15 October 2020
EMA/610236/2021
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/P46/010.3

Note

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

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Table of contents

Abbreviation	Definition
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BILI	bilirubin
BMI	body mass index
CF	cystic fibrosis
CFF	Cystic Fibrosis Foundation (US)
CFFPR	Cystic Fibrosis Foundation Patient Registry
CFTR	cystic fibrosis transmembrane conductance regulator gene
CFTR	cystic fibrosis transmembrane conductance regulator protein
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CSR	clinical study report
EU	European Union
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
GLI	Global Lung Function Initiative
IVA	ivacaftor
LUM	lumacaftor
n	size of subsample
N	total sample size
PEx	pulmonary exacerbation
ppFEV1	percent predicted forced expiratory volume in 1 second
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
ULN	upper limit of normal
US	United States

1. Introduction

On 20 November 2019, the MAH submitted a post-approval Observational Study to Evaluate the Long-term Effectiveness and Safety of Orkambi (Study 120), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure REC 10.1, recommendation to submit a final clinical study report of Study VX16 809 120.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study VX16 809 120 is a stand-alone study.

2.2. Clinical aspects

2.2.1. Introduction

At the time of the initial Orkambi approval in the EU, the Committee for Medicinal Products for Human Use (CHMP) requested the MAH to explore the possibility of a longer follow-up (i.e. 5 years) of study population enrolled in the phase 3 study (study 105) submitted in support of the indication in patients 12 years and older.

Because the majority of subjects had completed Study 105 at the time of this request, Vertex determined that extending this study for an additional 3 years was not feasible and has explored alternative approaches to evaluate long-term safety and efficacy in this population. Vertex explored the feasibility of identifying and evaluating Study 105 participants via existing national CF patient registries in US and EU. In general, to fulfill the study objectives, only large, research-experienced CF patient registries with broad national CF patient coverage, high quality standard data collection, and timely data availability can be used. The registries initially meeting these criteria included US Cystic Fibrosis Foundation Patient Registry (CFFPR), the largest CF patient registry worldwide, and a number of CF patient registries in EU countries. Based on further assessment of feasibility, evaluated EU registries were considered not suitable for the purposes of the study due to various reasons, including low national coverage (e.g., Spain, 50%), significant data availability lags and/or data quality issues (e.g., Italy; as of 2017, the most recent data available are from 2014), or very small Study 105 patient pool (e.g., UK, France, Germany, Sweden, Austria, and Denmark). Because a significant proportion of subjects who completed Study 105 Part A were from the US (N = 485; 53%), Vertex conducted Study 120 that followed only US subjects from Study 105 who were also enrolled in the US CFFPR for 3 years after the completion of Study 105.

Study 105 was a 96-week, Phase 3, parallel-group, multicentre, rollover study in subjects with CF, homozygous or heterozygous for F508del, who participated in Study 103 or Study 104 (homozygous subjects) or in Cohort 4 of Study 102 (heterozygous subjects). Study 105 Part A (referred to hereafter as Study 105) enrolled subjects from Studies 103 and 104, who were 12 years and older at screening in parent studies.

In Study 105 Part A treatment cohort, a total of 1030 subjects were enrolled of whom, 1029 subjects were dosed with LUM/IVA: 513 subjects received LUM 600 mg once daily (qd) with IVA (179 subjects received placebo in the previous study) and 516 subjects received LUM 400 mg every 12 hours (q12h) with IVA (176 subjects received placebo in the previous study). Subjects who received LUM/IVA in

Study 103 or 104 continued to receive the same dose and regimen of study drug in a double-blind fashion in Study 105 for 96 weeks in order to maintain the blind from the previous studies. Subjects who received placebo in Study 103 or 104 were randomized (1:1) to 1 of the 2 double-blind treatment groups. Randomization was stratified by age (<18 versus ≥18 years of age), sex (male versus female), and percent predicted forced expiratory volume in 1 second (ppFEV1) severity (<70% versus ≥70% predicted) collected at baseline or the Screening Visit of the subject's previous study.

As regard to the recommended Orkambi dose arm, 340 patients continued treatment with lumacaftor 400 mg every 12 h/ivacaftor 250 mg every 12 h; 176 patients who had received placebo in the parental studies (TRANSPORT or TRAFFIC studies) initiated treatment with lumacaftor 400 mg every 12 h/ivacaftor 250 mg every 12 h. These results have been published (Konstan et al, Lancet Respir Med, 2017) and in the publication the estimated annual rate of decline in percent predicted FEV1 (ppFEV1) in treated patients was compared with that of a matched registry cohort (Supplementary material to Konstan et al. Lancet Respir Med 2016; published online Dec 20).

The focus of the efficacy in the final analysis of Study 105 was based on the Cumulative Study Period, which starts from the first dose of the study drug in the previous study to the last day in Study 105. The analysis for efficacy endpoints was focused on within-group comparisons. No between groups comparisons were performed. The interpretation of Study 105 results is hampered by a large amount of missing data (mostly due to US patients who transitioned to commercially available Orkambi), and a combination of previous and current study periods.

Among the 1029 dosed subjects, 411 (39.9%) completed treatment and 618 (60.1%) prematurely discontinued treatment; the incidence of discontinuation was similar across all 4 treatment groups. The majority of discontinuations after Week 60 were US patients who transitioned to commercially available Orkambi. Because the decrease in sample size could affect the robustness of data analyses, the primary efficacy analyses were performed using data up to Week 72 of Study 105. Sensitivity analyses included data up to Week 96. Although the efficacy seems to be sustained during the initial 24 weeks, a trend of decaying beyond Week 24 was observed in Study 105: for subjects who received active treatment in both Study 103/104 and Study 105, the improvements in ppFEV1 from previous study baseline during Study 103/104 were generally sustained in Study 105 up to Extension Week 36 for L600qd/I group and Extension Week 24 for L400q12h/I group. The improvement in ppFEV1 decreased over time in both groups with small/no improvement in ppFEV1 at Extension Week 96. The least square (LS) mean absolute change from baseline in ppFEV1 for the L400q12h/I group (the authorized dose for this age group) was 1.6 percentage points (P = 0.0012) at Week 60; at Week 72, the L400q12h/I group result was numerically above baseline but lacked within-treatment statistical significance (P = 0.2806).

However, the treatment with LUM/IVA (L400q12h/I) in Study 105 showed a slower annual rate of ppFEV1 decline (-1.33 percentage points/year) vs. matched controls using data from 2012 to 2014 obtained from the US CFFPR (-2.29 percentage points/year).

For the L400q12h/I group, the change in BMI was 0·69 kg/m^2 (95%CI: 0·56 to 0·81) at extension week 72 and 0·96 kg/m^2 (95%CI: 0·81 to 1·11) at extension week 96, thus the effect was maintained with respect to baseline. The annualised pulmonary exacerbation (PEX) rate in patients continuing treatment through extension week 96 (0·65 events per patient-year, 95%CI: 0·56 to 0·75) for the L400q12h/I group remained lower than the PBO rate in pivotal trials, (Study 103/104: 1.19 events per patient-year).

The introduction in Study 105 of study drugs to the LUM/IVA-naïve subjects from Study 103/104 confirms reproducibility of efficacy.

Table 1: Long-term effect of Lumacaftor/Ivacaftor in Trial 3*

	Placebo transitioned to Lumacaftor 400 mg q12h/ Ivacaftor 250 mg q12h (n=176)**			Lumacaftor 400 mg q12h/ Ivacaftor 250 mg q12h (n=369)†		
Baseline and Endpoint	**Mean (SD)**	**LS Means (95% CI)**	**P value**	**Mean (SD)**	**LS Means (95% CI)**	**P value**
Baseline $ppFEV_1$‡	60.2 (14.7)			60.5 (14.1)		
Absolute change from baseline $ppFEV_1$ (percentage points)						
Extension Week 72		(n = 134) 1.5 (0.2, 2.9)	0.0254		(n = 273) 0.5 (-0.4, 1.5)	0.2806
Extension Week 96		(n = 75) 0.8 (-0.8, 2.3)	0.3495		(n = 147) 0.5 (-0.7, 1.6)	0.4231
Relative change from baseline $ppFEV_1$ (%)						
Extension Week 72		(n = 134) 2.6 (0.2, 5.0)	0.0332		(n = 273) 1.4 (-0.3, 3.2)	0.1074
Extension Week 96		(n = 75) 1.1 (-1.7, 3.9)	0.4415		(n = 147) 1.2 (-0.8, 3.3)	0.2372
Baseline BMI (kg/m^2)‡	20.9 (2.8)			21.5 (3.0)		
Absolute change from baseline in BMI (kg/m^2)						
Extension Week 72		(n = 145) 0.62 (0.45, 0.79)	< 0.0001		(n = 289) 0.69 (0.56, 0.81)	< 0.0001
Extension Week 96		(n = 80) 0.76 (0.56, 0.97)	< 0.0001		(n = 155) 0.96 (0.81, 1.11)	< 0.0001
Baseline CFQ-R Respiratory Domain Score (points)‡	70.4 (18.5)			68.3 (18.0)		
Absolute change in CFQ-R Respiratory Domain Score (points)						
Extension Week 72		(n = 135) 3.3 (0.7, 5.9)	0.0124		(n = 269) 5.7 (3.8, 7.5)	< 0.0001
Extension Week 96		(n = 81) 0.5 (-2.7, 3.6)	0.7665		(n = 165) 3.5 (1.3, 5.8)	0.0018
Number of Pulmonary exacerbations (events) ** † * **						
Number of events per patient- year (95% CI) (rate per 48 wks)		0.69 (0.56, 0.85)			0.65 (0.56, 0.75)	
Number of events requiring hospitalization per patient-year (95% CI) (rate per 48 wks)		0.30 (0.22, 0.40)			0.24 (0.19, 0.29)	
Number of events requiring intravenous antibiotics per patient-year (95% CI) (rate per 48 wks)		0.37 (0.29, 0.49)			0.32 (0.26, 0.38)	

* A total of 82% (421 of 516 eligible patients) completed 72 weeks of this study; 42% completed 96 weeks. Majority of patients discontinued for reasons other than safety.

** For patients rolled over from Trials 1 and 2 (placebo-to-lumacaftor/ivacaftor group) total exposure was up to 96 weeks. Presentation of the lumacaftor 400 mg q12h/ivacaftor 250 mg q12h dose group is consistent with recommended posology.
*** The event rate per patient-year was annualised to 48 weeks.
† For patients rolled over from Trials 1 and 2 (lumacaftor/ivacaftor-to-lumacaftor/ivacaftor group) total exposure was up to 120 weeks. Presentation of the lumacaftor 400 mg q12h/ivacaftor 250 mg q12h dose group is consistent with recommended posology.
‡ Baseline for the placebo transitioned to lumacaftor 400 mg q12h/ivacaftor 250 mg q12h group was the Trial 3 baseline. Baseline for the lumacaftor 400 mg q12h/ivacaftor 250 mg q12h group was the Trial 1 and 2 baseline.

2.2.2. Clinical study

A Post-approval Observational Study to Evaluate the Long-term Effectiveness and Safety of Orkambi in US Patients Who Completed Study VX12-809-105 Part A

Description

Methods

Objective

To evaluate the long-term effectiveness and safety of Orkambi in US patients who completed Study 105 using secondary data from the US CFFPR.

Study design

This was a 3-year observational study for the cohort A of Study 105 US subjects who were enrolled in the US CFFPR and provided consent for their US CFFPR data to be evaluated by the MAH.

Annual registry data from 2016 through 2018 were evaluated, ensuring 3 years of US CFFPR follow-up among subjects who completed Study 105.

Study population /Sample size

US subjects who completed treatment with LUM/IVA in Study 105, who continued to be treated with Orkambi, were enrolled in the US CFFPR, and provided consent for their US CFFPR data to be evaluated.

Inclusion criteria, patients:

1. were homozygous for F508del;
2. completed Part A of Study 105;
3. consented to have their data evaluated; and
4. had evidence of treatment with Orkambi following completion of Study 105 (as captured in the US CFFPR).

Patients who met the inclusion criteria are hereafter referred to as the Orkambi Cohort.

Sample size: a total of **485** subjects from the US completed Study 105 and were eligible to participate in Study 120 if they continued to be treated with Orkambi, were enrolled in the US CFFPR, and provided consent for their US CFFPR data to be evaluated.

Treatments Exposure

Orkambi exposure after the date of Study 105 completion for each patient was determined based on the record of Orkambi treatment as identified in the US CFFPR. Patients were considered to remain exposed to Orkambi until there was no evidence of treatment in the US CFFPR.

Precise Orkambi treatment initiation and discontinuation dates were not available in the US CFFPR. Because start and stop dates were not available from the US CFFPR, the algorithm to extrapolate the duration of exposure included the following rules: the date of the first encounter (evidence of Orkambi

exposure) was used as the start date. Patients were identified as exposed to Orkambi until a medications form was completed when Orkambi treatment was not reported, the patient was lost to follow-up, or the patient died. The Orkambi stop date was the first encounter date when exposure was not indicated, the patient was lost to follow-up, or the patient died.

In the analyses, Orkambi exposure was categorized into meaningful groups based on the duration of exposure, such as <1 year, ≥1 to <2 years, and ≥2 years.

CHMP comment

Limitations coming from the use of a registry as data source and also from only one selected source (US registry, only some sites) should be considered.

Moreover, the US CFFPR as a data source for this study utilizes encounter-based data collection and records the data from each patient visit in the real-world setting; the clinical outcome definitions used in the US CFFPR and the mechanisms and guidelines for data collection were different from those definitions used in Studies 105, 103, and 104.

Outcomes/endpoints

Statistical Methods

Data source: the US CFFPR tracks the treatments and health of people with CF across the US and is the largest CF patient registry in the geographic regions covered by Study 105. Information is collected on patients who receive care at more than 110 CFF-accredited care centers and who agree to participate in the registry. The US CFFPR includes approximately 29,000 patients with CF, representing 81% to 84% of all people with CF in the country.
Data from the US CFFPR were used for all study analyses.
Data management was maintained at the US CFFPR according to their internal processes. Only final analysis tables (i.e., no patient-level data from the registries) were provided to the marketing authorization holder

The CF centers were responsible for the quality of the US CFFPR data. The annual grants application signed by all center directors had a clause that stated that the registry data provided by the center were accurate to the best of the center director's knowledge.

Variables: all study variables were derived from existing data in the US CFFPR that were collected in prespecified data collection forms. Investigators (physicians with expertise in CF) from certified CF centers completed the forms according to the data guidelines and indicated the specified diagnoses for patients. The US CFFPR's own data entry guideline was used.

The US CFFPR independently determined the data to be collected within the US CFFPR.

Statistical methods: US CFFPR data were analyzed for 3 years. Separate annual analyses were performed based on the 2016, 2017, and 2018 data. All analyses were descriptive and based on observed trends over time.
Continuous variables were summarized using the following descriptive summary statistics in each of the analysis years: (1) number of patients (n); (2) mean; (3) SD; (4) SE; (5) median; (6) minimum value; (7) maximum value; and (8) 95% CI, as appropriate. Categorical variables were summarized using the number and percentage of patients and the 95% CI.
For event-based categorical endpoints (e.g., hospitalizations and PEx), the number of events and annual risks with 95% CI were calculated for each of the 3 analysis years. Percentages were presented to 1 decimal place, unless otherwise specified.
For each analysis year, only patients who continued to be treated with Orkambi were included, and the number and percentage of patients who did not have any record of Orkambi use within the whole calendar year was tabulated.
A stratified analysis of both continuous and categorical endpoints could be carried out as appropriate on important patient characteristics (e.g., ppFEV1 by patient characteristics [age, gender]).
No formal statistical hypothesis testing was performed. No imputation of missing data was conducted in the course of statistical analyses; however, sensitivity analyses could be performed if deemed necessary and applicable.

Summary statistics for the overall population and for the following **subgroups** was tabulated:
- Age at the start of Analysis Year 1 (<18 years, ≥18 years)
- Sex (male, female)

• ppFEV1 at the start of Analysis Year 1 (<70, ≥70)

Safety: all safety endpoint analyses were performed in the overall study population. The number and percentage of patients with i) LFT elevations (ALT, AST, BILI) relative to the upper limit of normal (ULN), ii) a record of hypertension, death (overall and by type of death), or organ transplantation (overall and by organ) were tabulated for each analysis year.

Ad hoc analyses were done as summarized below:
• BMI was stratified by age in 2016 (<20 and ≥20 years of age). Weight-for-age *z*-scores for patients <20 years of age in 2016 were also calculated;
• Sensitivity analyses of all endpoints in patients with evidence of Orkambi exposure in all 3 study years were performed.

CHMP comment

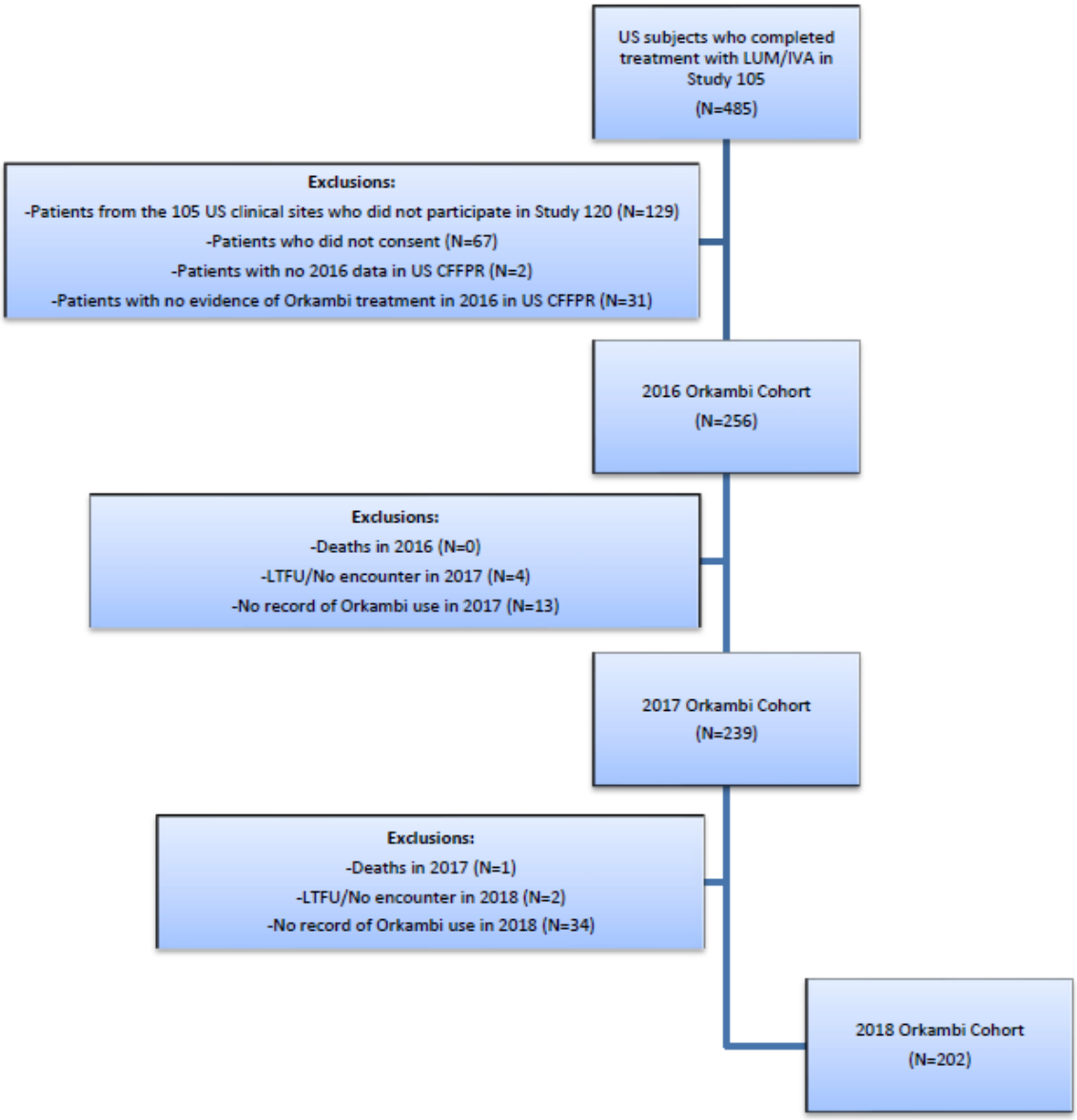
Variables derived from existing data in the US CFFPR that were collected in pre-specified data collection forms. The US CFFPR's own data entry guideline was followed, therefore a standardized procedure was in place for data collection. Statistical analyses were descriptive and not formal hypotheses were conducted.

With regard to the paediatric subset, the MAH conducted some subgroup or ad hoc analyses. It is highlighted that the focus of this procedure is the paediatric setting from 12 years and older and that these data are also submitted as part of the post-authorisation measure REC 10.1, recommendation to submit a final clinical study report of Study VX16-809-120.

Results

Recruitment/ Number analysed

Figure 1: Study population over time



CHMP comment

This study planned to include all US Study 105 Part A participants homozygous for F508del, who completed treatment with LUM/IVA, were enrolled in the US CFFPR, and provided consent for their US CFFPR data to be evaluated. However, only a subset of US sites consented to participate in Study 120.

Out of 485 subjects from US who completed study 105, roughly half were included in Study 120 (256 in the 2016; 239 in the 2017; 202 in the 2018). Reasons for exclusion were patients from the US Clinical sites who did not participate in Study 120 (n=129), patients who did not consent (n=67), patients with no evidence of Orkambi treatment in 2016 in US CFFPR (N=31).

From the available data, it seems that Orkambi discontinuation (desumed from the number of patients with no evidence of Orkambi treatment in US CFFPR) ranged between 5% and 14% per year (31/287, 11% in 2016; 13/256, 5% in 2017; 34/239, 14% in 2018). However, no information is available on the reasons for discontinuation, and no follow up data after Orkambi discontinuation have been provided. Thus, patients included in study 120 represent only a selected proportion of the patient population enrolled in study 105, and the external validity of study results appears questionable and should be further discussed by the MAH (OC).

Baseline data

Table 2: Demographic and clinic characteristics (Orkambi Cohort, 2016)

	Orkambi Cohort With Orkambi Exposure in 2016 N=256	Orkambi Cohort Patients With Orkambi Exposure in All 3 Years[a] N=202
Age as of 01 January 2016 (years), mean (SD)	28.4 (10.5)	27.5 (10.3)
Female sex, n (%)	123 (48.0)	91 (45.0)
ppFEV$_1$, mean (SD)	66.3 (16.6)	68.3 (15.7)
ppFEV$_1$, n (%)		
<40	17 (6.6)	7 (3.5)
≥40 – <70	126 (49.2)	99 (49.0)
≥70 – <90	96 (37.5)	79 (39.1)
≥90	17 (6.6)	17 (8.4)
CF medication use, n (%)		
Chronic antibiotics	217 (84.8)	166 (82.2)
Dornase alfa	240 (93.8)	187 (92.6)
Hypertonic saline	199 (77.7)	155 (76.7)
Bronchodilators	248 (96.9)	195 (96.5)
Corticosteroids	190 (74.2)	150 (74.3)

Source: US CFF Tables 1.0 and 1.1; and US CFF Ad Hoc Table 4.0

CF: cystic fibrosis; N: total sample size; n: size of subsample; ppFEV$_1$: percent predicted forced expiratory volume in 1 second

[a] Exposure in all 3 years is defined as at least 1 record of Orkambi exposure in the registry in each calendar year (2016 through 2018); patients may have a record of Orkambi exposure at every encounter or may have encounters where Orkambi is not checked but still have ≥1 encounter in each calendar year of the analysis period with a record of Orkambi exposure.

	PROGRESS		Rate of change analysis	
	Placebo transitioned to lumacaftor 400 mg every 12 h/ivacaftor 250 every 12 h* (n=176)	Lumacaftor 400 mg every 12 h/ivacaftor 250 every 12 h* (n=340)	CFFPR matched-controls† (n=1588)	Lumacaftor 400 mg every 12 h/ivacaftor 250 every 12 h‡ (n=455)
Women	86 (49%)	164 (48%)	745 (47%)	216 (47%)
Age (years)	24·9 (10·1)	25·1 (9·3)	25·2 (9·3)	25·8 (9·6)
Age groups (years)				
12–<18	47 (27%)	94 (28%)	396 (25%)	117 (26%)
≥18	129 (73%)	246 (72%)	1192 (75%)	338 (74%)
ppFEV$_1$§	60·2 (13·8)	60·4 (14·2)	61·8 (16·3)	59·8 (13·8)
Body-mass index (kg/m^2)	20·9 (2·8)	21·4 (2·9)	21·3 (3·1)	21·3 (2·9)
Pseudomonas positive	126 (72%)	261 (77%)	1178 (74%)	343 (75%)

Data are n (%) or mean (SD). CFFPR=Cystic Fibrosis Foundation Patient Registry. ppFEV$_1$=percent predicted FEV$_1$. *Data reported are baseline from TRAFFIC or TRANSPORT for patients who rolled over into PROGRESS. †Baseline was the later of two stable visits in 2012 (ie, no evidence of a care episode and no material change in ppFEV$_1$ or change in any routine drug treatment). ‡Baseline visit was the day of lumacaftor/ivacaftor start. §Wang-Hankinson equations were used to calculate ppFEV$_1$ in PROGRESS; Global Lungs Initiative equations were used to calculate ppFEV$_1$ in the rate of change analysis.

Table 1: **Patient demographics and baseline characteristics for patients who rolled over into PROGRESS and for patients included in the rate of change analysis**

CHMP comment

The two groups (Orkambi exposure in 2016 and Orkambi exposure across 3 years) appear balanced in terms of lung function (ppFEV1) and CF medication use at baseline.

Effectiveness endpoints

Lung function: percent predicted forced expiratory volume in 1 second (ppFEV1) calculated by Global Lung Function Initiative (GLI) standards as the average of the best available measurement for all quarters in each calendar year, categorized as <40, ≥40 to <70, ≥70 to <90, and ≥90.

Mean ppFEV1 values from 2016 through 2018 for the patients included in the Orkambi Cohort each year

Figure 2: Mean ppFEV1 (Orkambi Cohort, 2016 through 2018)

By age 3-years exposure

Table 3: Summary of ppFEV1 results by Year, by Age

Time point	Statistic	Age at start of 2016 < 18 (N=48)	Age at start of 2016 >= 18 (N=208)
2016	n (non-missing)	48	208
	Mean	76.40	64.02
	SD	10.61	16.83
	SE	1.53	1.17
	95% CI	73.32-79.48	61.72-66.32
	Median	77.3	62.2
	Min	53.3	27.1
	Max	99.1	99.2
2017	n (non-missing)	48	190
	Mean	74.30	62.95
	SD	11.97	17.72
	SE	1.73	1.29
	95% CI	70.82-77.78	60.41-65.48
	Median	76.2	60.8
	Min	48.4	21.1
	Max	99.0	101.6
2018	n (non-missing)	43	159
	Mean	73.64	64.40
	SD	13.05	17.10
	SE	1.99	1.36
	95% CI	69.62-77.65	61.72-67.08
	Median	75.8	62.0
	Min	46.3	22.8
	Max	96.9	101.8

Table 4: Summary of ppFEV1 results by Year, Patients with continuous 3-years Orkambi exposure, by Age

Time point	Statistic	<18 Orkambi Cohort (N=43)	>=18 Orkambi Cohort (N=159)
2016	n (non-missing)	43	159
	Mean	77.07	65.92
	SD	10.73	16.06
	SE	1.64	1.27
	95% CI	73.77-80.37	63.41-68.44
	Median	78.1	63.5
	Min	53.3	34.5
	Max	99.1	99.2
2017	n (non-missing)	43	159
	Mean	75.11	64.99
	SD	11.86	16.93
	SE	1.81	1.34
	95% CI	71.46-78.76	62.34-67.65
	Median	76.4	63.3
	Min	48.4	22.1
	Max	99.0	101.6
2018	n (non-missing)	43	159
	Mean	73.64	64.40
	SD	13.05	17.10
	SE	1.99	1.36
	95% CI	69.62-77.65	61.72-67.08
	Median	75.8	62.0
	Min	46.3	22.8
	Max	96.9	101.8

CHMP comment

Mean ppFEV1 was maintained from 2016 through 2018 in the Orkambi overall cohort. Stratification by sex or lung function by ppFEV1 categories showed consistent results, apart from patients with ppFEV1 start of 2016 ≥70 who underwent a mean decline of 1 percentage point per year (1.4 in 2017 and 0.9 in 2018).

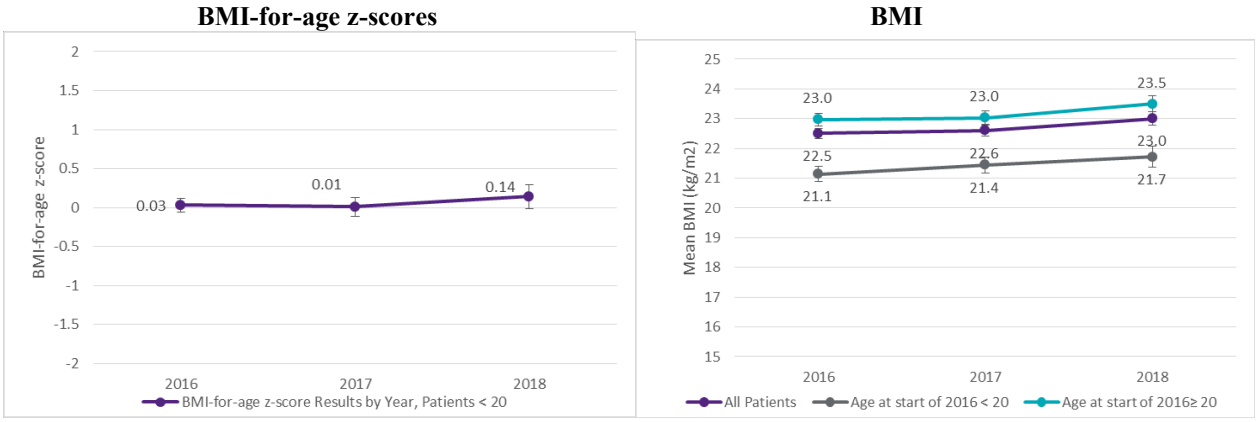
Importantly, an ad hoc analysis on stratification by age at start (≥ or < 18 years) in Orkambi treated patients with 3-years exposure showed, in the subgroup of patients <18 years, a mean decrease of -2.1 percentage point in the first year and of -0.66 in the second year. The mean decrease observed in subjects ≥18 years was -1.07 in the first year of observation, followed by a mean increase of 1.45 in the second year. It is noted that the baseline mean value of ppFEV1 was slightly higher in patients <18 years of age as compared to those ≥ 18 years.

The sensitivity analysis that included only subjects with continuous Orkambi exposure from 2016 to 2018, showed:
-in the overall population a mean decrease in ppFEV1 of -1.15 percentage point in the first year and of -0.79 in the second year.
- in the subgroup of patients <18 years a mean decrease in ppFEV1 of -1.96 percentage point in the first year and of-1.47 in the second year. The mean decrease observed in subjects ≥18 years was -0.93 in the first year of observation and -0.59 in the second year.
Across presented analyses, the observed decline in predicted ppFEV1 (measured as decrease in percentage point) over 3 years exposure was consistently higher in the younger (<18 years) age category as compared to the older one (≥18 years).

The observed decreases seem slightly lower than the mean -2.29 percentage point per year reported in US registry patients homozygous for F508del mutation and untreated with CFTR modulator therapy used as controls in the matched analysis of the PROGRESS Study (Konstan M, McKone E, Moss R, Marigowda G, Tian S, Waltz D, et al). Evidence for reduced rate of lung function decline and sustained benefit with combination lumacaftor and ivacaftor therapy in patients with CF homozygous for the F508del-CFTR mutation. Lancet Respir Med. 2017; 16: S2213-600). However, in these published data the results in the subgroup of controls <18 years of age have not been presented separately.
When comparing baseline characteristics of the 455 US patients who were included in the matched registry cohort (Konstan et al, 2017) with patients enrolled in Study 120, some differences are observed: ≥12-<18 years: US PROGRESS completers 25.7% vs Study 120 18.8%; ppFEV1 mean (SD) at baseline: 59.8 (13.8) vs 66.3 (16.6) percentage points.

Nutritional parameters: BMI, BMI-for-age *z*-score (age <20 years), and weight.

Figure 3: Mean BMI and BMI-for-age z-scores (Orkambi Cohort, 2016 through 2018)



BMI: body mass index

Table 5: Summary of BMI and BMI-for-age z-score results by year, patients with continuous 3-years Orkambi exposure, Patients < 20

Time point	Statistic	Orkambi Cohort (N=57)
2016	n (non-missing)	57
	Mean	0.09
	SD	0.74
	SE	0.10
	95% CI	-0.11-0.29
	Median	0.2
	Min	-2.0
	Max	1.7
2017	n (non-missing)	50
	Mean	0.07
	SD	0.90
	SE	0.13
	95% CI	-0.19-0.32
	Median	0.2
	Min	-2.5
	Max	2.5
2018	n (non-missing)	43
	Mean	0.14
	SD	0.97
	SE	0.15
	95% CI	-0.16-0.44
	Median	0.1
	Min	-1.9
	Max	3.9

Table 6: Summary of BMI results by year, patients with continuous 3-years Orkambi exposure

Time point	Statistic	Orkambi Cohort (N=202)	Age at start of 2016 < 20 Orkambi Cohort (N=57)	Age at start of 2016 >= 20 Orkambi Cohort (N=145)
2016	n (non-missing)	202	57	145
	Mean	22.62	21.26	23.15
	SD	2.92	2.05	3.04
	SE	0.21	0.27	0.25
	95% CI	22.21-23.02	20.71-21.80	22.65-23.65
	Median	22.0	20.9	22.5
	Min	16.6	17.4	16.6
	Max	32.0	27.4	32.0
2017	n (non-missing)	202	57	145
	Mean	22.78	21.59	23.25
	SD	2.88	2.29	2.96
	SE	0.20	0.30	0.25
	95% CI	22.38-23.18	20.98-22.19	22.76-23.73
	Median	22.2	21.5	22.7
	Min	17.5	17.6	17.5
	Max	32.2	29.1	32.2
2018	n (non-missing)	202	57	145
	Mean	23.00	21.71	23.50
	SD	3.11	2.67	3.13
	SE	0.22	0.35	0.26
	95% CI	22.57-23.43	21.00-22.42	22.99-24.02
	Median	22.6	21.2	23.1
	Min	16.6	16.8	16.6
	Max	33.8	32.0	33.8

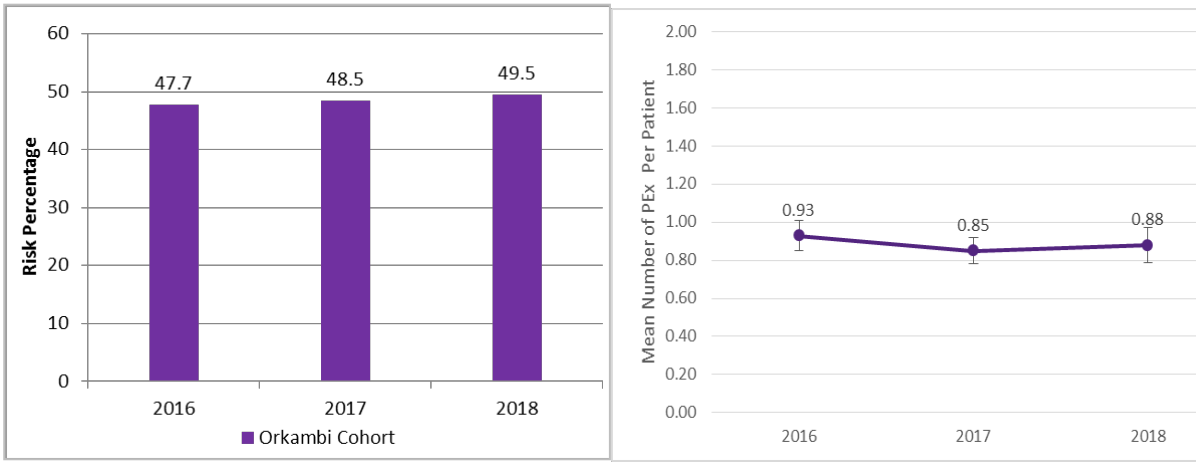
CHMP comment

BMI for age-z score and mean BMI were stable with a slight trend to increase in the overall Orkambi cohort as well as in the population stratified by age (≥ or < 20 years). However, it is not clear why the cut-off of 20 years was used.

PEx: defined by evidence of a CF care episode with PEx as the reason.

The annual risk of PEx, defined in the registry as ≥1 episode of intravenous antibiotics at home or in the hospital.

Figure 4: Proportion of Patients Who Had ⩾1 PEx and PEx Rate Over Time (Orkambi Cohort, 2016 through 2018)



Proportion of Patients Who Had ≥1 PEx **PEx Rate**

PEx: pulmonary exacerbation

Table 7: Pulmonary exacerbations over time, patients with continuous 3-years Orkambi exposure

Statistic	Orkambi Cohort (N=202)
2016	
n (non-missing	202
Number of patients with at least one PEx, n (%)	91 (45.0)
Number of PEx per patient	
n (non-missing)	202
Mean	0.86
SD	1.30
SE	0.09
95% CI	0.68-1.04
Median	0.0
Min	0.0
Max	7.0
2017	
n (non-missing	202
Number of patients with at least one PEx, n (%)	94 (46.5)
Number of PEx per patient	
n (non-missing)	202
Mean	0.83
SD	1.17
SE	0.08
95% CI	0.67-0.99
Median	0.0
Min	0.0
Max	6.0
2018	
n (non-missing	202
Number of patients with at least one PEx, n (%)	100 (49.5)

Statistic	Orkambi Cohort (N=202)
Number of PEx per patient	
n (non-missing)	202
Mean	0.88
SD	1.27
SE	0.09
95% CI	0.71-1.06
Median	0.0
Min	0.0
Max	8.0

CHMP comment

In Study 120, PEx was defined by evidence of a CF care episode with PEx as the reason. The proportion of patients who had ≥1 PEx in the overall Orkambi cohort of patients slightly increased over the 3 –year of exposure (from 47.7 in 2016 to 49.5 in 2018).
Mean number per patient over 3 years exposure slightly reduced (from 0.93 in 2016 to 0.88 in 2018).
It is highlighted that no analysis of PEx (both as proportion of patients with at least one PEx and PEx annualized event rate) is provided in paediatric patients aged ≥12 years. The MAH should provide these analyses.

In Study 105, PEx was defined as a new or change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the followingsigns/symptoms: Change in sputum; New or increased hemoptysis; Increased cough; Increased dyspnea; Malaise, fatigue, or lethargy; Temperature above 38°C (equivalent to approximately 100.4°F); Anorexia or weight loss; Sinus pain or tenderness; Change in sinus discharge; Change in physical examination (PE) of the chest; Decrease in pulmonary function by 10%; and Radiographic changes indicative of pulmonary infection. This definition was based on the definition of a PEx used in previous clinical studies including IVA clinical studies.

SmPC Table

Table 6: Long-term effect of Lumacaftor/Ivacaftor in Trial 3*

	Placebo transitioned to Lumacaftor 400 mg q12h/ Ivacaftor 250 mg q12h (n=176)**	Lumacaftor 400 mg q12h/ Ivacaftor 250 mg q12h (n=369)†
Number of Pulmonary exacerbations (events) ** † * **		
Number of events per patient- year (95% CI) (rate per 48 wks)	0.69 (0.56, 0.85)	0.65 (0.56, 0.75)
Number of events requiring hospitalization per patient-year (95% CI) (rate per 48 wks)	0.30 (0.22, 0.40)	0.24 (0.19, 0.29)
Number of events requiring intravenous antibiotics per patient-year (95% CI) (rate per 48 wks)	0.37 (0.29, 0.49)	0.32 (0.26, 0.38)

* A total of 82% (421 of 516 eligible patients) completed 72 weeks of this study; 42% completed 96 weeks. Majority of patients discontinued for reasons other than safety.

** For patients rolled over from Trials 1 and 2 (placebo-to-lumacaftor/ivacaftor group) total exposure was up to 96 weeks. Presentation of the lumacaftor 400 mg q12h/ivacaftor 250 mg q12h dose group is consistent with recommended posology.

*** The event rate per patient-year was annualised to 48 weeks.

† For patients rolled over from Trials 1 and 2 (lumacaftor/ivacaftor-to-lumacaftor/ivacaftor group) total exposure was up to 120 weeks. Presentation of the lumacaftor 400 mg q12h/ivacaftor 250 mg q12h dose group is consistent with recommended posology.

‡ Baseline for the placebo transitioned to lumacaftor 400 mg q12h/ivacaftor 250 mg q12h group was the Trial 3 baseline. Baseline for the lumacaftor 400 mg q12h/ivacaftor 250 mg q12h group was the Trial 1 and 2 baseline.

Konstan et al, 2017

	TRAFFIC or TRANSPORT		PROGRESS*	
	Placebo (n=371)	Lumacaftor 400 mg every 12 h/ ivacaftor 250 every 12 h (n=369)	Placebo transitioned to lumacaftor 400 mg every 12 h/ivacaftor 250 every 12 h (n=176)	Continued lumacaftor 400 mg every 12 h/ivacaftor 250 every 12 h (n=369)
Absolute change from baseline (Wang-Hankinson) in ppFEV$_1$, least squares mean, 95% CI (percentage points), p value†				
Week 24	−0·4 (−1·2 to 0·4), p=0·3494	2·2 (1·3 to 3·0), p<0·0001	..	..
Extension week 72	..	..	1·5 (0·2, 2·9), p=0·0254	0·5 (−0·4 to 1·5), p=0·2806
Extension week 96	..	..	0·8 (−0·8, 2·3), p=0·3495	0·5 (−0·7 to 1·6), p=0·4231
Absolute change from baseline (GLI) in ppFEV$_1$, least squares mean, 95% CI (percentage points), p value††‡				
Week 24	−0·3 (−1·1 to 0·5), p=0·4715	2·1 (1·3 to 3·0), p<0·0001	..	..
Extension week 72	..	..	1·9 (0·6 to 3·2), p=0·0040	0·9 (0·0 to 1·9), p=0·0500
Extension week 96	..	..	1·1 (−0·5 to 2·6), p=0·1696	1·1 (0·0 to 2·2), p=0·0535
Relative change from baseline (Wang-Hankinson) in ppFEV$_1$, least squares mean, 95% CI, (%), p value†				
Week 24	−0·3 (−1·7 to 1·1), p=0·6375	4·1 (2·7 to 5·5), p<0·0001	..	..
Extension week 72	..	..	2·6 (0·2 to 5·0), p=0·0332	1·4 (−0·3 to 3·2), p=0·1074
Extension week 96	..	..	1·1 (−1·7 to 3·9), p=0·4415	1·2 (−0·8 to 3·3), p=0·2372
Absolute change from baseline in body-mass index , least squares mean, 95% CI, (kg/m^2), p value†				
Week 24	0·13 (0·04 to 0·23), p=0·0066	0·37 (0·28 to 0·47), p<0·0001	..	..
Extension week 72	..	..	0·62 (0·45 to 0·79), p<0·0001	0·69 (0·56 to 0·81), p<0·0001
Extension week 96	..	..	0·76 (0·56 to 0·97), p<0·0001	0·96 (0·81 to 1·11), p<0·0001
Absolute change from baseline in CFQ-R respiratory domain score, least squares mean, 95% CI, (points), p value†				
Week 24	1·9 (0·3 to 3·5), p=0·0213	4·1 (2·5 to 5·7), p<0·0001	..	..
Extension week 72	..	..	3·3 (0·7 to 5·9), p=0·0124	5·7 (3·8 to 7·5), p<0·0001
Extension week 96	..	..	0·5 (−2·7 to 3·6) p=0·7665	3·5 (1·3 to 5·8) p=0·0018
Pulmonary exacerbation events, 95% CI‡				
Number of events per patient-year	1·14 (0·97 to 1·34)	0·70 (0·57 to 0·84)	0·69 (0·56 to 0·85)	0·65 (0·56 to 0·75)
Number of events requiring hospital admission per patient-year	0·45 (0·36 to 0·57)	0·17 (0·12 to 0·25)	0·30 (0·22 to 0·40)	0·24 (0·19 to 0·29)
Number of events requiring intravenous antibiotics per patient-year	0·58 (0·47 to 0·72)	0·25 (0·19 to 0·33)	0·37 (0·29 to 0·49)	0·32 (0·26 to 0·38)

CFQ-R=Cystic Fibrosis Questionnaire-Revised. GLI=Global Lungs Initiative. ppFEV$_1$=percent predicted FEV$_1$. *Change from baseline data in PROGRESS are shown at extension week 72 (the main efficacy analysis) and at extension week 96 (sensitivity analysis). With the main efficacy analysis, patients who remained on lumacaftor/ivacaftor received up to 96 weeks of active treatment. With the sensitivity analysis, patients who remained on lumacaftor/ivacaftor received up to 120 weeks of active treatment. †For the placebo and lumacaftor/ivacaftor groups, baseline from TRAFFIC or TRANSPORT was used; for the placebo transitioned to lumacaftor/ivacaftor group, baseline from PROGRESS was used. All p values (including for TRAFFIC or TRANSPORT data) are within treatment. ‡The pulmonary exacerbations analyses for TRAFFIC or TRANSPORT included events through to week 24 of TRAFFIC or TRANSPORT. The pulmonary exacerbations analyses for PROGRESS included events throughout the cumulative study period (TRAFFIC or TRANSPORT and PROGRESS), such that the placebo transitioned to lumacaftor/ivacaftor group received up to 96 weeks of active treatment and the lumacaftor/ivacaftor group received up to 120 weeks of active treatment.

Table 3: Summary of efficacy outcomes in TRAFFIC or TRANSPORT[18] and PROGRESS

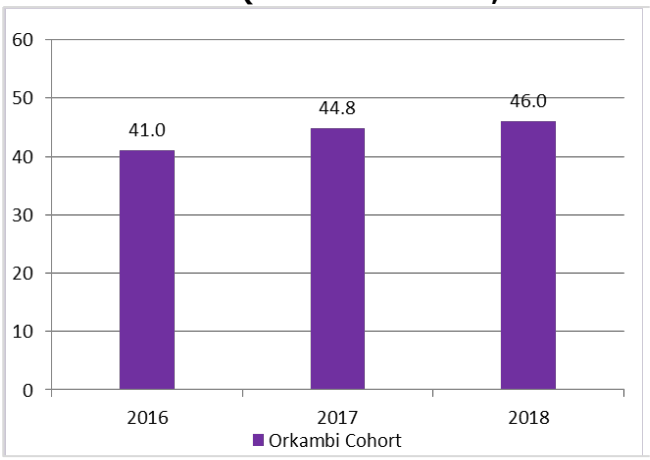
The PEx rate (mean number of PEx per patient: 0.93, 0.85, 0.88 respectively in 2016, 2017 and 2018) in Study 120 was higher compared to Study 105 (number of events per patient year: 0.65), however due to the different definitions used in the two studies, no definitive conclusion may be drawn.

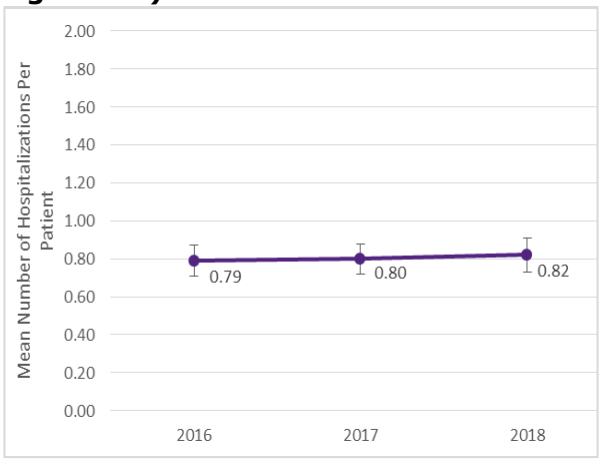
Unfortunately, the comparison of the rate of change in annualized PExs between Orkambi treated patients and matched controls was not among the outcome measures in the publication by Konstan and co-workers (Supplementary material to Konstan et al. Lancet Respir Med 2016; published online Dec 20).

In Study 120 the US registry definition was used, thus a comparison with the untreated matched registry cohort published by Konstan and co-workers should be provided at least for the 3 years follow-up.

Hospitalizations: defined if there was evidence of a hospitalization that occurred for any reason. Reasons for hospitalization were evaluated as recorded in the US CFFPR database (e.g., PEx, pulmonary complication, gastrointestinal complication, transplant-related, sinus infection, nontransplant surgery, and other).

Figure 5: Proportion of Patients Who Had ⩾1 Hospitalization and Hospitalization Rate Over Time (Orkambi Cohort, 2016 through 2018)





Proportion of Patients Who Had ≥1 Hospitalization **Hospitalization Rate**

Hospitalization Information	2016 (N=202) n/N1	%	2017 (N=202) n/N1	%	2018 (N=202) n/N1	%
Number of Patients with Any Hospitalization	76 / 202	37.62	86 / 202	42.57	93 / 202	46.04
Reason for Hospitalization*:						
Pulmonary Exacerbation	72 / 76	94.74	81 / 86	94.19	85 / 93	91.40
Pulmonary Complication	3 / 76	3.95	1 / 86	1.16	4 / 93	4.30
Gastrointestinal (GI) Complication	6 / 76	7.89	4 / 86	4.65	6 / 93	6.45
Transplant-Related	0 / 76	0.00	0 / 86	0.00	0 / 93	0.00
Sinus Infection	1 / 76	1.32	1 / 86	1.16	0 / 93	0.00
Non-Transplant Surgery	4 / 76	5.26	3 / 86	3.49	3 / 93	3.23
Other	7 / 76	9.21	10 / 86	11.63	12 / 93	12.90

CHMP comment

The proportion of patients who had ≥1 hospitalization in the overall Orkambi cohort increased over the 3 –year of exposure (from 41% in 2016 to 46% in 2018).
The annualized hospitalization rate over 3 year exposure slightly increased (from 0.79 in 2016 to 0.82 in 2018). It is highlighted that no analyses on hospitalization are provided (both as proportion of patients who had ≥1hospitalization and as hospitalization rate) in paediatric patients aged ≥12 years. The main reason of hospitalization was PEx.

Safety results

Liver function tests (LFTs): alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin (BILI) as recorded in the registry.

Table 8: Frequency of ALT and AST elevations relative to ULN (Orkambi cohort, 2016 through 2018)

	Orkambi Cohort (N=256)		
Year	>3 × ULN	>5 × ULN	>8 × ULN
ALT			
2016 (n=238), n (%)	4 (1.7)	0 (0.0)	0 (0.0)
2017 (n=215), n (%)	2 (0.9)	1 (0.5)	0 (0.0)
2018 (n=193), n (%)	5 (2.6)	1 (0.5)	0 (0.0)
AST			
2016 (n=239), n (%)	2 (0.8)	1 (0.4)	0 (0.0)
2017 (n=215), n (%)	1 (0.5)	0 (0.0)	0 (0.0)
2018 (n=192), n (%)	3 (1.6)	2 (1.0)	1 (0.5)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; N: total sample size; n: size of subsample; ULN: upper limit of normal

Table 9: Frequency of BILI elevations relative to ULN (Orkambi cohort, 2016 through 2018)

	Orkambi Cohort (N=256)
Year	>2 × ULN
2016 (n=221), n (%)	3 (1.4)
2017 (n=204), n (%)	1 (0.5)
2018 (n=186), n (%)	2 (1.1)

BILI: bilirubin; N: total sample size; n: size of subsample; ULN: upper limit of normal

Hypertension as recorded in the registry

Table 10: Prevalence of hypertension (Orkambi cohort, 2016 through 2018)

Year	Orkambi Cohort (N=256)
2016 (n=256), n (%)	10 (3.9)
2017 (n=239), n (%)	12 (5.0)
2018 (n=202), n (%)	8 (4.0)

• **Death:** defined as evidence of a date of death in the US CFFPR. The cause of death was evaluated as recorded in the US CFFPR database (e.g., respiratory/cardiorespiratory, liver disease, trauma, suicide, transplant related, other, and unknown).

Over the duration of Study 120, 1 (0.39%) out of 256 patients died. The patient had a ppFEV1 value of 25.12% at the last registry record. The recorded cause of death in the registry was Respiratory/Cardio-Respiratory.

• **Organ transplantations**: defined as evidence of organ transplantation in the US CFFPR. The type of transplantation was evaluated as recorded in the US CFFPR database (e.g., lung, liver, and other).
Over the duration of Study 120, 2 (0.78%) out of the 256 patients had a record of lung transplants; 1 in 2016 and 1 in 2017

CHMP comment

Safety data coming from this longer follow-up in the observational study seem to confirm the safety profile described in study 105.

2.2.3. Discussion on clinical aspects

At the time of the initial Orkambi approval in the EU, the CHMP requested the MAH to explore the possibility of a longer follow-up (i.e. 5 years) of study population enrolled in the phase 3 study (study 105) submitted in support of the indication in patients 12 years and older. Because the majority of subjects had completed Study 105 at the time of this request, the MAH determined that extending this study for an additional 3 years was not feasible and explored the feasibility of identifying and evaluating Study 105 participants via existing national CF patient registries in US and EU.

Based on further assessment of feasibility, evaluated EU registries were considered not suitable for the purposes of the study due to various reasons, including low national coverage (e.g., Spain, 50), significant data availability lags and/or data quality issues (e.g., Italy; as of 2017, the most recent data available are from 2014), or very small Study 105 patient pool (e.g., UK, France, Germany, Sweden, Austria, and Denmark). Because a significant proportion of subjects who completed Study 105 Part A were from the US (N = 485; 53%), the MAH planned to conduct Study 120, following only US subjects from Study 105 Part A (patients homozygous for F508del coming from parent studies 103 and 104) who were also enrolled in the US Cystic Fibrosis Foundation Patient Registry (CFFPR) for 3 years after the completion of Study 105. Given the limitations of Study 105, the study was considered by the MAH to be hypotheses-generating rather than hypothesis-testing.

The protocol for the observational study 120 has been considered acceptable by CHMP in the Post-Authorisation Measure REC 10.1, dated 15 March 2018. The concern initially raised that the pool of patients ultimately available for analysis could be small and that the number of analysable patients could not be sufficient to provide a clear and relevant response to the CHMP request, was not pursued as it was considered acceptable to supplement the data from Study 120 with that from PASS study 108, to fulfil the CHMP request on additional data on safety and efficacy. Similarly, the initial request to discuss the possibility of including a matched control group from the registry was not pursued, as the much larger PASS study 108 has a large Orkambi treated and control arm that comprise the safety cohort from the US registry.

With this application, the MAH is submitting the final results of Study 120. Out of 485 subjects from US who completed study 105, only roughly half (256/485, 53%) were included in the Orkambi Cohort Study 120. Thus, patients included in study 120 represent only a selected subgroup (roughly 25%) of the patient population enrolled in study 105 (only from US and only some from US sites who consented to participate).

The number of patients with no evidence of Orkambi treatment in US CFFPR per year ranged between 5% and 14% per year during the 3 years of Study 120 registry follow-up (31/287, 11% in 2016; 13/256, 5% in 2017; 34/239, 14% in 2018). No information is available for these patients as, in the study protocol, the MAH had pre-specified that only if an attrition greater than 20% was observed, available patient characteristics would have been examined in order to understand if there were systematic differences related to exposure between individuals who remained in the study and those who were lost to follow-up.

When comparing baseline characteristics of the 455/485 US patients included in Study 105, who were included in the published analysis with the matched registry cohort (Konstan et al, 2017), these appear to partially differ from patients enrolled in Study 120 (% of subjects ≥12-<18 years: 25.7% vs 18.8%; mean ppFEV1 at baseline: 59.8 vs 66.3 percentage points, respectively in US study 105 completers compared with subjects participating in Study 120).

The post-approval commitment requested by the CHMP was to provide data to evaluate the safety and effectiveness of Orkambi treatment over a period of 5 years, whereas the provided follow up is of only 3 years. For this reason the MAH was requested to complement results on the effectiveness and safety

endpoints evaluated in Study 120 (ppFEV1, BMI and weight, pulmonary exacerbation, liver function tests, hypertension, organ transplantation) with results on the same endpoints obtained during the 2 years of Study 105, in order to have an overall period of observation of 5 years. The MAH was requested to provide these results both in the overall Study 120 population and separately in the subgroups <18 years of age and ≥18 years of age.

Moreover, given that part of the 256 US subjects included in Study 120 are included also in the published analysis of the matched registry cohort the MAH was requested to provide the 5 year follow up of these patients in comparison with their matched controls, according to the same methodology followed in the publication by Konstan et al. 2017. Limitedly to a 3 year follow up, the MAH was also been requested to provide the rate of change in annualized Pex in Orkambi treated patients and matched registry controls (overall and by age, using the 18 yrs cut-off), given that both Study 120 and the US registry used the same definition of Pex. Following the request of supplementary information, the MAH stated that the request for matched control analyses using the same methodology followed in Konstan et al. are beyond the scope of the approved protocol and would not be feasible because a sufficient pool of CFTR modulator naïve F/F patients cannot be identified during this period to appropriately match to study participants in Study 120. Given that in the Final Assessment Report for the Post-Authorisation Measure REC 10.1, dated 15 March 2018, the safety data generated from the larger PASS study 108 with an Orkambi treated and a control arm, was considered sufficient to fill in the lacunae in information from the absence of a control group in study 120, the initial request of a matched controlled analysis was not pursued further.

The required results have been provided by the MAH for both overall Study 120 population and separately in adult and paediatric subgroups, although in the paediatric setting results should be interpreted with caution because of the small sample size (n = 48).

Similarly to what observed in Study 105, a trend towards a numerical decaying of effect on lung function (ppFEV1) with longer treatment duration was observed in Orkambi treated subjects in Study 120; however the indirect comparison with published cohorts of US registry patients homozygous for F508del mutation untreated with CFTR modulator therapy (Konstan et al, 2017; Wegener et al, 2018), seem to indicate a numerically slower annual rate of ppFEV1 decline in Orkambi treated subjects.

In Study 120, mean BMI was stable in the overall Orkambi cohort as well as in the subgroups ≥ or < 18 years. For the paediatric subgroup in Study 105, BMI-for-age z-scores were negative but generally improved throughout Study 105. In Study 120, in the subgroup <18 years, there was numerically a slight decrease of BMI for age Z scores during Study 120, although with values close to zero.

In the subgroup of Study 120 paediatric subjects (12-<18 years) the PEx rate seems higher compared to Study 105, however due to the different definitions used in the two studies, no conclusion may be drawn. The proportion of patients who had ≥1 hospitalization in the Study 120 overall Orkambi cohort slightly increased over the 3 -year of exposure (from 41% in 2016 to 46% in 2018), as well as the annualized hospitalization rate (from 0.79 in 2016 to 0.82 in 2018), with PEx being the main reason of hospitalization (>90%).

Overall, the trends observed in safety endpoints in Study 120 were consistent with the safety profile described in study 105.

Given that patients included in study 120 represent only a selected subgroup (roughly 25%) of the patient population enrolled in study 105 (only from US and only some from US sites who consented to participate), the comparison between Study 120 and Study 105 results is subject to limitations. It is acknowledged that due to the differences in data collection and endpoint definitions, it may not be appropriate to combine the clinical data from Study 105 and the registry-based data from Study 120 or directly compare the reported values for each endpoint. For these reasons, even though the MAH has

not provided the results of the two years of treatment in Study 105 separately for the subset of patients enrolled in Study 120, the issue was not further pursued.

In the 3rd interim analysis from the ongoing PASS (Study 108, a 5-year long-term observational study), results from the comparative safety analysis from the US CFFPR generally favoured the Orkambi Safety Cohort over the Comparator Safety Cohort. The 4th interim analysis report of the ongoing PASS Study (expected in December 2020) will provide additional data on the long-term effects of Orkambi, including subgroups of adult and paediatric patients.

3. CHMP overall conclusion and recommendation

The MAH provided the results on the effectiveness and safety endpoints evaluated in Study 120. However, interpretation of Study 120 results are hampered by the limited number of patients enrolled (only a roughly 25% of the patient population enrolled in study 105 were enrolled in Study 120) and the comparison between data from Study 120 (clinical study) and Study 105 (registry-based data) is subject to limitations, also due to differences in data collection and endpoint definitions. Moreover, the paediatric subgroup results for Study 120 should be interpreted with caution because of the small sample size (n = 48).

Although a trend towards a numerical decaying of effect on lung function (ppFEV1) with longer treatment duration was observed in Orkambi treated subjects in Study 120, the indirect comparison with published cohorts of US registry patients homozygous for F508del mutation untreated with CFTR modulator therapy provides some reassurance indicating a slower annual rate of ppFEV1 decline.

Overall trends observed in the effectiveness and safety endpoints in Study 120 were consistent with those in Study 105.

The 4th interim analysis report of the ongoing PASS Study (expected in December 2020) will provide additional data on the long-term effects of Orkambi, including subgroups of adult and paediatric patients.

☒ Fulfilled:

No regulatory action required.

4. Additional clarification requested

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

1) Patients included in study 120 represent only a selected proportion of the patient population enrolled in study 105, and the external validity of study results appears questionable and should be further discussed by the MAH.

2) The post-approval commitment requested by the CHMP was to provide data to evaluate of the safety and effectiveness of Orkambi treatment over a period of 5 years, whereas the provided follow up is of only 3 years. Results on the effectiveness and safety endpoints evaluated in Study 120 (ppFEV1, BMI and weight, pulmonary exacerbation, liver function tests, hypertension, organ transplantation) should be complemented with results on the same endpoints obtained during the 2 years of Study 105, in order to have an overall period of observation of 5 years. The MAH is requested to provide these results both in the overall Study 120 population and separately in the subgroups <18 years of age and ≥18 years of age.

3) Given that part of the 256 US subjects included in Study 120 are included also in the published analysis of the matched registry cohort (Konstan et al, Lancet Resp Med 2017), the MAH should provide the 5 year follow up of these patients in comparison with their matched controls, according to the same methodology followed in the publication by Konstan et al. 2017. Limitedly to a 3 year follow up, the MAH should also provide the rate of change in annualized PEx in Orkambi treated patients and

matched registry controls (overall and by age, using the 18 yrs cut-off), given that both Study 120 and the US registry used the same definition of PEx.

MAH responses to the 1st Request for supplementary information

Question 1

Patients included in study 120 represent only a selected proportion of the patient population enrolled in study 105, and the external validity of study results appears questionable and should be further discussed by the MAH.

MAH's Response

Vertex acknowledges that the Study 120 population includes only the subset of Study VX12-809-105 (Study 105) participants enrolled in the US Cystic Fibrosis Foundation Patient Registry (CFFPR) who provided consent. The Study 120 protocol was designed with input from the CHMP; the final protocol was reviewed and endorsed by the CHMP (see Final Assessment Report for the Post-Authorisation Measure REC 10.1, dated 15 March 2018 and hereafter referred to as "Assessment Report REC 10.1"). During the assessment of the protocol, the CHMP acknowledged that only a subset of subjects from Study 105 would enroll in Study 120, that Study 120 would be descriptive only, and that data from the large postauthorization safety study (PASS) VX14-809-108 (Study 108) could be used to supplement Study 120 data and would be acceptable to fulfill the CHMP's request for additional safety and efficacy data.

Vertex believes that the Rapporteur's concerns regarding the external validity of results of this study are mitigated by the following:

• The US registry-based approach identified and evaluated a significant proportion of the subjects in the US, which was the country with the largest subpopulation of Study 105 subjects.

• The phenotype and clinical course of cystic fibrosis (CF) in the F508del homozygous (F/F) population does not substantially differ by geographic region; therefore, data from the US patient population captured by the US CFFPR are appropriate for assessing long-term safety and efficacy, and trends can be extrapolated for all global regions.

• The trends observed in Study 120 are consistent with the trends observed in Study 105.

• The results from Study 120 are consistent with the results from other studies evaluating the long-term effects of Orkambi therapy, including the ongoing 5-year PASS (Study 108), a much larger real-world comparator-controlled study. In the 3rd interim analysis report for the PASS (Study 108) submitted 26 November 2019, key clinical outcomes of 4,628 F/F patients in the Orkambi® Cohort are compared to 5,666 patients heterozygous for F508del in the Comparator Cohort, with results that support the current benefit-risk profile of Orkambi.

Based on the above, Vertex concludes that, although the Study 120 population represents a selected proportion of the Study 105 subjects, the consistency of the results with clinical and real-world studies minimizes concerns regarding the external validity of the results. Vertex is committed to continue evaluating the long-term effects of Orkambi in the ongoing PASS (Study 108); the Study 108 data can be used to supplement Study 120 data, as endorsed by the CHMP in the Assessment Report REC 10.1. Furthermore, additional efficacy data will be obtained from a post-authorization efficacy study VX18-809-128, which was requested by the EMA as part of the approval of procedure EMEA/H/C/003954/X/0034/G (Vertex submitted the protocol for Scientific Advice in procedure EMEA/H/SA/1448/6/2019/PED/II and intends to submit the protocol to the EMA in Q2 2020).

Assessment of the MAH's Response

The MAH emphasizes that the final protocol was reviewed and endorsed by the CHMP (see Final Assessment Report for the Post-Authorisation Measure REC 10.1, dated 15 March 2018). During the assessment of the protocol, the CHMP acknowledged that only a subset of subjects from Study 105 would enrol in Study 120, that Study 120 would be descriptive only, and that data from the large post authorization safety study (PASS) VX14-809-108 (Study 108) could be used to supplement Study 120 data and would be acceptable to fulfill the CHMP's request for additional safety and efficacy data.

The MAH's opinion is that, although the Study 120 population represents a selected proportion of the Study 105 subjects, the trends observed in Study 120 are consistent with the trends observed in Study 105 and the results from Study 120 are consistent with the 3rd interim analysis report for the PASS (Study 108) submitted 26 November 2019; in the MAH's opinion consistency of the results with clinical and real-world studies minimizes concerns regarding the external validity of the results.

The MAH will continue evaluating the long-term effects of Orkambi in the ongoing PASS (Study 108).

Furthermore, the MAH emphasizes that additional efficacy data will be obtained from a post-authorization efficacy study VX18-809-128, for patients 2- to 5-years-old at initiation of Orkambi.

It is acknowledged that in the Final Assessment Report for the Post-Authorisation Measure REC 10.1, dated 15 March 2018, the concern initially raised that the pool of patients ultimately available for analysis could be small and that the number of analysable patients could not be sufficient to provide a clear and relevant response to the CHMP request, was not pursued as it was considered acceptable to supplement the data from Study 120 with that from PASS study 108, to fulfil the CHMP request on additional data on safety and efficacy.

Patients included in study 120 represent only a selected subgroup of the patient population enrolled in study 105 (only from US and only some from US sites who consented to participate).

The MAH's opinion that, although the Study 120 population represents a selected proportion of the Study 105 subjects, the trends observed in Study 120 are consistent with the trends observed in Study 105 is not agreed. As further discussed in the assessment of the response to question 2, given that only 53% of subjects who completed study 105 were from US, and given that out of 485 subjects from US who completed study 105, only roughly half were included in Study 120 (256 in the 2016; 239 in the 2017; 202 in the 2018), it is not considered appropriate to compare the overall 2 year results of Study 105 with the 3 year follow up in Study 120. Please refer to assessment of Question 2 for further aspects on this issue.

Question 2

The post-approval commitment requested by the CHMP was to provide data to evaluate of the safety and effectiveness of Orkambi treatment over a period of 5 years, whereas the provided follow up is of only 3 years. Results on the effectiveness and safety endpoints evaluated in Study 120 (ppFEV1, BMI and weight, pulmonary exacerbation, liver function tests, hypertension, organ transplantation) should be complemented with results on the same endpoints obtained during the 2 years of Study 105, in order to have an overall period of observation of 5 years. The MAH is requested to provide these results both in the overall Study 120 population and separately in the subgroups <18 years of age and ≥18 years of age.

MAH's Response

Vertex clarifies that, according to the approved protocol, Study 120 follows subjects of Study 105 for an additional 3 years following the conclusion of Study 105. While the focus of the results in Study 120 is on the most recent 3-year follow-up period, these subjects were exposed to Orkambi for a total of 5 years or longer because they initiated treatment in clinical Study 105 or one of the 2 feeder studies, Study VX12-809-103 or Study VX12-809-104. During the assessment of the protocol (Assessment

Report REC 10.1), the CHMP confirmed that it would be acceptable for trends over 5 years to be described in the final clinical study report for Study 120, including a discussion of relevant data from the previously completed 2-year Study 105 and the summary of results of the 3-year follow-up after Study 105 obtained via the US CFFPR. This information was provided in the Study 120 CSR/Sections 8.2 and 13.1.

Due to the important differences in the data collection and definitions of the clinical outcomes during the periods of participation in Study 105 and subsequent real-world registry-based Study 120, it is not appropriate to combine the datasets or to perform a direct comparison of outcomes between the periods (e.g., to compare the clinical study and the real-world registry based follow-up period). The US CFFPR data from Study 120 are observational in nature, collected over the course of routine care without scheduled visit intervals or standardized assessments. In contrast, Study 105 data were collected under the rigorous standards for clinical study data collection, including predefined intervals between assessments, standardized measurements and procedures, and standardized definitions of clinical outcomes/endpoints. The differences in clinical outcome definition are exemplified by the definitions for pulmonary exacerbation (PEx). The US CFFPR defines PEx as an episode requiring intravenous antibiotic use at home or in the hospital. However, PEx in Study 105 was strictly defined by criteria standardized across Vertex CF clinical studies[a], where most of these criteria are based upon assessments that are not captured in registry data (e.g., change in sputum and change in sinus discharge).

While the Study 120 data cannot be combined with Study 105 data due to these critical differences in data collection, the trends observed for the clinical outcomes during the 3-year follow-up in Study 120 are nonetheless consistent with those observed from the 2-year follow-up in Study 105. Specifically, the effectiveness outcomes in subjects in Study 120 demonstrated overall stable trends in percent predicted forced expiratory volume in 1 second (ppFEV1), body mass index (BMI) values, annual risk of PEx, annualized PEx rate, and annualized rate of hospitalizations, which was consistent with the long-term maintenance of the treatment effect demonstrated in Study 105 for the relevant endpoints. In addition, no new safety concerns or trends, including elevated alanine transaminase or aspartate transaminase values, were identified in Study 120, and low rates of death and lung transplantation were observed.

[a] In Study 105, PEx was defined as a new, or change in, antibiotic therapy (intravenous, inhaled, or oral) for any 4 or more of the following signs/symptoms: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; temperature above 38°C (equivalent to approximately 100.4°F); anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10%; and radiographic changes indicative of pulmonary infection.

Assessment of the MAH's Response

The MAH states that due to the important differences in the data collection and definitions of the clinical outcomes during the periods of participation in Study 105 (data collected under the rigorous standards for clinical study data collection) and subsequent real-world registry-based Study 120 (observational data, collected over the course of routine care without scheduled visit intervals or standardized assessments), it is not appropriate to combine the datasets or to perform a direct comparison of outcomes between the periods (e.g., to compare the clinical study and the real-world registry based follow-up period).

Furthermore, the MAH's opinion is that while the Study 120 data cannot be combined with Study 105 data due to these critical differences in data collection, the trends observed for the clinical outcomes during the 3-year follow-up in Study 120 are nonetheless consistent with those observed from the 2-year follow-up in Study 105. Specifically, the MAH states that the effectiveness outcomes in subjects in

Study 120 demonstrated overall stable trends in percent predicted forced expiratory volume in 1 second (ppFEV1), body mass index (BMI) values, annual risk of PEx, annualized PEx rate, and annualized rate of hospitalizations, which was consistent with the long-term maintenance of the treatment effect demonstrated in Study 105 for the relevant endpoints. In addition, no new safety concerns were identified in Study 120.

During the assessment of the protocol (Assessment Report REC 10.1), the MAH was requested to confirm that trends over 5 years will be described i.e. the relevant data from the two-year study 105 will also be included in the description of long term safety and efficacy and the MAH confirmed that trends over 5 years will be described in the final clinical study report for Study 120, including a discussion of relevant data from the previously completed 2-year Study 105.

In Study 105, although the efficacy seemed to be sustained during the initial 24 weeks, a trend of decaying beyond Week 24 was observed: for subjects who received active treatment in both Study 103/104 and Study 105, the improvements in ppFEV1 from previous study baseline during Study 103/104 were generally sustained in Study 105 up to Extension Week 36 for L600qd/I group and Extension Week 24 for L400q12h/I group. The improvement in ppFEV1 decreased over time in both groups with small/no improvement in ppFEV1 at Extension Week 96. The least square (LS) mean absolute change from baseline in ppFEV1 for the L400q12h/I group (the authorized dose for this age group) was 1.6 percentage points (P = 0.0012) at Week 60; at Week 72, the L400q12h/I group result was numerically above baseline but lacked within-treatment statistical significance (P = 0.2806).

The differences in the data collection and definitions of the clinical outcomes during the periods of participation in Study 105 (clinical study data) and in Study 120 (real-world registry-based data) are known limitations of the protocol proposed by the MAH in order to fulfil the post-authorization commitment. Nevertheless, in the Final Assessment Report REC 10.1, the MAH has confirmed that trends over 5 years will be described in the final clinical study report for Study 120, including a discussion of relevant data from the previously completed 2-year Study 105.

In Study 105, although the efficacy seemed to be sustained during the initial 24 weeks, a trend of decaying beyond Week 24 was observed with small/no improvement in ppFEV1 at Extension Week 96. At Week 72, the L400q12h/I group result was numerically above baseline but lacked within-treatment statistical significance (P = 0.2806) (see CHMP AR EMEA/H/C/003954/II/0017). Given that only 53% of subjects who completed study 105 were from US, and given that out of 485 subjects from US who completed study 105, only roughly half were included in Study 120 (256 in the 2016; 239 in the 2017; 202 in the 2018), it is not considered appropriate to compare the overall 2 year results of Study 105 with the 3 year follow up in Study 120. The issue is not resolved.

The request to provide results on the effectiveness and safety endpoints evaluated in Study 120 (ppFEV1, BMI and weight, pulmonary exacerbation, liver function tests, hypertension, organ transplantation) complemented with results on the same endpoints obtained during the 2 years of Study 105, in order to have an overall period of observation of 5 years is reiterated. Also, the request to provide these results both in the overall population and separately in the subgroups <18 years of age and ≥18 years of age is reiterated.

Question 3

Given that part of the 256 US subjects included in Study 120 are included also in the published analysis of the matched registry cohort (Konstan et al, Lancet Resp Med 2017), the MAH should provide the 5 year follow up of these patients in comparison with their matched controls, according to the same methodology followed in the publication by Konstan et al. 2017. Limitedly to a 3 year follow up, the MAH should also provide the rate of change in annualized PEx in Orkambi treated patients and

matched registry controls (overall and by age, using the 18 yrs cut-off), given that both Study 120 and the US registry used the same definition of PEx.

MAH's response

In accordance with the Assessment Report REC 10.1, Study 120 was designed as a single-arm study without a comparator group. Given the limitations of the design elements for Study 120, data from the ongoing PASS (Study 108) is provided as a supplement to the Study 120 analyses to provide additional data in the assessment of long-term outcomes of Orkambi. This approach is also in accordance with the Assessment Report REC 10.1.

Vertex acknowledges the additional request for matched control analyses using the same methodology followed in Konstan et al.1 but would like to clarify that such analyses are beyond the scope of the approved protocol and would not be feasible due to the following:

• The matched control analyses described in Konstan et al. were performed before approval and commercialization of Orkambi in the US, thus the authors were able to evaluate a large pool of F/F patients who were naïve to CFTR modulators, specifically Orkambi.

• Study 120 focuses on the 3-year period predominantly following approval and commercialization of Orkambi, and, subsequently, Symdeko® in the US (2016 through 2018); thus, a sufficient pool of CFTR modulator naïve F/F patients cannot be identified during this period to appropriately match to study participants in Study 120.

Although additional matched control analyses would not be possible, the patterns observed in Study 120 are favorable in the context of natural history of these outcomes among patients untreated with CFTR modulators. Specifically, in Konstan et al.,[1] the rate of lung function decline among US registry F/F patients who were untreated with CFTR modulator therapy was 2.29 percentage points per year. In Study 120, lung function remained relatively stable over the course of the 3-year follow-up. Similarly, in a real-world registry-based study of disease progression among patients treated with ivacaftor (Kalydeco Long-term Safety Study),[2] a comparator cohort of patients untreated with CFTR modulators had an increasing annual proportion of patients with ≥1 PEx and increasing annualized PEx event rate over time. In Study 120, both the annual proportion of patients with ≥1 PEx and annualized PEx event rate were relatively stable over the course of the 3 years following completion of Study 105.

In summary, single cohort data for Study 120 and comparative cohort data from the ongoing long-term PASS (Study 108) are complementary and sufficient to evaluate the long-term effects of Orkambi therapy under the real-world conditions of use and are in accordance with the Assessment Report REC 10.1. In addition, the trends in efficacy outcomes in Study 120 remain favorable when compared to other comparator cohort data from patients untreated with CFTR modulators in previously published studies.[1, 2]

REFERENCES

1 Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation(PROGRESS): a phase 3, extension study. Lancet Respir Med. 2017;5(2):107-18.

2 Volkova N, Moy K, Evans J, Campbell D, Tian S, Simard C, et al. Disease progression in patients with cystic fibrosis treated with ivacaftor: Data from national US and UK registries. J Cyst Fibros. 2020;19(1):68-79.

Assessment of the MAH's Response

The MAH states that the request for matched control analyses using the same methodology followed in Konstan et al. are beyond the scope of the approved protocol and would not be feasible because a sufficient pool of CFTR modulator naïve F/F patients cannot be identified during this period to appropriately match to study participants in Study 120.

Furthermore, the MAH states that the patterns observed in Study 120 are favourable in the context of natural history of these outcomes among patients untreated with CFTR modulators (Konstan et al, 2017; Volkova et al 2020).

Even though in the assessors opinion the previously requested matched control analysis would have allowed to better assess changes in efficacy over time, it is acknowledged that the issue of the absence of a matched control group from the registry, initially raised as a concern to the proposed protocol for this study, was not pursued in the Final Assessment Report for the Post-Authorisation Measure REC 10.1, dated 15 March 2018, on the basis of the argumentation that the safety data generated from the larger PASS study 108 with an Orkambi treated and a control arm, was considered sufficient to fill in the lacunae in information from the absence of a control group in study 120.

The issue is not pursued further.

2nd Request for supplementary information

The differences in the data collection and definitions of the clinical outcomes during the periods of participation in Study 105 (clinical study data) and in Study 120 (real-world registry-based data) are known limitations of the protocol proposed by the MAH in order to fulfil the post-authorization commitment. Nevertheless, in the Final Assessment Report REC 10.1, the applicant has confirmed that that trends over 5 years will be described in the final clinical study report for Study 120, including a discussion of relevant data from the previously completed 2-year Study 105.

In Study 105, although the efficacy seemed to be sustained during the initial 24 weeks, a trend of decaying beyond Week 24 was observed with small/no improvement in ppFEV1 at Extension Week 96. At Week 72, the L400q12h/I group result was numerically above baseline but lacked within-treatment statistical significance (P = 0.2806).

Given that only 53% of subjects who completed study 105 were from US, and given that out of 485 subjects from US who completed study 105, only roughly half were included in Study 120 (256 in the 2016; 239 in the 2017; 202 in the 2018), it is not considered appropriate to compare the overall 2 year results of Study 105 with the 3 year follow up in Study 120.

The request to provide results on the effectiveness and safety endpoints evaluated in Study 120 (ppFEV1, BMI and weight, pulmonary exacerbation, liver function tests, hypertension, organ transplantation) complemented with results on the same endpoints obtained during the 2 years of Study 105, in order to have an overall period of observation of 5 years is reiterated. Also the request to provide these results both in the overall population and separately in the subgroups <18 years of age and ≥18 years of age is reiterated.

MAH response to 2nd Request for supplementary information

Summary of the MAH's response

As requested, Vertex is providing the results on the effectiveness and safety endpoints evaluated in Study 120, complemented with the results on the same endpoints observed in Study 105. The requested effectiveness and safety endpoints include: percent predicted forced expiratory volume in 1 second (ppFEV1), body mass index (BMI) and weight, pulmonary exacerbations (PEx), liver function

tests (LFTs), hypertension, and organ transplantation. In addition, results are also provided for the pediatric (12 to <18 years of age) and adult subgroups (≥18 years of age) for both studies. A complete list of the tables summarizing the pediatric and adult subgroup data is provided in Appendix 1 for Study 105 and in Appendix 2 for Study 120.

Overall, the trends observed in the effectiveness and safety endpoints in Study 120 were consistent with the long-term maintenance of the treatment effect demonstrated in Study 105, in the overall population as well as pediatric and adult subgroups.

It is important to note that due to the critical differences between interventional clinical studies and observational studies, these results should be interpreted with caution. These differences include data collection methodology, the nature of the collected data, and the endpoint definitions. For example, Study 105 data were collected under the rigorous standards for clinical study data collection, including predefined intervals between assessments, standardized measurements and procedures, and standardized definitions of clinical outcomes/endpoints. In contrast, Study 120 data was observational in nature, collected over the course of routine care without scheduled visit intervals or standardized assessments. Differences in endpoint definitions (e.g., PEx) between the studies are discussed in further detail below. Given these limitations, it is not appropriate to combine the clinical data from Study 105 and the registry-based data from Study 120 or directly compare the reported values for each endpoint. Instead of comparing specific values, directional consistency of outcomes should be evaluated. In addition, the pediatric subgroup results for Study 120 should be interpreted with caution because of the small sample size (n = 48).

Demographics and Baseline Characteristics

A summary of the demographics and baseline characteristics of the overall population and pediatric subgroups in Study 105 and Study 120 are summarized in Table 11.

The overall distribution of patients by sex and race are similar between the overall population and pediatric subgroups for both Study 105 and Study 120. The baseline age (mean and range) for both the overall population and pediatric subgroups was higher in Study 120 than in Study 105, which was expected because the baseline year for Study 120 was 2016, approximately 2.5 years after the baseline of Study 105 (Study 103/104 baseline). Mean ppFEV1 at baseline for the pediatric subgroup was higher than that of the overall population for both Studies 105 and 120, which was consistent with the expected lung function in cystic fibrosis (CF) patients of this age group.

Table 11 Summary of Demographics and Baseline Characteristics, Overall and Pediatric Subgroup

Category	Study 105 Overall N = 1029	Study 105 Pediatric Subgroup N = 281	Study 120 Overall N = 256	Study 120 Pediatric Subgroup N = 48
Sex, n (%)				
Male	524 (50.9)	141 (50.2)	133 (52.0)	22 (45.8)
Female	505 (49.1)	140 (49.8)	123 (48.0)	26 (54.2)
Age (years)[a]				
n	1029	281	256	48
Mean (SD)	24.8 (9.62)	14.5 (1.66)	28.4 (10.5)	16.0 (1.1)
Median	23.0	14.0	27.3	16.1
Min, max	12, 64	12, 17	14.3, 66.4	14.3, 17.8
Race, n (%)				
White	1019 (99.0)	276 (98.2)	254 (99.2)	47 (97.9)
Black or African American	1 (0.1)	0	NC	NC
Asian	1 (0.1)	1 (0.4)	NC	NC
American Indian or Alaska Native	1 (0.1)	1 (0.4)	NC	NC
Not collected per local regulations	3 (0.3)	2 (0.7)	NC	NC
Other	4 (0.4)	1 (0.4)	2 (0.8)	1 (2.1)
$ppFEV_1$ at baseline[b] (percentage points)				
n	1018	276	256	48
Mean (SD)	60.5 (13.9)	67.2 (13.1)	66.3 (16.6)	76.4 (10.6)
Median	60.6	68.6	66.1	77.3
Min, max	31.1, 99.8	31.1, 96.5	27.1, 99.2	53.3, 99.1

max: maximum value; min: minimum value; N: total sample size; n: size of subsample; NC: not collected; $ppFEV_1$: percent predicted forced expiratory volume in 1 second

[a] In Study 105, baseline age was based on the most recent measurement before the first dose of study drug in Studies 103/104. In Study 120, baseline age was the age as of 01 January 2016.

[b] In Study 120, baseline $ppFEV_1$ was calculated using Global Lung Initiative; average of the best available measurement for all quarters in each calendar year.

ppFEV1

Overall Analysis

For subjects in Study 105 who received lumacaftor (LUM)/ivacaftor (IVA) in parent Study 103/104, improvements in ppFEV1 observed in Study 103/104 were generally sustained during the additional 96 weeks of treatment in Study 105. For subjects who received placebo in Study 103/104, improvements in ppFEV1 upon receiving LUM/IVA in Study 105 were similar to those observed for the LUM/IVA group in Study 103/104 and were generally sustained throughout Study 105. At Study 105 Week 96, ppFEV1 was above baseline for all treatment groups (Study 105 CSR/ Table 14.2.1.1a). Data from Study 120 showed that ppFEV1 remained generally stable over the subsequent 3 years for a subset of participating Study 105 subjects (Figure 1).

Subgroup Analysis

The ppFEV1 results for the adult subgroup in Study 105 and Study 120 (US CFF [Age ≥18]) were consistent with the trends observed for the overall population for each study. The trends in ppFEV1 observed in the adult subgroup over the 2-year Study 105 and over the subsequent 3 years of follow-up in Study 120 were consistent with those observed in the overall population. The ppFEV1 results for the pediatric subgroup in Study 105 and Study 120 (US CFF [Age <18]) were consistent with the trends observed for the overall population for each study. Mean ppFEV1 at baseline for the pediatric subgroup was higher than that of the overall population for both studies, which was consistent with the expected lung function in CF patients of this age group. In the pediatric subgroup, ppFEV1 improvements from baseline were observed and generally sustained in Study 105. Over the 3-year follow-up in Study 120, a numerical decrease in ppFEV1 was observed, which was not statistically significant as illustrated by the wide and overlapping standard error bars (Figure 6).

Figure 6 Summary of Mean ppFEV1 Overall and the Pediatric Subgroup.

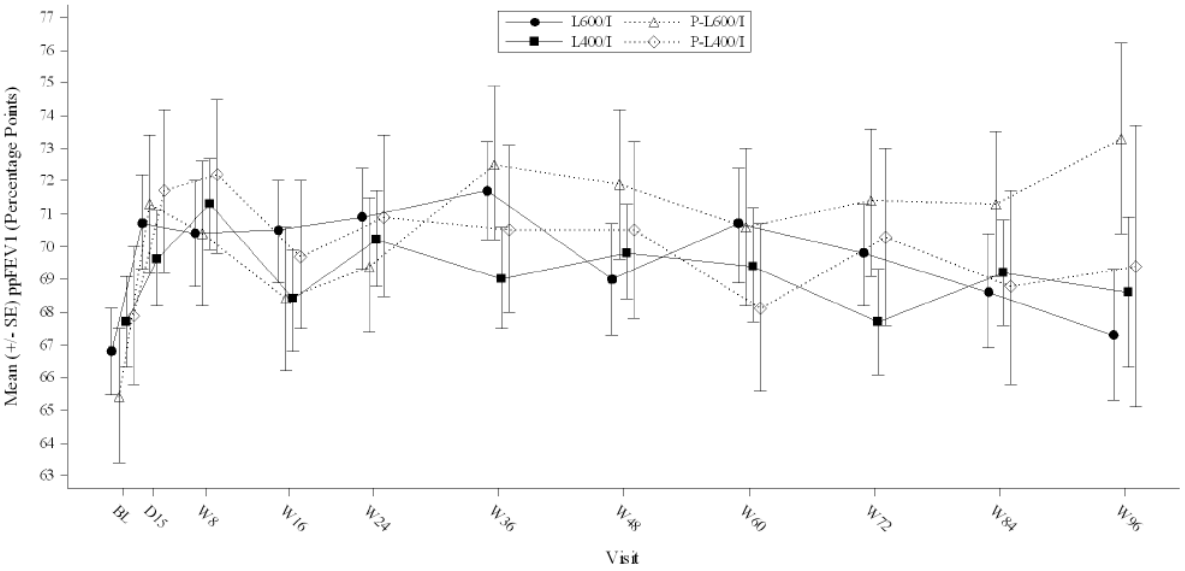
Sources: Study 105 CSR/Table 14.2.1.1a, Ad Hoc Table 14.2.1.1a, and US CFF (Age <18) Table 2.0

BL: baseline; D: day; n: size of subsample; P: placebo; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; W: week

Notes: For L600/I and L400/I, baseline was defined as the most recent non-missing measurement before intake of the first dose of study drug in Studies 103 or 104. For P-L600/I and P-L400/I, baseline is defined as the most recent non-missing measurement before intake of the first dose of study drug in Study 105.

Ad Hoc Figure 7: Mean ppFEV1 (percentage points) at Each Visit of Study 105 for Subjects Less Than 18 Years Old at 103/104 Baseline for Part A Treatment Cohort, 105 Full Analysis Set

Ad Hoc Figure 14.2.1.1.2a
Mean $ppFEV_1$ at Each Visit of Study 105 for Subjects Less Than 18 Years Old at 103/104 Baseline for Part A Treatment Cohort
105 Full Analysis Set



-For L600/I and L400/I, Baseline is defined as the most recent non-missing measurement before intake of the first dose of study drug in Studies 103 or 104. For P-L600/I and P-L400/I, Baseline is defined as the most recent non-missing measurement before intake of the first dose of study drug in Study 105.
-BL = Baseline, D = Day, W = Week.

Ad Hoc Table 12: Percent predicted FEV 1 (percentage points) at each visit of Study 105 for Subjects 12 to <18 Years Old at Baseline for Part A Treatment Cohort, 105 full Analysis Set

		103/104 and 105			
Visit	Statistic	L600/I N = 334	P-L600/I N = 179	L400/I N = 340	P-L400/I N = 176
Number of Subjects in the Subgroup	n	93	47	94	47
Baseline	n	92	47	94	47
	Mean (SD)	66.8 (12.6)	65.4 (14.1)	67.7 (13.2)	67.9 (14.3)
	SE	1.3	2.0	1.4	2.1
	Median	68.0	68.1	68.7	68.1
	Min, Max	31.1, 92.3	34.2, 90.6	36.3, 96.5	37.0, 95.9
Ext. Day 15	n	88	46	87	42
	Mean (SD)	70.7 (13.8)	71.3 (14.3)	69.6 (13.8)	71.7 (16.3)
	SE	1.5	2.1	1.5	2.5
	Median	72.4	71.6	70.6	75.0
	Min, Max	35.7, 106.7	38.7, 96.9	31.7, 93.5	38.1, 97.6
Absolute Change from Baseline at Ext. Day 15	n	87	46	87	42
	Mean (SD)	4.2 (8.4)	5.5 (11.2)	1.8 (8.3)	3.7 (7.0)
	SE	0.9	1.7	0.9	1.1
	Median	4.2	3.9	1.9	4.0
	Min, Max	-16.8, 26.2	-16.8, 54.5	-23.6, 23.8	-11.0, 23.3
Ext. Week 8	n	83	42	89	45
	Mean (SD)	70.4 (14.6)	70.4 (14.2)	71.3 (13.1)	72.2 (15.6)
	SE	1.6	2.2	1.4	2.3
	Median	73.5	71.5	72.3	73.5
	Min, Max	29.0, 97.9	34.2, 94.4	37.7, 104.0	32.0, 95.2

-N: Number of subjects in the 105 Full Analysis Set for Part A Treatment Cohort.
-For L600/I and L400/I, Baseline is defined as the most recent non-missing measurement before intake of the first dose of study drug in studies 103 or 104. For P-L600/I and P-L400/I, Baseline is defined as the most recent non-missing measurement before intake of the first dose of study drug in Study 105.

		103/104 and 105			
Visit	Statistic	L600/I N = 334	P-L600/I N = 179	L400/I N = 340	P-L400/I N = 176
Absolute Change from Baseline at Ext. Week 8	n	82	42	89	45
	Mean (SD)	3.0 (8.7)	4.8 (11.3)	3.6 (9.0)	4.1 (8.8)
	SE	1.0	1.7	1.0	1.3
	Median	2.3	2.5	3.4	2.9
	Min, Max	-19.4, 26.0	-18.4, 47.7	-23.7, 33.7	-15.8, 32.7
Ext. Week 16	n	85	43	85	43
	Mean (SD)	70.5 (14.3)	68.4 (14.6)	68.4 (14.3)	69.7 (14.8)
	SE	1.5	2.2	1.5	2.3
	Median	73.0	71.6	69.6	72.1
	Min, Max	31.5, 106.2	28.0, 90.3	30.2, 102.9	27.1, 92.4
Absolute Change from Baseline at Ext. Week 16	n	84	43	85	43
	Mean (SD)	3.7 (10.4)	4.0 (12.1)	1.4 (9.6)	3.0 (9.1)
	SE	1.1	1.8	1.0	1.4
	Median	1.8	2.9	1.4	2.4
	Min, Max	-13.3, 46.5	-19.8, 40.7	-28.4, 34.9	-19.9, 29.9
Ext. Week 24	n	83	43	86	45
	Mean (SD)	70.9 (14.2)	69.4 (13.6)	70.2 (13.3)	70.9 (16.7)
	SE	1.6	2.1	1.4	2.5
	Median	71.2	71.6	72.3	74.7
	Min, Max	34.8, 103.4	31.4, 89.9	37.3, 102.5	34.5, 95.5

-N: Number of subjects in the 105 Full Analysis Set for Part A Treatment Cohort.
-For L600/I and L400/I, Baseline is defined as the most recent non-missing measurement before intake of the first dose of study drug in studies 103 or 104. For P-L600/I and P-L400/I, Baseline is defined as the most recent non-missing measurement before intake of the first dose of study drug in Study 105.

		103/104 and 105			
Visit	Statistic	L600/I N = 334	P-L600/I N = 179	L400/I N = 340	P-L400/I N = 176
Absolute Change from Baseline at Ext. Week 24	n	82	43	86	45
	Mean (SD)	3.2 (10.4)	4.4 (9.7)	2.9 (8.4)	3.5 (10.3)
	SE	1.1	1.5	0.9	1.5
	Median	2.1	2.3	2.5	4.0
	Min, Max	-16.7, 49.0	-13.6, 37.5	-24.7, 28.6	-24.5, 34.8
Ext. Week 36	n	81	38	86	43
	Mean (SD)	71.7 (13.6)	72.5 (14.3)	69.0 (14.2)	70.5 (16.7)
	SE	1.5	2.3	1.5	2.5
	Median	73.3	75.2	71.3	74.2
	Min, Max	28.9, 103.5	33.8, 95.1	25.0, 100.5	25.4, 99.3
Absolute Change from Baseline at Ext. Week 36	n	80	38	86	43
	Mean (SD)	3.9 (8.4)	6.8 (11.0)	2.0 (9.0)	3.2 (9.5)
	SE	0.9	1.8	1.0	1.5
	Median	2.9	3.8	1.5	3.9
	Min, Max	-12.0, 29.8	-11.4, 39.6	-14.8, 35.3	-20.9, 20.3
Ext. Week 48	n	78	37	81	42
	Mean (SD)	69.0 (15.4)	71.9 (14.2)	69.8 (13.3)	70.5 (17.6)
	SE	1.7	2.3	1.5	2.7
	Median	70.7	73.0	71.0	70.2
	Min, Max	26.0, 99.6	29.0, 93.8	35.8, 96.6	22.2, 99.1

-N: Number of subjects in the 105 Full Analysis Set for Part A Treatment Cohort.
-For L600/I and L400/I, Baseline is defined as the most recent non-missing measurement before intake of the first dose of study drug in studies 103 or 104. For P-L600/I and P-L400/I, Baseline is defined as the most recent non-missing measurement before intake of the first dose of study drug in Study 105.

Visit	Statistic	103/104 and 105 L600/I N = 334	P-L600/I N = 179	L400/I N = 340	P-L400/I N = 176
Absolute Change from Baseline at Ext. Week 48	n	77	37	81	42
	Mean (SD)	1.9 (10.1)	6.2 (11.2)	2.8 (10.1)	2.8 (11.1)
	SE	1.2	1.8	1.1	1.7
	Median	1.7	3.5	1.9	2.7
	Min, Max	-19.9, 24.9	-7.3, 47.0	-19.5, 39.6	-18.3, 37.3
Ext. Week 60	n	77	36	81	39
	Mean (SD)	70.7 (15.5)	70.6 (14.4)	69.4 (15.7)	68.1 (15.7)
	SE	1.8	2.4	1.7	2.5
	Median	72.5	73.0	73.8	71.9
	Min, Max	26.6, 100.4	24.6, 97.6	28.8, 102.8	34.3, 96.7
Absolute Change from Baseline at Ext. Week 60	n	76	36	81	39
	Mean (SD)	2.9 (10.3)	5.7 (10.9)	2.0 (8.9)	-0.3 (13.8)
	SE	1.2	1.8	1.0	2.2
	Median	2.8	3.6	0.9	-0.2
	Min, Max	-17.2, 29.3	-12.4, 42.0	-16.7, 22.2	-47.2, 27.6
Ext. Week 72	n	81	40	83	35
	Mean (SD)	69.8 (13.9)	71.4 (14.2)	67.7 (14.6)	70.3 (15.9)
	SE	1.5	2.3	1.6	2.7
	Median	70.4	73.2	70.4	69.9
	Min, Max	31.4, 98.0	32.9, 95.3	30.5, 98.8	43.3, 98.2

-N: Number of subjects in the 105 Full Analysis Set for Part A Treatment Cohort.
-For L600/I and L400/I, Baseline is defined as the most recent non-missing measurement before intake of the first dose of study drug in studies 103 or 104. For P-L600/I and P-L400/I, Baseline is defined as the most recent non-missing measurement before intake of the first dose of study drug in Study 105.

Visit	Statistic	103/104 and 105 L600/I N = 334	P-L600/I N = 179	L400/I N = 340	P-L400/I N = 176
Absolute Change from Baseline at Ext. Week 72	n	80	40	83	35
	Mean (SD)	2.2 (9.3)	5.8 (10.9)	1.2 (9.9)	2.3 (10.4)
	SE	1.0	1.7	1.1	1.8
	Median	0.9	5.3	-0.7	1.0
	Min, Max	-17.4, 28.6	-13.5, 42.0	-23.3, 30.6	-16.6, 31.8
Ext. Week 84	n	71	36	67	33
	Mean (SD)	68.6 (15.0)	71.3 (13.3)	69.2 (13.3)	68.8 (17.0)
	SE	1.8	2.2	1.6	3.0
	Median	68.2	73.8	71.0	72.1
	Min, Max	29.3, 97.0	34.2, 90.9	32.6, 97.5	26.3, 95.9
Absolute Change from Baseline at Ext. Week 84	n	70	36	67	33
	Mean (SD)	1.1 (11.4)	3.6 (11.6)	0.4 (10.2)	0.6 (10.0)
	SE	1.4	1.9	1.2	1.7
	Median	0.1	1.4	0.0	2.2
	Min, Max	-34.5, 28.7	-20.0, 30.3	-28.6, 22.8	-25.3, 24.5
Ext. Week 96	n	56	19	50	19
	Mean (SD)	67.3 (15.1)	73.3 (12.6)	68.6 (16.0)	69.4 (18.9)
	SE	2.0	2.9	2.3	4.3
	Median	68.0	75.2	71.9	71.7
	Min, Max	29.4, 100.7	46.0, 94.9	27.5, 104.7	36.2, 107.0

-N: Number of subjects in the 105 Full Analysis Set for Part A Treatment Cohort.
-For L600/I and L400/I, Baseline is defined as the most recent non-missing measurement before intake of the first dose of study drug in studies 103 or 104. For P-L600/I and P-L400/I, Baseline is defined as the most recent non-missing measurement before intake of the first dose of study drug in Study 105.

Visit	Statistic	103/104 and 105 L600/I N = 334	P-L600/I N = 179	L400/I N = 340	P-L400/I N = 176
Absolute Change from Baseline at Ext. Week 96	n	56	19	50	19
	Mean (SD)	-0.5 (9.0)	3.6 (11.2)	-0.4 (9.9)	3.0 (11.2)
	SE	1.2	2.6	1.4	2.6
	Median	0.0	5.5	-0.9	1.8
	Min, Max	-22.2, 16.4	-15.7, 28.0	-28.5, 22.5	-22.5, 21.8
Ext. Safety Follow-up	n	82	38	76	37
	Mean (SD)	67.6 (15.6)	67.6 (16.9)	68.5 (14.9)	70.7 (18.2)
	SE	1.7	2.7	1.7	3.0
	Median	68.1	71.0	70.1	71.3
	Min, Max	25.6, 98.6	26.1, 93.5	28.3, 103.9	36.7, 105.0
Absolute Change from Baseline at Ext. Safety Follow-up	n	81	38	76	37
	Mean (SD)	0.7 (12.1)	2.4 (11.7)	0.4 (10.7)	2.3 (9.5)
	SE	1.3	1.9	1.2	1.6
	Median	-0.1	1.1	-1.2	1.1
	Min, Max	-27.2, 45.8	-15.3, 31.5	-25.5, 39.1	-16.3, 27.5

-N: Number of subjects in the 105 Full Analysis Set for Part A Treatment Cohort.
-For L600/I and L400/I, Baseline is defined as the most recent non-missing measurement before intake of the first dose of study drug in studies 103 or 104. For P-L600/I and P-L400/I, Baseline is defined as the most recent non-missing measurement before intake of the first dose of study drug in Study 105.

It is important to interpret the results observed in this small paediatric subgroup in context of the greater expected rate of lung function decline in the absence of CFTR modulator treatment. For instance, based on the analysis of US Cystic Fibrosis Foundation (CFF) registry data, the annualized rate of lung function decline in patients homozygous for F508del and 13 through 17 years of age not treated with a CFTR modulator has been previously estimated at -2.66 percentage points per year (Wegener et al, J Cyst Fibros. 2018;17(4):503-10). However, in the Study 120 paediatric subgroup, the absolute change in ppFEV1 was smaller at approximately -1.4 percentage points per year, which supports a lower rate of lung function decline.

Furthermore, additional support for a lower rate of lung function decline with Orkambi treatment was observed in the 3rd interim analysis of the ongoing comparator-controlled Orkambi post-authorization safety study (PASS; Study 108 Interim Analysis Report 3 [IA3]), which showed that in the subgroup of patients 12 to <18 years of age at the time of Orkambi initiation who remained on treatment through 2018 (n = 716), lung function change over 4 years (from pre-treatment baseline year 2014 to 2018) was -3.84 percentage points (approximately -1.0 percentage point per year) versus -7.62 percentage points (approximately -1.9 percentage points per year) in the untreated comparator patients (n = 803) (Study 108 IA3/Table 2.1).

Overall, the patterns observed in Study 120 and the PASS are consistent with the previously published rate of lung function decline analysis in Orkambi-treated patients 12 years of age and older (Konstan et al.). This analysis was performed using propensity scores and matching a subset of Study 105 subjects (n = 455) with US CFF Patient Registry control patients (n = 1,588) who were not treated with a CFTR modulator. The estimated annualized rate of lung function decline was -1.33 percentage points in the Orkambi-treated group, which was significantly less than the rate in matched controls (-2.29 percentage points, probability [P]< 0.001). This represents a 42% decrease in the rate of ppFEV1 decline in LUM/IVA-treated patients compared with matched controls.

Weight

Overall Analysis

For subjects in Study 105 who received LUM/IVA in Study 103/104, weight remained above baseline and generally continued to improve at all visits in Study 105. For subjects who received placebo in Study 103/104, weight improved upon initiating LUM/IVA treatment and generally continued to

improve throughout Study 105. Over the additional 3- year follow-up in Study 120, weight remained stable.

Subgroup Analysis

Improvements in weight were observed in the adult and pediatric subgroups for both Studies 105 and 120, similar to those observed in the overall population. Specifically, improvements in weight were seen throughout Study 105. Similar trends of increased weight were observed over the additional 3-year follow-up in Study 120.

Table Summary of Weight (kg) Results by Year (Table done by the Assessors)

	Study 120	
Weight (kg)	**≥18 years**	**<18 years**
2016		
N	208	48
Mean (SD)	64.79 (11.14)	58.70 (9.05)
Median	64.40	59.05
95% CI	63.26-66.31	56.07-61.33
2017		
N	191	48
Mean (SD)	65.14 (11.19)	60.51 (10.07)
Median	64.50	60.20
95% CI	63.54-66.73	57.59-63.44
2018		
N	159	43
Mean (SD)	66.78 (11.47)	61.87 (11.70)
Median	66.70	60.30
95% CI	64.99-68.58	58.27-65.48

BMI

Overall Analysis

The trends observed in Study 105 and Study 120 for the overall population was similar to those observed for weight. BMI increased at treatment initiation and continued to improve in Study 105. Over the additional 3-year follow-up in Study 120, BMI remained stable.

Subgroup Analysis

The trends observed for the adult and pediatric subgroups in Study 105 and Study 120 (US CFF [Age ≥ 18] Table 3.0 and US CFF [Age <18] Table 3.0) were consistent with the trends observed for the overall population in each study.

Table Summary of BMI Results by Year (Table done by the Assessors)

	Study 120	
BMI (kg/m^2)	**≥18 years**	**<18 years**
2016		
N	208	48
Mean (SD)	22.85 (2.90)	21.01 (1.98)
Median	22.46	20.75
95% CI	22.45-23.24	20.44-21.59
2017		
N	191	48
Mean (SD)	22.88 (2.85)	21.50 (2.37)
Median	22.24	21.41
95% CI	22.47-23.29	20.82-22.19
2018		
N	159	43
Mean (SD)	23.32 (3.13)	21.82 (2.75)
Median	23.02	21.31
95% CI	22.83-23.81	20.97-22.66

BMI-for-age Z-score

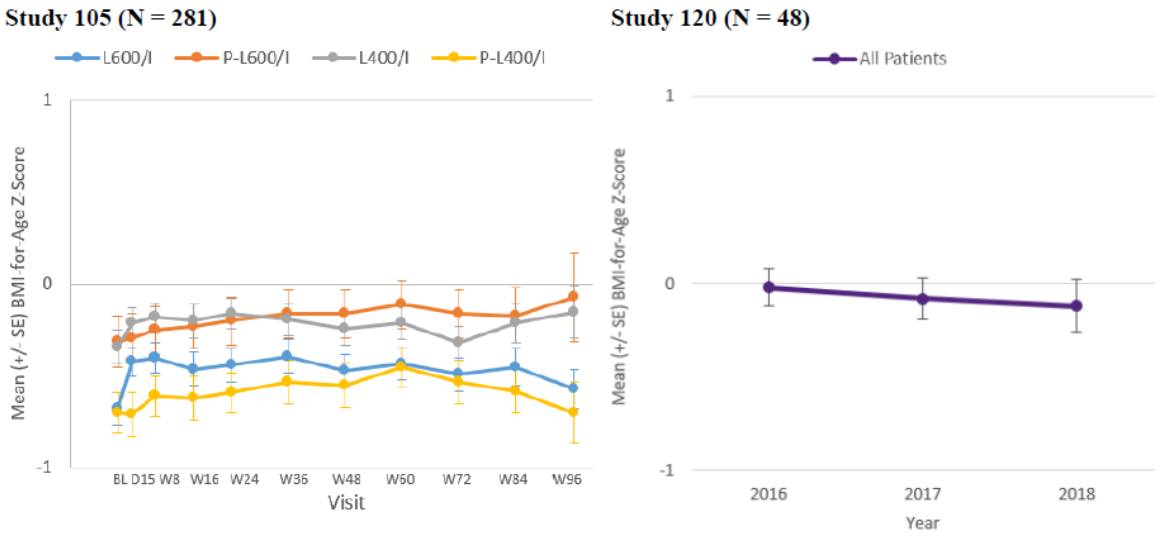
Overall Analysis

For both Studies 105 and 120, BMI-for-age z-score was analyzed only in subjects/patients <20 years of age. For subjects in Study 105 who received LUM/IVA in Study 103/104, improvements observed in the parent studies were generally sustained in Study 105. For subjects who received placebo in Study 103/104, BMI-for-age z-score improved upon initiating LUM/IVA through Week 36, and generally stabilized thereafter. Over the additional 3-year follow-up in Study 120, BMI-for-age z-score in patients <20 years of age remained stable.

Subgroup Analysis

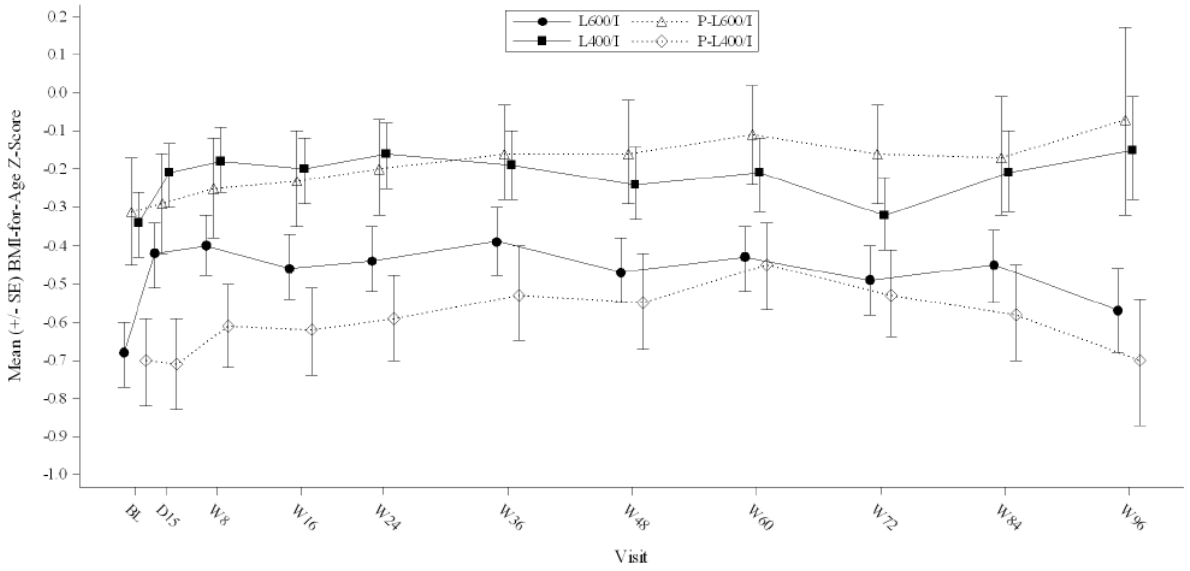
For the pediatric subgroup in Study 105, BMI-for-age z-scores were negative but generally improved throughout Study 105. BMI-for-age z-scores were generally stable in Study 120 with values close to 0 (US CFF [Age <18].

Figure 8: Summary of Mean BMI-for-age Z-score in the Pediatric Subgroup



BL: baseline; BMI: body mass index; D: day; n: size of subsample; P: placebo; W: week
Notes: For L600/I and L400/I, baseline is defined as the most recent non-missing measurement before intake of the first dose of study drug in Studies 103 or 104. For P-L600/I and P-L400/I, baseline is defined as the most recent non-missing measurement before intake of the first dose of study drug in Study 105.

Figure 9: Mean BMI Z-Score at Each Visit of Study 105 for Subjects Less Than 18 Years Old at 103/104 Baseline for Part A Treatment Cohort 105, Full Analysis Set



-For L600/I and L400/I, Baseline is defined as the most recent non-missing measurement before intake of the first dose of study drug in Studies 103 or 104. For P-L600/I and P-L400/I, Baseline is defined as the most recent non-missing measurement before intake of the first dose of study drug in Study 105.
-BL = Baseline, D = Day, W = Week.

Table 13: Summary of BMI-for-age z-score results by year, patients < 18

Time point	Statistic	Orkambi Cohort (N=48)
2016	n (non-missing)	48
	Mean	-0.02
	SD	0.66
	SE	0.10
	95% CI	-0.21-0.18
	Median	0.05
	Min	-1.43
	Max	1.53
2017	n (non-missing)	48
	Mean	-0.08
	SD	0.74
	SE	0.11
	95% CI	-0.29-0.14
	Median	-0.00
	Min	-1.62
	Max	1.80
2018	n (non-missing)	43
	Mean	-0.12
	SD	0.90
	SE	0.14
	95% CI	-0.39-0.16
	Median	-0.05
	Min	-3.04
	Max	2.09

Program: Table4_0)BMIPercentile.sas run on 2020-07-21
• Evaluations are based on the average of the best available measurement for all quarters in each calendar year

PEx

It is important to note that the definitions of the PEx-related endpoints for Studies 105 and 120 are different. The US CFFPR defines PEx as an episode requiring intravenous (IV) antibiotic use at home or in the hospital. However, PEx in Study 105 was strictly defined by criteria standardized across Vertex CF clinical studies, where most of these criteria are based upon assessments that are not captured in registry data (e.g., change in sputum and change in sinus discharge).

Overall Analysis

In Study 105, the annualized event rate of PEx for subjects who received LUM/IVA in Study 103/104 was lower than that for the placebo group in Study 103/104. For subjects who received placebo in Study 103/104, the annualized event rate of PEx had a similar event rate as was observed by the LUM/IVA group in Study 103/104. Over the additional 3-year follow-up in Study 120, the annualized event rate of PEx was stable over the 3-year study duration.

Subgroup Analysis

The trends observed for the adult subgroup in Study 105 and Study 120 (US CFF [Age ≥18]) were consistent with the trends observed for the overall population in Study 105 and over the additional 3-year follow-up in Study 120. For the pediatric subgroup in Study 105, the annualized event rate ranged

between 0.56 and 0.75 across the treatment groups. For the pediatric subgroup in Study 120, the event rates were generally stable over the 3-year study duration, and were 0.94 (95% CI: 0.49, 1.38), 0.92 (95% CI: 0.54, 1.29) and 1.14 (95% CI: 0.71, 1.57) in 2016, 2017, and 2018 respectively (US CFF [Age <18). These results should be interpreted with caution given the small sample size (n = 43 to 48) as well as differences in the PEx definitions between the clinical study and registry data.

Table 14: Study VX16-809-120: Pulmonary Exacerbations over Time (for Patients Age less than 18 on 1/1/2016)

Statistic	Orkambi Cohort (N=48)
2016	
n (non-missing)	48
Number of patients with at least one PEx, n (%)	20 (41.7)
Number of PEx per patient	
n (non-missing)	48
Mean	0.94
SD	1.54
SE	0.22
95% CI	0.49-1.38
Median	0.00
Min	0.0
Max	7.0
2017	
n (non-missing)	48
Number of patients with at least one PEx, n (%)	23 (47.9)
Number of PEx per patient	
n (non-missing)	48
Mean	0.92
SD	1.30
SE	0.19
95% CI	0.54-1.29
Median	0.00
Min	0.0
Max	5.0
2018	
n (non-missing)	43
Number of patients with at least one PEx, n (%)	25 (58.1)
Number of PEx per patient	
n (non-missing)	43
Mean	1.14
SD	1.41
SE	0.21
95% CI	0.71-1.57
Median	1.00
Min	0.0
Max	5.0

Program: Table6_0_PE.sas run on 2020-07-07
• PEx is defined as the use of IV antibiotics at home or in the hospital

Table 15: Study VX16-809-120 Pulmonary Exacerbations over Time (for Patients Age 18 and above on 1/1/2016)

Statistic	Orkambi Cohort (N=208)
2016	
n (non-missing)	208
Number of patients with at least one PEx, n (%)	102 (49.0)
Number of PEx per patient	
n (non-missing)	208
Mean	0.93
SD	1.31
SE	0.09
95% CI	0.75-1.11
Median	0.00
Min	0.0
Max	7.0
2017	
n (non-missing)	191
Number of patients with at least one PEx, n (%)	93 (48.7)
Number of PEx per patient	
n (non-missing)	191
Mean	0.84
SD	1.12
SE	0.08
95% CI	0.68-1.00
Median	0.00
Min	0.0
Max	6.0
2018	
n (non-missing)	159
Number of patients with at least one PEx, n (%)	75 (47.2)
Number of PEx per patient	
n (non-missing)	159
Mean	0.81
SD	1.22
SE	0.10
95% CI	0.62-1.00
Median	0.00
Min	0.0
Max	8.0

Program: Table6_0_PE.sas run on 2020-07-07

- PEx is defined as the use of IV antibiotics at home or in the hospital

Table 16: Number of pulmonary exacerbations by age group at baseline of studies 103/104 for part A treatment cohort 105 FAS

Age at 103/104 Baseline: 12 to <18 Years

	L600/I N = 334	P-L600/I N = 179	L400/I N = 340	P-L400/I N = 176
Number of Subjects in the Subgroup	93	47	94	47
Number of Subjects with Events	55	22	55	25
Total Number of Patient-Days (Patient-Years)	73806 (219.7)	28084 (83.6)	75756 (225.5)	29752 (88.5)
Number of Events	158	63	126	61
Number of Events per Patient-Year	0.72	0.75	0.56	0.69

-N: Number of subjects in the 105 Full Analysis Set for Part A Treatment Cohort.
-Analysis includes all events in the Cumulative Study Period for L600/I and L400/I, and all events in the Current Study period (Study 105) for P-L600/I and P-L400/I.
-Total number of days on each study period = end date of the Study Period - first dose date of the corresponding Study Period + 1.
-Total number of patient-years (48 weeks): Total number of patient-days/336.
-Pulmonary Exacerbation: treatment with new or changed antibiotic therapy for ≥4 sinopulmonary signs/symptoms.

Age at 103/104 Baseline: ≥18 Years

	L600/I N = 334	P-L600/I N = 179	L400/I N = 340	P-L400/I N = 176
Number of Subjects in the Subgroup	241	132	246	129
Number of Subjects with Events	174	74	157	73
Total Number of Patient-Days (Patient-Years)	183617 (546.5)	77776 (231.5)	185616 (552.4)	74333 (221.2)
Number of Events	541	202	434	174
Number of Events per Patient-Year	0.99	0.87	0.79	0.79

LFTs

Overall Analysis

In Study 105, the incidence of subjects with LFT elevations (including alanine transaminase [ALT], aspartate transaminase [AST], and bilirubin) that met threshold criteria was low and similar across all treatment groups. The majority of elevated transaminase events were mild or moderate in severity, non-serious, and did not lead to study drug discontinuation. Over the additional 3-year follow-up in Study 120, the frequency of patients with any ALT, AST, or bilirubin value exceeding the threshold of >3, >5, and >8 × upper limit of normal (ULN) was low. There were no discernible trends in LFTs exceeding the prespecified threshold of ULN over time.

Subgroup Analysis

The incidence of subjects with LFT elevations in the adult and pediatric subgroups of Study 105, was also low and similar across treatment groups (Ad Hoc Table 4.1.3.4.3.2a). Over the 3-year follow-up in Study 120, the prevalence of patients with any elevated LFTs was low in both subgroups: ≤3.3% in the

adult subgroup (US CFF [Age ≥18] Table 8.0) and only 1 patient in the pediatric subgroup had an elevated LFT (ALT >5 × ULN; US CFF [Age <18]).

Table 17: Study VX16-809-120 Liver Function Tests by Type (for Patients Age less than 18 on 1/1/2016)

	2016 (N=48)		2017 (N=48)		2018 (N=43)	
Outcome Information	n/N1	(%)	n/N1	(%)	n/N1	(%)
Number of Patients with Any Liver Function Test	46 / 48	95.83	45 / 48	93.75	43 / 43	100.00
n (non-missing)	46		45		43	
Mean number of any LTFs per patient	1.8		1.4		1.9	
SD	1.1		0.9		1.3	
Median	1.0		1.0		1.0	
Min	1.0		1.0		1.0	
Max	6.0		5.0		6.0	
Patients with Any Elevated LFT*	1 / 46	2.17	1 / 45	2.22	3 / 43	6.98
ALT						
>3*ULN	1 / 46	2.17	1 / 45	2.22	3 / 43	6.98
>5*ULN	0 / 46	0.00	0 / 45	0.00	1 / 43	2.33
>8*ULN	0 / 46	0.00	0 / 45	0.00	0 / 43	0.00
AST						
>3*ULN	0 / 46	0.00	0 / 45	0.00	1 / 43	2.33
>5*ULN	0 / 46	0.00	0 / 45	0.00	0 / 43	0.00
>8*ULN	0 / 46	0.00	0 / 45	0.00	0 / 43	0.00
Total Bilirubin						
>2*ULN	0 / 40	0.00	0 / 41	0.00	0 / 40	0.00

Program: Table8_0_Hosp.sas run on 2020-07-07
- Only those patients with LFT (ALT, AST, or total bilirubin) available in the year. Any elevated LFT is defined as ALT >3*ULN, or AST >3*ULN, or total bilirubin >2*ULN.
- n is the number of patients with the event and N1 is the number of patients with a non-missing measurement of the event.

Table 18: Study VX16-809-120 Liver Function Tests by Type (for Patients Age 18 and above on 1/1/2016)

	2016 (N=208)		2017 (N=191)		2018 (N=159)	
Outcome Information	n/N1	(%)	n/N1	(%)	n/N1	(%)
Number of Patients with Any Liver Function Test	194 / 208	93.27	171 / 191	89.53	150 / 159	94.34
n (non-missing)	194		171		150	
Mean number of any LTFs per patient	2.4		1.9		2.0	
SD	3.2		1.9		1.5	
Median	2.0		1.0		1.0	
Min	1.0		1.0		1.0	
Max	37.0		18.0		7.0	
Patients with Any Elevated LFT*	5 / 194	2.58	2 / 171	1.17	5 / 150	3.33
ALT						
>3*ULN	3 / 192	1.56	1 / 170	0.59	2 / 150	1.33
>5*ULN	0 / 192	0.00	1 / 170	0.59	0 / 150	0.00
>8*ULN	0 / 192	0.00	0 / 170	0.00	0 / 150	0.00
AST						
>3*ULN	2 / 193	1.04	1 / 170	0.59	2 / 149	1.34
>5*ULN	1 / 193	0.52	0 / 170	0.00	2 / 149	1.34
>8*ULN	0 / 193	0.00	0 / 170	0.00	1 / 149	0.67
Total Bilirubin						
>2*ULN	3 / 181	1.66	1 / 163	0.61	2 / 146	1.37

Program: Table8_0_Hosp.sas run on 2020-07-07
- Only those patients with LFT (ALT, AST, or total bilirubin) available in the year. Any elevated LFT is defined as ALT >3*ULN, or AST >3*ULN, or total bilirubin >2*ULN.
- n is the number of patients with the event and N1 is the number of patients with a non-missing measurement of the event.

Hypertension

It is important to note that the definitions of the hypertension events for Studies 105 and 120 are different. In Study 105, incident hypertension events were reported as adverse events (AEs), while in Study 120 prevalent events of hypertension are captured in the registry (i.e., includes incident and any pre-existing hypertension).

Overall Analysis

In Study 105, 12 (1.2%) subjects had AEs of hypertension. The majority of events were mild to moderate in severity, non-serious, and not assessed as related or possibly related to the study drug. Over the 3-year follow-up in Study 120, the prevalence of hypertension was low (≤5%) with no discernible pattern.

Subgroup Analysis

In the adult subgroup, 11 (1.5%) subjects had an AE of hypertension in Study 105; the incidence was low and similar across all treatment groups. In Study 120, the prevalence of patients with a record of hypertension was low (4.8 to ≤6.3%) over the 3-year follow-up (US CFF [Age ≥18]).

In the pediatric subgroup, only 1 (0.4%) subject had an AE of hypertension in Study 105 and no patients had a record of hypertension in Study 120 (US CFF [Age <18]).

Organ Transplants

Overall Analysis

There were no organ transplants reported during Study 105). Over the 3-year follow-up in Study 120, 2 (0.78%) out of the 256 patients had a record of lung transplants; 1 in 2016 and 1 in 2017.

Subgroup Analysis

There were no organ transplants in the pediatric subgroup for Study 105 or Study 120 (US CFF [Age <18]).

Summary

Overall, the trends observed in the effectiveness and safety endpoints in Study 120 were consistent with the long-term maintenance of treatment effect demonstrated in Study 105, in the overall population as well as pediatric and adult subgroups.

Additional data from PASS Study 108

Importantly, the results from the ongoing PASS, a much larger, comparator-controlled real-world study, provides additional data to evaluate the long-term effects of Orkambi. Data from the 3rd annual interim analysis (submitted 26 November 2019) included 4,628 patients in the Orkambi Safety Cohort and 5,666 patients in the Comparator Safety Cohort. Key results in Orkambi treated for the same efficacy and safety outcomes are discussed further below:

• ppFEV1: A smaller decline in lung function over 4 years was observed in the Orkambi Disease Progression Cohort (n = 2,287) compared to the Comparator Disease Progression Cohort (n = 3,527) (Study 108 IA3/Figure 5). In subgroup analysis, the same trend was observed in patients 12 to <18 years of age (Orkambi Disease Progression Cohort: n = 773; Comparator Disease Progression Cohort: n = 845; Study 108 IA3).

· BMI: Among patients ≥18 years of age, a greater increase in mean BMI was observed from 2014 to 2018 in the Orkambi Disease Progression Cohort than in the Comparator Disease Progression Cohort (Study 108 IA3/US 2018 Objective 3). Among patients <18 years of age, mean BMI percentile increased from 2014 to 2018 in the Orkambi Disease Progression Cohort whilst decreasing in the Comparator Disease Progression Cohort.

• PEx: From 2014 to 2018, the annual proportion of patients with PEx and the annualized PEx rate per patient were stable for patients receiving Orkambi, while the annual proportion of patients with a PEx and the annualized PEx rate increased in the Comparator Disease Progression Cohort (Study 108 IA3).

• LFTs: The proportion of patients with any LFTs >1 × ULN was numerically lower in the Orkambi Safety Cohort compared to the Comparator Cohort. The proportion of patients with ALT and AST >3 × ULN and total bilirubin >2 × ULN was overall relatively uncommon and proportions were generally numerically lower in the Orkambi Safety Cohort or comparable between the 2 cohorts (Study 108 IA3).

• Organ Transplant: Overall, the risk of transplantation was significantly lower in the Orkambi versus the Comparator Safety Cohort (relative risk [RR] = 0.36; 95% CI: 0.23, 0.57) (Study 108 IA3).

The 4th interim analysis report is expected in December 2020 and will provide additional insights to the long-term effects of Orkambi, including subgroups of adult and pediatric patients.

Assessor's comment

As requested, the MAH has provided Study 120 effectiveness and safety endpoints separately in the subgroups <18 years of age and ≥18 years of age. The paediatric subgroup results for Study 120 should be interpreted with caution because of the small sample size (n = 48).

ppFEV1: Study 120 results showed that, in the overall population, ppFEV1 remained generally stable over the 3-year study duration (mean ppFEV1 66.34, 65.24, and 66.36, respectively in 2016, 2017, 2018). The sensitivity analysis that included only subjects with continuous Orkambi exposure from 2016 to 2018, showed in the overall population a mean decrease in ppFEV1 of -1.15 percentage point

in the first year and of -0.79 in the second year. These results are consistent with the previously published rate of lung function decline analysis in Orkambi-treated patients 12 years of age and older from Study 105 (PROGRESS Study) (Konstan et al 2017). This analysis was performed using propensity scores and matching a subset of Study 105 subjects (n = 455) with US CFF Patient Registry control patients (n = 1,588) who were not treated with a CFTR modulator. The estimated annualized rate of lung function decline was -1.33 percentage points in the Orkambi-treated group, which was significantly less than the rate in matched controls (-2.29 percentage points, probability [P]< 0.001).

In the subgroup of paediatric patients 12-<18 years in Study 105, treated with Orkambi L400q12h/I both in the parent study and in Study 105, a mean absolute change from baseline of 2.8 percentage points was observed at 48 weeks, of 1.2 percentage points at 72 weeks, and of -0.4 percentage points observed at week 96.

In Study 120, in the subgroup of paediatric patients 12-<18 years (n=48), a mean decrease of -2.1 percentage point in the first year and of -0.66 in the second year was observed in mean ppFEV1 (mean ppFEV1 76.40, 74.30, 73.64 percentage points, respectively in 2016, 2017, 2018). The sensitivity analysis that included only subjects with continuous Orkambi exposure from 2016 to 2018 (N=43), showed in the subgroup of patients <18 years a mean decrease in ppFEV1 of -1.96 percentage point in the first year and of -1.47 percentage points in the second year. The observed decrease seems slightly lower than 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).

Additional support for a lower rate of lung function decline with Orkambi treatment compared with an untreated cohort was observed in the 3rd interim analysis of the ongoing comparator-controlled Orkambi post-authorization safety study (PASS; Study 108 Interim Analysis Report 3 [IA3]). A smaller decline in lung function over 4 years was observed in the Orkambi Disease Progression Cohort (n = 2,287) compared to the Comparator Disease Progression Cohort (n = 3,527) (Study 108 IA3/Figure 5). in the subgroup of patients 12 to <18 years of age at the time of Orkambi initiation who remained on treatment through 2018 (n = 716), lung function change over 4 years (from pre-treatment baseline year 2014 to 2018) was -3.84 percentage points (approximately -1.0 percentage point per year) versus -7.62 percentage points (approximately -1.9 percentage points per year) in the untreated comparator patients (n = 803).

Thus, similarly to what observed in Study 105, although a trend towards a numerical decaying of effect on lung function (ppFEV1) with longer treatment duration was observed in Orkambi treated subjects in Study 120, the indirect comparison with published cohorts of US registry patients homozygous for F508del mutation untreated with CFTR modulator therapy **(**Konstan et al, 2017; Wegener et al, 2018), seem to indicate a slower annual rate of ppFEV1 decline in Orkambi treated patients.

BMI: In Study 120, mean BMI was stable in the overall Orkambi cohort as well as in the subgroups ≥ or < 18 years. In the subgroup <18 years, there was numerically a slight decrease of BMI for age Z scores during Study 120 (2016: -0.02; 2017: -0.08; 2018: -0.12), although with overlapping confidence intervals, and with values close to zero. For the paediatric subgroup in Study 105, BMI-for-age z-scores were negative but generally improved throughout Study 105.

PEx: In the paediatric subgroup (12-<18 years) of patients enrolled in Study 120 (n=48), there was a numerical increase in the proportion of subjects with at least one PEx per year, over the three year study duration (2016: 20/48, 41.7%; 2017: 23/48: 47.9%; 2018: 25/43: 58.1%), although event rates showed overlapping CI [2016: 0.94 (95% CI: 0.49, 1.38), 2017: 0.92 (95% CI: 0.54, 1.29) and 2018: 1.14 (95% CI: 0.71, 1.57)].

In the adult subgroup (≥18 years) of subjects enrolled in Study 120, the proportion of subjects with at least one PEx per year was stable over the 3-year study duration (2016: 102/208, 49%; 2017: 93/191: 48.7%; 2018: 75/159: 47.2%; annualized event rate of PEx: 0.93, 0.84 and 0.81, respectively in 2016, 2017 and 2018).

In Study 105, for the paediatric subgroup treated with Orkambi L400q12h/I both in the parent study and in Study 105, the annualized event rate was 0.56. For subjects ≥18 years treated with Orkambi L400q12h/I both in the parent study and in Study 105, the annualized event rate was 0.79. In Study 120, in the subgroup of paediatric subjects (12-<18 years), the PEx rate seems higher compared to Study 105. However due to the different definitions used in the two studies, no conclusion may be drawn.

In the 3rd interim analysis of the ongoing PASS Study (Study 108) the annual proportion of patients with pulmonary exacerbations remained similar from 2014 to 2018 (36.6% in 2014 and 36.7% in 2018). By contrast the proportion of patients in the Comparator group increased by 8.5%. The MAH has been requested to stratify this data by age in the next interim report of the ongoing PASS study.

Safety data coming from Study 120 seem consistent with the safety profile described in study 105.

Given that patients included in study 120 represent only a selected subgroup (roughly 25%) of the patient population enrolled in study 105 (only from US and only some from US sites who consented to participate), the comparison between Study 120 and Study 105 results is subject to limitations. It is acknowledged that due to the differences in data collection and endpoint definitions, it may not be appropriate to combine the clinical data from Study 105 and the registry-based data from Study 120 or directly compare the reported values for each endpoint. For the reasons above, even though the MAH has not provided the results of the two years of treatment in Study 105 for the subset of patients enrolled in Study 120, the issue is not further pursued.

The 4th interim analysis report of the ongoing PASS Study (expected in December 2020) will provide additional data on the long-term effects of Orkambi, including subgroups of adult and paediatric patients.

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