points versus -7.62 percentage points in the untreated comparator patients (n = 845).

The overall positive benefit-risk balance of Orkambi in F/F patients, including the 12- through 17-year-old age group, has been well established in pivotal and long-term clinical studies. Post-approval safety studies, real world evidence and post-marketing surveillance data continue to support the favourable efficacy and safety profile with Orkambi.

Assessor's comment

The MAH provided the requested post-hoc subgroup analyses of the paediatric patients 12 through 17 years of age from Study 117.

Distribution of Paediatric Patients Enrolled Across Sites: paediatric patients (n=30) were enrolled in four of the eight participating US sites.

Demographics and Baseline Characteristics: The mean (SD) age at the index date was 14.4 (1.80) years, mean (SD) weight was 47.0 (10.61) kg, mean (SD) height was 156.00 (11.00) cm, mean (SD) BMI was 19.1 (2.67) kg/m2, with no relevant differences between early and late initiators. The proportion of male patients was 43.3% (early initiators: 47.1%; late initiators: 38.5%). The most commonly reported CF comorbid conditions during the pre-index period or ongoing at index date were chronic sinusitis and asthma, followed by CF related diabetes. However, the interpretation of these data is limited, as most baseline comorbid conditions were categorized as "Others" (16/30, 53.3%). The mean (SD) ppFEV1 was 89.5 (20.51) percentage points (early initiators: 84.8 [SD: 23.80] percentage points; late initiators: 95.2 [14.42] percentage points). The proportion of paediatric patients with PEx was 16.7% (early initiators: 23.5%; late initiators: 7.7%). The proportion of paediatric patients treated with IV antibiotics was 6.7% (early initiators:11.8%; late initiators: 0.0%) and the proportion of paediatric patients with CF-related inpatient hospitalizations was 6.7% (early initiators: 11.8%; late initiators: 0.0%), supporting a more severe pattern of baseline disease characteristics in early initiators as compared to late initiators.

Effectiveness: The paediatric subgroup analysis of 30 patients from Study 117 showed improvements in **BMI** [mean change from baseline: 1.1 kg/m2 (95% CI: 0.6, 1.6)] and **weight** [mean change from baseline 4.4 kg (95% CI: 3.3, 5.6)].

A numerical decrease in ppFEV1 was observed in the paediatric subgroup, the mean absolute change in **ppFEV1** from baseline to the last available assessment within the 12-month post-index period was -

2.9 percentage points (95% CI: -9.1, 3.4). The observed decrease is similar to the annualized rate of lung function decline reported in a published analysis of US Cystic Fibrosis Foundation (CFF) registry data in patients homozygous for F508del, aged 13 through 17 years, **not treated** with a CFTR modulator (-2.66 percentage points per year; Wegener et al, J Cyst Fibros. 2018;17(4):503-10) therefore not suggesting a positive trend on ppFEV1 However, given the small sample size of Study 117 paediatric subgroup and the wide CI that crosses 0, no conclusions can be made regarding the effect of Orkambi treatment on ppFEV1 in this subgroup. Of note, supportive results of Orkambi effectiveness on $ppFEV_1$ are coming from the larger, ongoing comparator-controlled PASS, on average from 2014 to 2018 the $ppFEV_1$ decreased by 3.7 percentage points in the Orkambi Disease Progression Cohort and decreased by 6.9 percentage points in the Comparator Disease Progression Cohort.

No major differences, although with numerical slight decreases, were observed in the paediatric subgroup between pre-index period and post index period for: **annualized PEx rate** [PEx per patient per year (SD) was 1.1 (1.52) in the pre-index period and 0.9 (1.01) in the post-index period]; **rate of hospitalizations** [hospitalizations per patient per year (SD) was 1.2 (2.17) in the pre-index period and 0.8 (1.19) in the post-index period], **outpatient visits** [outpatient visits per patient per year) (SD) was 6.0 (4.62) in the pre-index period and 5.4 (2.81) in the post-index period], **acute antibiotic prescriptions** [acute antibiotic prescriptions per patient per year (SD) was 3.4 (4.03) in the pre-index period and 3.1 (5.01) in the post-index period], and the **proportion of patients with positive P. aeruginosa** after Orkambi initiation (56.7% before Orkambi initiation and 50% after Orkambi initiation). There were no lung transplants or deaths in the paediatric subgroup.

As regards to **Use of CF Medications Other than Antibiotics**, most categories of concomitant medications other than antibiotics remained unchanged or decreased between pre and post-index period, apart from the categories "anti-flammatory drug" and "diabetes control" that showed a 3.3% increase; however the interpretation of these data is limited, as most concomitant medications were categorized as "Others" (18/30, 60% in the pre index period and 15/30, 50% in the post index period).

Conclusion:

The MAH provided the requested descriptive results regarding Orkambi effectiveness in the subgroup of paediatric patients 12 through 17 years of age from Study 117. These data present limitations and should be interpreted with caution due to the low number of paediatric subjects aged 12-17 years enrolled (N=30, among them N=17 'early initiators' and N=13 'late initiators'), the retrospective data collection from patient medical records and the exploratory nature of the study.

A more severe pattern of baseline disease characteristics was observed in early initiators as compared to late initiators.

Results seem not suggesting a positive trend on ppFEV1. However, given the small sample size of Study 117 paediatric subgroup and the wide CI that crosses 0, no conclusions can be made. Of note, supportive results of Orkambi effectiveness on $ppFEV_1$ are coming from the larger, ongoing comparator-controlled PASS.

Increases in weight and BMI were observed in the paediatric subgroup between pre-index period and post index period. There were no major differences for other variables/outcomes; slight numerical decreases were observed.

Issue resolved

Question 2

In order to allow to contextualize the higher frequency of treatment discontinuation (20%) observed in Study 117 in adolescents 12 through 17 years of age, compared to the one

observed in the same age range in pivotal clinical trials (1.0%, 3/290 subjects), baseline clinical characteristics of the subgroup of 30 paediatric subjects included in Study 117 are needed. Baseline clinical characteristics of the subgroup of 30 paediatric subjects included in Study 117 should be discussed by the MAH in comparison with baseline clinical characteristics of adolescents 12 through 17 years of age, enrolled in the pooled placebo-controlled Phase 3 studies (pivotal Studies 103 and 104).

Summary of the MAH's Response

The demographics and baseline characteristics of the 30 paediatric patients from Study 117 are discussed in the response to Question 1 and provided in Ad Hoc Table 24.

As discussed in the response to Question 1, Study 117 paediatric subgroup results should be interpreted with caution due to the exploratory nature of the study and the small sample size. In addition, it is not appropriate to compare baseline characteristics between a real-world evidence study and randomized, controlled clinical studies that differ with respect to inclusion and exclusion criteria. Inclusion in Study 117 was based on a treatment initiation date within 6 months of Orkambi approval, while Studies 103/104 had inclusion and exclusion criteria relating to CF disease status, comorbidities, medical history, and ppFEV1.

A brief summary of the available baseline characteristics for the paediatric subgroups for both Study 117 and Studies 103/104 is provided in Table 2. A few baseline characteristics that were collected in Study 117 were not collected in Studies 103/104, including CF comorbid conditions, PEx, intravenous (IV) antibiotics, inpatient hospitalizations for CF, and CF-related PEx.

Table 24 Summary of Baseline Clinical Characteristics for the Paediatric Subgroups in Study 117 and Studies 103/104

Endpoint Category	Study 117 N = 30	Studies 103/104 N = 290
Weight (kg)		
n	29	290
Mean (SD)	47.0 (10.61)	49.55 (9.939)
Median (min, max)	45.6 (33.8, 72.8)	49.00 (27.0, 77.0)
Height (cm)		
n	29	290
Mean (SD)	156.0 (11.00)	161.3 (10.56)
Median (min, max)	156.0 (141.0, 179.7)	161.0 (133, 189)
BMI (kg/m^2)		
n	29	290
Mean (SD)	19.1 (2.67)	18.88 (2.261)
Median (min, max)	18.7 (16.2, 27.2)	18.75 (14.1, 25.1)
$ppFEV_1$ (percentage points)		
n	29	285
Mean (SD)	89.5 (20.51)	67.30 (13.022)
Median (min, max)	89.9 (38.5, 128.8)	68.60 (31.3, 96.5)
***P. aeruginosa* status**[a]		
Negative	13 (43.3%)	115 (39.7%)
Positive	17 (56.7%)	175 (60.3%)

BMI: body mass index; max: maximum value; min: minimum value; N: total sample size, n: subsample size; ppFEV$_1$: percent predicted forced expiratory volume in 1 second

Note: For Study 117: Percentages are calculated relative to the overall sample size in the relevant sub-population (presented in the first row of each listed event).

[a] For Study 117, *P. aeruginosa* status represents any positive results for mucoid or non-mucoid *P. aeruginosa* during the pre-index period. For Study 103/104, *P. aeruginosa* status represents status before first dose of study drug.

Assessor's comment

The MAH provided the requested data.

It is acknowledged that comparing baseline characteristics between a real-world evidence study and randomized, controlled clinical studies presents limitations and that Study 117 paediatric subgroup results should be interpreted with caution due to the small sample size.

Some baseline characteristics that were collected in Study 117 were not collected in Studies 103/104, such as CF comorbid conditions

It is of note that ppFEV1 value of patients 12 to 17 years of age enrolled in Study 117 is higher (mean 89.5, SD 20.51) in comparison to patients of the same age range enrolled in pivotal studies 103/104 (mean 67.3, SD 13.0) underlying a quite different lung function as measured by ppFEV1 at baseline surely limiting indirect comparability of study results but possibly not substantially contributing to a higher treatment discontinuation observed in the 117 study.

Conclusion: The issue is not pursued further.

Question 3

The MAH is requested to discuss the high frequency of discontinuation (35.8%) and to discuss available data on the reasons for discontinuations observed in the adult population of patients enrolled in Study 117.

Summary of the MAH's response

The reasons for treatment discontinuation after first initiation in the overall population in Study 117 were (in order of most common to least common): respiratory adverse event (AE) (39 patients [52.0%]), other reason (17 patients [22.7%]), other AE (9 patients [12.0%]), lack of effectiveness (5 patients [6.7%]), unknown (3 patients [4.0%]), and gastrointestinal AE (2 patients [2.7%]) (Study 117 CSR/Table 6). Additional information from the study case report forms (CRFs) that was entered by the site as free text is provided in Table 3 for the adult subgroup (≥18 years of age), and provides additional context for those patients who had "other reason" and "other AE" listed as the primary reason for treatment discontinuation. Overall, the distribution of the primary reasons for discontinuation was generally consistent with that observed in clinical experience, with respiratory AEs being the most common, consistent with the SmPC.

Annual interim analysis results from the larger, registry-based, 5-year post-authorization safety study (PASS) Study 108 represents a more robust data set and indicates a lower discontinuation rate than that observed in Study 117. The proportion of patients in the Orkambi Safety Cohort who had no record of Orkambi use in the subsequent calendar year suggests a discontinuation rate of 10.1% for the 2016 Orkambi Safety Cohort (N= 5,553) and 12.2% for the 2017 Orkambi Safety Cohort (N = 6,664). The data from this study, given the larger sample size and longer duration, may be considered more representative of the real-world Orkambi experience.

Table 25 Reasons for Discontinuation for Patients ⩾18 Years of Age

Patient[a]	Primary Reason for Discontinuation (Category)	Reason for Discontinuation Specified by Free Text (Verbatim)
1	Respiratory AE	chest tightness and SOB
2	Respiratory AE	increased chest tightness and shortness of breath
3	Respiratory AE	dyspnea
4	Respiratory AE	decrease in FEV1
5	Respiratory AE	chest tightness, increased SOB
6	Respiratory AE	shortness of breath, chest tightness
7	Respiratory AE	difficulty breathing
8	Respiratory AE	increased shortness of breathe
9	Respiratory AE	chest tightness
10	Respiratory AE	Persistent chest tightness
11	Respiratory AE	Declining Lung Function and Chest Tightness Overall.
12	Respiratory AE	patient had declining lung function and saw improvement after stopping orkambi
13	Respiratory AE	respiratory symptoms and chest tightness, had hemoptysis
14	Respiratory AE	Patient reported he had stopped therapy due to Chest tightness
15	Respiratory AE	persistent chest tightness
16	Respiratory AE	Chest tightness
17	Respiratory AE	Shortness of breath, Chest tightness
18	Respiratory AE	CF Exacerbation
19	Respiratory AE	Chest tightness
20	Respiratory AE	Chest Tightness
21	Respiratory AE	Increased asthma and diarrhea.
22	Respiratory AE	decreased PFTs
23	Respiratory AE	Chest Tightness
24	Respiratory AE	Chest Tightness
25	Respiratory AE	Extreme Shortness of Breath and Oxygen Dependence while sleeping
26	Respiratory AE	Worsening respiratory efficiency
27	Respiratory AE	shortness of breath and hemoptysis
28	Respiratory AE	shortness of breath
29	Respiratory AE	shortness of breath
30	Respiratory AE	Chest Tightness
31	Respiratory AE	Dyspnea

Patient[a]	Primary Reason for Discontinuation (Category)	Reason for Discontinuation Specified by Free Text (Verbatim)
32	Respiratory AE	increased cough, increased shortness of breath
33	Respiratory AE	severe chest tightness, chest pain and shortness of breath
34	Respiratory AE	chest tightness, increased cough, increased sputum production, and intermittent nausea, and approximately 4-6 moderate size loose stools, abdominal cramping, flatulence
35	Respiratory AE	Chest tightness, malaise
36[b]	Respiratory AE	acute hypoxic respiratory failure
	Respiratory AE	side effects
37[b]	Respiratory AE	shortness of breath, chest tightness, increased cough, weakness
	Respiratory AE	increased cough, chest congestion, sputum production, shortness of breath
38[b]	Respiratory AE	increased cough, increased sputum, shortness of breath
	Other reason	shortness of breath
39	Other reason	dizziness, joint pain, increased cough, diarrhea
40	Other reason	raash and hives
41	Other reason	Patient to start fertility treatments and will stay off until [redacted] is completed these treatments and/or pregnancy
42	Other reason	Elevated CK and mild elevated in LFT
43	Other reason	Deceased
44	Other reason	Patient received Lung Transplant
45	Other reason	elevated LFTs increased >5 times ULN
46	Other reason	Expense of Medication
47	Other reason	Stevens- Johnsons syndrome
48	Other reason	Lung Transplant
49	Other reason	Patient stopped due to side effect
50	Other reason	side effects
51	Other reason	Death
52	Other reason	Patient forgot to order Orkambi
53[b]	Other reason	hemoptysis
	Other reason	patient not using ORKAMBI therefore taken off medication list; patient last filled ORKAMBI prescription [redacted]
54[b]	Other reason	malaise, dizziness and fatigue
	Respiratory AE	"symptoms of exacerbation"
55	Other AE	psyh issues amd abdominal pain issues
56	Other AE	elevated liver enzymes
57	Other AE	Urinary Hesitancy, Headaches, Leg Cramps
58	Other AE	Worsened depression
59	Other AE	rash,chest tightness
60	Lack of effectiveness	--
61	Lack of effectiveness	--
62	Lack of effectiveness	--
63	Lack of effectiveness	--
64	Unknown	--
65	Unknown	--

Patient[a]	Primary Reason for Discontinuation (Category)	Reason for Discontinuation Specified by Free Text (Verbatim)
66	Unknown	--
67	GI AE	expolsive diarrhea

AE: adverse event; CK: creatine kinase; GI: gastrointestinal; LFT: liver function test; ULN: upper limit of normal
Source: Data on file

[a] The listed patient numbers do not reflect individual study identification numbers.

[b] These patients discontinued Orkambi after the first initiation of treatment and had a second discontinuation after re-initiation of Orkambi during Study 117.

Assessor's comment

The MAH provided the requested data.

A high frequency of discontinuation (35.8%) was observed in the overall population of Study 117.

The reasons for treatment discontinuation were respiratory AEs (39 patients [52.0%]), other reason (17 patients [22.7%]), other AE (9 patients [12.0%]), lack of effectiveness (5 patients [6.7%]), unknown (3 patients [4.0%]), and gastrointestinal AE (2 patients [2.7%]) (Study 117 CSR/Table 6).

As regards to discontinuation categorized as "Other reason" or "Other AE", the MAH provided the information from the study case report forms (CRFs) that was entered by the site as free text: 5 out of 9 patients categorized as "Other AEs" discontinued due to the following reasons (one patient each): psych issues and abdominal pain issues, elevated liver enzymes, urinary hesitancy/ headaches/ leg cramps, worsened depression, rash/ chest tightness. Among the 17 patients that discontinued due to other reasons, most patients discontinued due to AEs [n=10; the AEs were the following: respiratory AEs (2), dizziness (2), cutaneous AE (2, including one event of Steven Johnson), elevated LFT (2), side effects unspecified (2)]. Two discontinuation each were due to death and organ transplant.

As regards to the types of AEs leading to discontinuation, the events were mostly known ADRs for Orkambi.

In the annual interim analysis results from the larger, registry-based, 5-year post-authorization safety study (PASS) Study 108, the proportion of patients in the Orkambi Safety Cohort who had no record of Orkambi use in the subsequent calendar year suggests a discontinuation rate of 10.1% for the 2016 Orkambi Safety Cohort (N= 5,553) and 12.2% for the 2017 Orkambi Safety Cohort (N = 6,664).

Conclusion:

A high frequency of discontinuation (35.8%) was observed in the overall population of Study 117, however the adverse events leading to discontinuation were mostly known ADRs for Orkambi. It is acknowledged that the data from the PASS study, given the larger sample size and longer duration, may be considered more representative of the real-world Orkambi experience.

Issue resolved

Question 4

The MAH is requested to provide all available information (including age) of the 7 subjects requiring lung transplant after Orkambi initiation and of the 2 deaths observed during the post index period. The higher proportion of patients requiring at least one organ transplantation after Orkambi initiation in Study 117 (3.2%) in comparison to the proportion of patients with a history of any organ transplant (0.4%) in the Orkambi Safety Cohort in 2018 in PASS Study 108 should be discussed.

Summary of the MAH's response

Table 26 provides the age at the time that Orkambi was prescribed for the 7 patients who had a lung transplant and the 2 patients who died during the post-index period. For death and organ transplant, there was no option in the CRFs for the sites to provide any additional description regarding these events. As such, no further information is available on these patients.

Table 26 Age for Patients Who Had Lung Transplant or Death

Patient[a]	Lung Transplant or Death During Post-index Period	Index Date	Age at Orkambi Prescription (Years)
44	Lung Transplant	[redacted]	[redacted]
48	Lung Transplant		
5	Lung Transplant		
65	Lung Transplant		
58	Lung Transplant		
68	Lung Transplant		
28	Lung Transplant		
69	Death		
51	Death		

Source: Data on file

[a] The listed patient numbers do not reflect individual study identification numbers.

As discussed previously, Study 117 was an exploratory chart study to explore the early treatment patterns following the initial US approval. The ongoing PASS Study 108 is a comparator controlled, registry-based study that is collecting real-world data from a much larger population of CF patients and over a longer observational period. The results from the ongoing PASS have demonstrated a significantly lower risk of death and organ transplantation in Orkambi-treated patients and will continue to provide real-world data on the Orkambi experience.

Assessor's comment

The age at the time that Orkambi was prescribed for the 7 patients who had a lung transplant ranged from 23 to 56 years of age. There were 2 patients who died during the post-index period. The MAH clarified that no further information is available on these patients, given that for death and organ transplant, there was no option in the CRFs for the sites to provide any additional description regarding these events.

In the third interim analysis of the ongoing PASS, cconsistently with the previous 2 interim reports, the risk of death and organ transplant was statistically significantly lower in the Orkambi Cohort compared to the Comparator Cohort.

Conclusion:

In Study 117, a higher proportion of patients (3.2%) required lung transplant after Orkambi initiation in comparison to the proportion of patients with a history of any organ transplant (0.4%) in the Orkambi Safety Cohort in 2018 in PASS Study 108.

It is acknowledged that the data from the PASS study, given the larger sample size and longer duration, may be considered more representative of the real-world Orkambi experience.

Issue resolved.

Overall, the MAH has addressed all questions raised during the procedure satisfactorily. There are no further points. The benefit-risk assessment is considered favourable.