23 July 2015
EMA/534823/2015 Corr.1[1]
Committee for Medicinal Products for Human Use (CHMP)

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

Kalydeco

International non-proprietary name: ivacaftor

Procedure No. EMEA/H/C/002494/P46 021.1

Note

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

[1] Subject and site IDs redacted

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LIST OF ABREVIATIONS

AE adverse event

ALT alanine aminotransferase

AST aspartate aminotransferase

BHM Bayesian Hierarchical Model

BRM Bayesian Regression Model

BMI body mass index

CF cystic fibrosis

CFQ-R Cystic Fibrosis Questionnaire–Revised

CFTR cystic fibrosis transmembrane conductance regulator protein

CFTR cystic fibrosis transmembrane conductance regulator gene

CI confidence interval

CRF case report form

CSR clinical study report

CYP cytochrome P450

DNA deoxyribonucleic acid

EAP exploratory analysis plan

ECG Electrocardiogram

EOS end of study

ePRO electronic patient-reported outcome

EU European Union

FAS Full Analysis Set

FEF25%-75% forced midexpiratory flow rate

FEV1 forced expiratory volume in 1 second

FRC functional residual capacity

FSH follicle stimulating hormone

FVC forced vital capacity

G551D a missense mutation that results in the replacement of a glycine residue at position

551 of CFTR with an aspartic acid residue

GCP Good Clinical Practice

GGT gamma-glutamyl transpeptidase

GPS Global Patient Safety (Vertex)

HNV Hankinson Normal Values

ICF informed consent form

ICH International Conference on Harmonization

IEC independent ethics committee

IRB institutional review board

IUD intrauterine device

LCI lung clearance index

MBW multiple breath washout

MedDRA Medical Dictionary for Regulatory Activities

mRNA messenger RNA

n number of observations

n-of-1 multiple within-subject crossover

1. Introduction

On 1 December 2014, the MAH submitted one completed paediatric study (VX10-770-107) for Kalydeco (Ivacaftor), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Kalydeco and that no consequential regulatory action is required.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study VX10-770-107 is a stand-alone study. No line listing is provided, since the study is not specifically part of a development program.

2.2. Information on the pharmaceutical formulation used in the studies

The pharmaceutical formulation used in this study was ivacaftor 150-mg film coated tablets, essentially the same as the currently approved formulation. Ivacaftor 150-mg tablets were used for the adolescent subjects recruited in the study; hence no specific paediatric formulation was required for this study.

Ivacaftor 150-mg tablets were administered under similar conditions as the approved SmPC for Kalydeco:

- Orally at a dosage of 150 mg q12h
- Recommended to take study drug 30 minutes after the start of a standard "CF" high fat, high calorie meal or snack.

2.3. Clinical aspects

2.3.1. Introduction

Kalydeco (ivacaftor) was first authorised 23 July 2012 via the centralised procedure in the European Union. Kalydeco is currently indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.

The MAH submitted final reports for:

- Study VX10-770-107, A Phase 2, Single-Blind, Placebo-Controlled Study to Evaluate the Effect of VX-770 (ivacaftor) on Hyperpolarized Helium-3 Magnetic Resonance Imaging in Subjects with Cystic Fibrosis, the G551D Mutation, and FEV1 ≥40% Predicted.

2.3.2. Clinical studies

Study VX10-770-107

Description

The purpose of this exploratory study was to evaluate the effects of ivacaftor on hyperpolarized helium-3 magnetic resonance imaging (3He-MRI), with the view to determine if the latter could be a potential biomarker of lung function in CF trials.

Methods

- ***Objective(s)***

Primary Objective

The primary objectives of the study were to assess the short-term (28 days, part A) and long-term (48 weeks, part B) effects of ivacaftor on hyperpolarized helium-3 magnetic resonance imaging (He-MRI), with the aim to explore the possibility of using this imaging technique as a potential biomarker of lung function in CF studies.

Secondary Objectives

To evaluate the safety and efficacy of VX-770 in subjects aged 12 years and older with CF who have the G551D-CFTR mutation on at least 1 allele.

Exploratory Objective

To evaluate 3He-MRI "Ventilation Segmentation" automated quantification method.

- ***Study design***

Part A: a Phase 2, single-blind, placebo-controlled study of orally administered VX-770 in subjects with CF. The study included a Screening Visit, 4 weeks of VX-770 treatment, 4 weeks of placebo treatment, and a follow-up telephone call.

Part B: a Phase 2, open-label, 48-week study of orally administered VX-770 in subjects with CF. The study included a Screening Visit, 48 weeks of VX-770 treatment, and a Follow-up Visit.

- ***Study population /Sample size***

Male and female subjects with CF who were ages 12 years and older with G551D-CFTR mutation on at least 1 allele and≥40% predicted forced expiratory volume in 1 second (FEV1) value.

The number of subjects planned in part A was 2 to 8 subjects; a maximum of 12 subjects were planned to be enrolled in part B. The chosen sample sizes were based primarily on operational considerations. Thus, no power analysis was performed.

- ***Treatments***

VX-770 -matched placebo tablet was administered orally q12h (recommended to take study drug 30 minutes after the start of a standard "CF" high fat, high calorie meal or snack).

Blue, film-coated tablet with wax.

Subjects were not allowed to take Grapefruit/grapefruit juice, Seville orange/marmalade, CYP3A4 inhibitors and inducers, Inhaled hypertonic saline treatment or commercially Kalydeco™. Subjects were allowed to continue their prior inhaled antibiotics and bronchodilators during the study periods.

- ***Outcomes/endpoints***

In Part A, the primary efficacy variable was change from Day 15 Visit to Day 43 Visit in total ventilation defect. Average change from Day 15 Visit to Day 29 and Day 43 Visits were also summarized.

In Part B, the primary efficacy variable, average change from baseline through Week 48 in total ventilation defect was summarized by human reader and by ventilation segmentation algorithm. Change from baseline to each scheduled visit was also summarized.
In both parts of the study, safety was assessed in terms of the following secondary (safety) endpoints: Incidence of treatment-emergent adverse events (TEAEs); Clinical laboratory values (including coagulation studies); Electrocardiogram (ECG) outcomes, and Vital signs.
Total defect volume (L), total lung volume (L), and total number of defects were obtained from the 3He-MRI record of each subject as exploratory endpoints in both parts of the study. Total ventilation defect was defined as the ratio of total defect volume to total lung volume, expressed as a percentage. Analysis for total ventilation defect was determined by "Ventilation Segmentation" algorithm was performed per the schedule of assessments. Each individual parameter was also summarized.

A Pharmacokinetic (PK) Evaluation was conducted in Part A only. Blood pharmacokinetic samples were to be collected to determine the plasma concentrations of VX-770 and metabolites M1 and M6 at the Day 29, Day 43, and Early Termination Visits.

- **Statistical Methods**

For efficacy and safety assessments, the Full Analysis Set (FAS) was used, which included all enrolled subjects who received at least 1 dose of study drug (i.e., VX-770 or placebo).

Efficacy Analyses:
Wilcoxon signed rank test was performed to assess within subject change. Raw values and changes from baseline were also summarized. Total ventilation defect was further summarized by FEV1 severity. Additional summary included: total ventilation defect by human reader, and each individual parameter (total defect volume, total lung volume, and total number of defects), evaluated by reader-averaged value and by individual reader.

Predicted FEV1 (KNUFEV [L]) was calculated using the Knudson method and percent predicted FEV1 was the ratio of FEV1 to KNUFEV, expressed as a percentage. Responder rate defined by $\geq$5 percentage point change from baseline at each visit (including the Safety Follow-up Visit) in percent predicted FEV1 were summarized.

Change from baseline in sweat chloride was calculated as Left Right Base mean (SW_{right} , SW_{left})-SW_{base} , where SW_{Left} and SW_{Right} were the measurements obtained on the left and right arms, respectively, at a particular visit and SWbase was the mean of right and left baseline measurements. If 1 of the 2 measurements at a time point was missing, the other was used as the mean. In Part A, change from Day 15 Visit to Day 43 Visit, average change from Day 15 Visit to Day 29 and Day 43 Visits in sweat chloride were summarized. Raw values and changes from baseline in each treatment phase were also summarized. In Part B, average change from baseline through Week 48, change from baseline to each scheduled visit (including the Safety Follow-up Visit) in sweat chloride were summarized.

Safety analysis: Continuous variables (e.g., blood pressure) were summarized by means of descriptive statistics and categorical variables (e.g., presence of an adverse event [AE]) were summarized by contingency tables. Only descriptive analysis of safety were performed (i.e., no statistical testing was performed).

Pharmacokinetics Analyses (Part A only): PK of VX-770 and metabolites, M1 and M6, were characterized as trough concentration. Bioanalysis was not conducted on samples when subjects were administered placebo.

Summary statistics were calculated for the number of observations (N), arithmetic mean, standard deviation (SD) and coefficient of variation (CV) in Part A on Day 29 and 43.

Compliance was informally assessed by identifying subjects with abhorrent plasma concentration values with drug accountability records.

Results

Recruitment/ Number analysed

In Part A, 8 subjects were enrolled; the FAS and the Safety Set were identical. All subjects completed dosing and there were no discontinuations from the study.

A total of 9 subjects enrolled in Part B. Four of the subjects from part A were allowed to enrol in part B of this study. Eight subjects completed dosing, and 7 subjects completed the safety follow-up visit. The reason for not completing the study in the 2 subjects who discontinued was withdrawal of consent after the last dose (and they did not complete their safety follow-up visits).

Baseline data

Most of the subjects in Part A were White (n=7, 87.5%) with a mean age of 18.9 years (range: 12, 25) and mean baseline percent predicted FEV1 of 89.95%. There were an equal number of male and female subjects. Six out of 8 subjects had G551D/F508del-CFTR mutations, 1 subject had G551D/unknown mutations, and 1 subject had G551D/G542X mutations.

In Part B, all 9 (100%) subjects were White, with a mean age of 24.4 years (range: 13, 48) and mean baseline percent predicted FEV1 of 74.08%. Six out of 9 (66.7%) subjects were male. Seven out of 9 subjects had G551D/F508del-CFTR mutations, 1 subject had G551D/Unknown mutations, and 1 subject had G551D/G551D mutations.

Efficacy results

Part A

Primary endpoint

During Placebo Run-in, the mean total ventilation defect values showed small changes from baseline (mean [SD] of 2.20 [7.583] by human reader and 1.79 [6.098] by ventilation segmentation algorithm) that were not statistically significant. During VX-770 Treatment Period, the total ventilation defect decreased significantly in the first 2 weeks of treatment (Days 15 to 29 mean [SD] change from baseline of -8.50 [8.580] by human reader and -6.28 [16.378] by ventilation segmentation algorithm) and remained decreased through the second 2 weeks of treatment (Days 15 to 43 mean [SD] change from baseline of -8.20 [9.013] by human reader and -12.81 [10.047] by ventilation segmentation algorithm). After the Placebo Washout, the total ventilation defect values returned to levels similar to those at the start of the Placebo Run-in.

Table 11-1 Within-Subject Change from Baseline in Total Ventilation Defect (%) by Hyperpolarized 3He-MRI by Treatment Phase, Full Analysis Set, Part A

Analysis Method	Statistics	Placebo Run-in Days 1 to 15 N = 8	VX-770 Treatment Days 15 to 29 N = 8	VX-770 Treatment Days 15 to 43 N = 8	Placebo Washout Days 43 to 57 N = 8
Human reader	n	8	8	8	8
	Mean (SD)	2.20 (7.583)	-8.50 (8.580)	-8.20 (9.013)	6.58 (10.310)
	Median (min, max)	-0.43 (-7.1, 18.1)	-8.43 (-19.6, 5.0)	-7.66 (-24.7, 2.4)	2.88 (-2.6, 30.4)
	P value	0.9453	0.0391	0.0547	0.0547
Ventilation segmentation algorithm	n	8	8	8	8
	Mean (SD)	1.79 (6.098)	-6.28 (16.378)	-12.81 (10.047)	8.54 (7.429)
	Median (min, max)	2.88 (-7.4, 10.1)	-8.51 (-23.1, 29.4)	-11.87 (-30.9, -1.7)	7.86 (1.3, 23.5)
	P value	0.5469	0.1953	0.0078	0.0078

Sources: Table 14.2.1.1.1 and Table 14.2.5.1.1

Secondary endpoints

Table 11-3 provides the within-subject absolute change from baseline in percent predicted FEV1 by treatment phase. During Placebo Run-in, the percent predicted FEV1 values showed a decrease from baseline (mean [SD] of -3.95 [4.929]). During VX-770 Treatment Period, the percent predicted FEV1 increased significantly from baseline (mean [SD] of 9.57 [11.297]) for the first 2 weeks [Day 15 to Day 29]) and this increase sustained through Day 43 (mean [SD] of 12.78 [9.203]). After the Placebo Washout, the percent predicted FEV1 returned to similar level as Day 1.

Table 11-3 Within-Subject Absolute Change From Baseline in Percent Predicted FEV1 (%) by Treatment Phase, Full Analysis Set, Part A

Endpoint	Statistics	Placebo Run-in N = 8	VX-770 Treatment N = 8		Placebo Washout N = 8
		Days 1 to 15	Days 15 to 29	Days 15 to 43	Days 43 to 57
Percent predicted FEV_1 (%)	n	8	8	8	8
	Mean (SD)	-3.95 (4.929)	9.57 (11.297)	12.78 (9.203)	-10.96 (5.967)
	Median (min, max)	-4.37 (-11.9, 3.7)	8.90 (-9.7, 28.3)	11.26 (2.8, 30.5)	-9.59 (-24.5, -5.5)
	P value	0.0547	0.0547	0.0078	0.0078

Source: Table 14.2.2.1.1

Table 11-4 provides within-subject absolute change from baseline in the sweat chloride values by treatment phase. During Placebo Run-in, the sweat chloride values showed a decrease from baseline (mean [SD] of -2.88 [8.943]). During VX-770 Treatment Period, the sweat chloride decreased significantly from baseline (mean [SD] of -39.19 [13.541]) for the first 2 weeks (Day 15 to Day 29) and this decrease sustained through Day 43 (mean [SD] of -42.31 [13.475]). After the Placebo Washout, the sweat chloride values returned to the similar level as Day 1.

Table 11-4 Within-Subject Absolute Change From Baseline in Sweat Chloride (mmol/L) by Treatment Phase, Full Analysis Set, Part A

Endpoint	Statistics	Placebo Run-in N = 8	VX-770 Treatment N = 8		Placebo Washout N = 8
		Days 1 to 15	Days 15 to 29	Days 15 to 43	Days 43 to 57
Sweat chloride (mmol/L)	n	8	8	8	8
	Mean (SD)	-2.88 (8.943)	-39.19 (13.541)	-42.31 (13.475)	45.56 (13.510)
	Median (min, max)	-1.50 (-17.5, 8.5)	-37.50 (-60.5, -14.0)	-42.75 (-57.0, -14.0)	44.50 (26.5, 70.0)
	P value	0.5469	0.0078	0.0078	0.0078

Source: Table 14.2.3.1

Table 11-5 provides the within-subject absolute change from baseline in pooled CFQ-R respiratory domain score by treatment phase. During Placebo Run-in, the CFQ-R values showed a small increase from baseline (mean [SD] of 2.78 [6.640]). During VX-770 Treatment Period, the score decreased from baseline (mean [SD] of -2.08 [25.361] during Day 15 to Day 29 and -7.64 [27.529] during Day 15 to Day 43). The mean CFQ-R respiratory domain score continued to decrease during the Placebo Washout. This observation was not consistent with other studies with VX-770, and the mean CFQ-R respiratory domain score during the VX-770 treatment period may have been influenced by a small number of outlying values.

Table 11-5 Within-Subject Absolute Change From Baseline in Pooled CFQ-R Respiratory Domain Score by Treatment Phase, Full Analysis Set, Part A

Endpoint	Statistics	Placebo Run-in N = 8	VX-770 Treatment N = 8		Placebo Washout N = 8
		Days 1 to 15	Days 15 to 29	Days 15 to 43	Days 43 to 57
CFQ-R Score (Pooled Adolescents/Adults and Children Versions)	n	8	8	8	8
	Mean (SD)	2.78 (6.640)	-2.08 (25.361)	-7.64 (27.529)	-2.08 (25.707)
	Median (min, max)	0.00 (-5.6, 16.7)	5.56 (-55.6, 16.7)	0.00 (-61.1, 16.7)	-2.78 (-27.8, 55.6)
	P value	0.3750	0.9375	0.8125	0.6250

Source: Table 14.2.4.1

Part B

Primary endpoint

Table 11-2 provides the within-subject change from baseline in total ventilation defect by study visit. With the exception of the human reader result at Day 15, the decrease in total ventilation defect by human reader and by ventilation segmentation algorithm was greater during VX-770 treatment (Day 1 through Week 48) than after the treatment (Week 52). The effect across time appeared to be reasonably stable. After the end of VX-770 Treatment Period, the total ventilation defect values returned to levels similar to those at baseline.

The changes from baseline in total ventilation defect were consistent with those observed in Part A and generally not statistically significant; however, the analysis was limited by the sample size of the study.

Table 11-2 Within-Subject Change From Baseline in Total Ventilation Defect (%) by 3He-MRI by Study Visit, Full Analysis Set, Part B

		VX-770 Treatment					
Analysis Method	Statistics	Day 15 N = 9	Week 12 N = 9	Week 24 N = 9	Week 36 N = 9	Week 48 N = 9	Week 52 (Safety Follow-up) N = 9
Human reader	n	9	8	8	8	8	7
	Mean (SD)	-1.42 (6.755)	-7.73 (5.524)	-9.61 (12.021)	-7.24 (11.179)	-6.33 (11.859)	-2.14 (9.217)
	Median (min, max)	-2.32 (-9.7, 12.8)	-8.35 (-13.9, 0.8)	-8.50 (-31.2, 8.9)	-9.66 (-20.9, 10.5)	-8.15 (-26.2, 9.0)	-1.40 (-13.4, 10.4)
	P value	0.3594	0.0156	0.0781	0.1484	0.1953	0.5781
Ventilation segmentation algorithm	n	9	8	8	8	8	7
	Mean (SD)	-5.46 (5.707)	-6.64 (7.083)	-8.98 (11.915)	-5.83 (8.740)	-8.95 (12.158)	-0.63 (6.068)
	Median (min, max)	-4.41 (-19.2, 0.1)	-6.98 (-15.8, 1.4)	-7.54 (-35.4, 5.3)	-5.87 (-20.8, 5.6)	-6.75 (-31.9, 5.5)	0.91 (-10.6, 6.8)
	P value	0.0078	0.0781	0.0234	0.1484	0.0547	0.9375

Sources: Table 14.2.1.1.1.b and Table 14.2.5.1.1.b

Secondary endpoints

Table 11-6 provides the within-subject absolute change from baseline in percent predicted FEV1 by study visit. During VX-770 Treatment Period, the mean percent predicted FEV1 increased significantly from baseline (Day 1 through Week 48) than after the treatment ended (Week 52). At Safety Follow-up Visit (Week 52) the percent predicted FEV1 values returned to levels similar to baseline, reflecting a loss of the effect of VX-770.

Table 11-6 Within-Subject Absolute Change From Baseline in Percent Predicted FEV1 (%) by Study Visit, Full Analysis Set, Part B

		VX-770 Treatment					
Endpoint	Statistics	Day 15 N = 9	Week 12 N = 9	Week 24 N = 9	Week 36 N = 9	Week 48 N = 9	Week 52 (Safety Follow-up) N = 9
Percent predicted FEV_1 (%)	n	9	8	8	8	8	7
	Mean (SD)	7.06 (6.916)	7.41 (10.997)	6.50 (8.846)	7.37 (7.690)	5.17 (9.422)	-2.07 (3.691)
	Median (min, max)	4.94 (1.5, 21.0)	7.31 (-5.9, 26.6)	6.44 (-9.7, 19.4)	9.09 (-5.9, 15.5)	6.22 (-7.1, 18.1)	-0.59 (-8.0, 1.8)
	P value	0.0039	0.1094	0.1094	0.0547	0.1953	0.2969

Source: Table 14.2.2.1.1.b

Table 11-7 provides within-subject absolute change from baseline in the sweat chloride values by study visit. During VX-770 Treatment Period, the mean sweat chloride decreased significantly from baseline (Day 1 through Week 48). At Safety Follow-up Visit (Week 52) the sweat chloride values returned to levels similar to baseline reflecting the loss of effect of VX-770.

Table 11-7 Within-Subject Absolute Change From Baseline in Sweat Chloride (mmol/L) by Study Visit, Full Analysis Set, Part B

		VX-770 Treatment					
Endpoint	Statistics	Day 15 N = 9	Week 12 N = 9	Week 24 N = 9	Week 36 N = 9	Week 48 N = 9	Week 52 (Safety Follow-up) N = 9
Sweat chloride (mmol/L)	n	9	8	8	8	8	7
	Mean (SD)	-52.61 (11.640)	-47.13 (21.461)	-53.94 (12.428)	-49.88 (15.359)	-48.88 (22.271)	3.93 (7.613)
	Median (min, max)	-53.00 (-72.0, -38.5)	-50.50 (-70.5, -6.0)	-51.25 (-75.5, -34.5)	-44.25 (-78.5, -31.5)	-49.75 (-74.5, -7.0)	2.00 (-5.5, 15.0)
	P value	0.0039	0.0078	0.0078	0.0078	0.0078	0.3750

Source: Table 14.2.3.1.b

Table 11-8 provides within-subject absolute change from baseline in the pooled CFQ-R respiratory domain score by study visit. During VX-770 Treatment Period, the mean score increased significantly from baseline (Day 1 through Week 48). At Safety Follow-up Visit (Week 52) the mean score returned to the levels similar to baseline, reflecting the loss of effect of VX-770.

Table 11-8 Within-Subject Absolute Change from Baseline in Pooled CFQ-R Respiratory Domain Score by Study Visit, Full Analysis Set, Part B

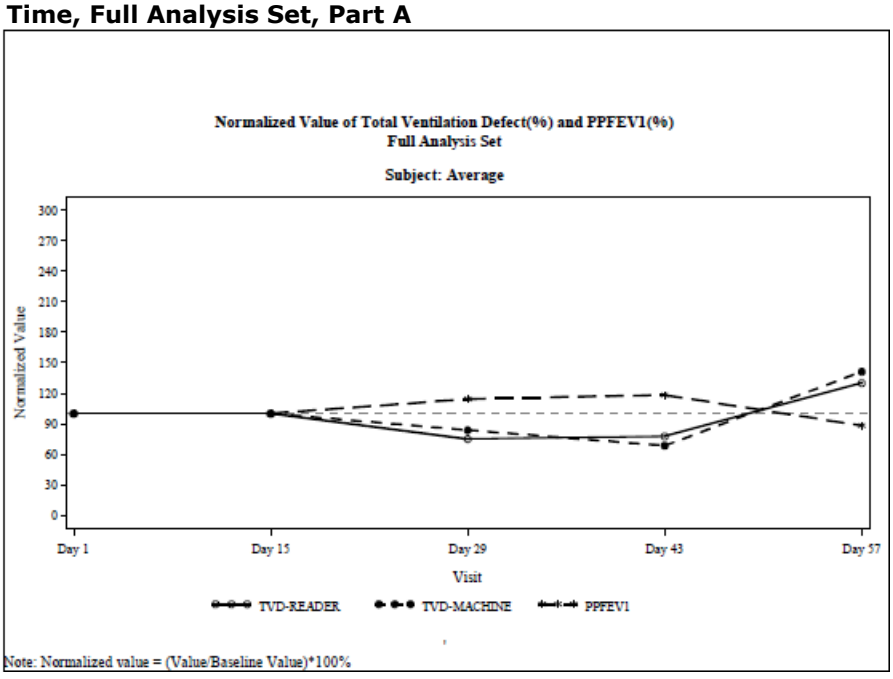
		VX-770 Treatment					
Endpoint	Statistics	Day 15 N = 9	Week 12 N = 9	Week 24 N = 9	Week 36 N = 9	Week 48 N = 9	Week 52 (Safety Follow-up) N = 9
CFQ-R Score (Pooled Adolescents/ Adults and Children Versions)	n	9	8	8	8	7	7
	Mean (SD)	12.96 (10.758)	11.81 (16.650)	14.58 (14.829)	14.58 (16.782)	15.08 (7.667)	0.00 (10.143)
	Median (min, max)	11.11 (0.0, 33.3)	13.89 (-11.1, 38.9)	13.89 (-5.6, 38.9)	5.56 (0.0, 44.4)	16.67 (5.6, 22.2)	0.00 (-16.7, 11.1)
	P value	0.0156	0.0938	0.0469	0.0313	0.0156	1.0000

Source: Table 14.2.4.1.b

Correlation Analysis

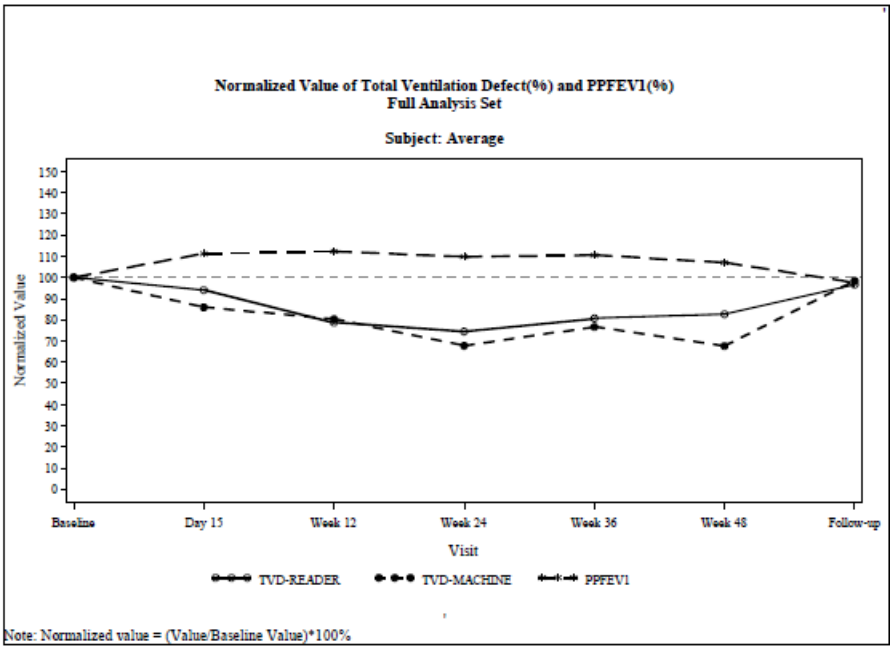
Mean changes in total ventilation defect and mean changes in percent predicted FEV1 values for all 8 subjects in Part A (Day 15 Visit to Day 57 Visit) are shown in Figure 11-11 and for all 9 subjects in Part B (Day 1 to Week 52) are shown in Figure 11-12, respectively. In Part A and Part B, the total ventilation defect during VX-770 treatment decreased significantly (both as quantified by the human reader and by a computer algorithm) and percent predicted FEV1 increased significantly. After the end of VX-770 treatment, total ventilation defect values and percent predicted FEV1 values returned to levels similar to those at baseline.

Figure 11-11 Average of Mean Total Ventilation Defect and Percent Predicted FEV1 Values over Time, Full Analysis Set, Part A



Source: vx10-770-107-a-14-2-adhoc-figure20130820

Figure 11-12 Average of Mean Ventilation Defect and Percent Predicted FEV1 Values Over Time, Full Analysis Set, Part B



Source: vx10-770-107-b-14-2-adhoc-figure20130805

In Part A, with the exception of 1 subject (Subject), all subjects had a reduction in ventilation defect volume relative to Day 15 following treatment with VX-770. While ventilation defects were not completely eliminated, use of this absolute metric identified 1 subject who had an especially marked reduction such that only approximately 30% of total ventilation defect remained following treatment.

Spearman correlation was calculated between the primary efficacy variable and each of the secondary efficacy variables for Part A and Part B.

In Part A, the change from baseline in total ventilation defect (%) by human reader versus absolute change from baseline in percent predicted FEV1 (%) showed a moderate, negative correlation during Day 15 to Day 43 (-0.5238). In Part B, the total ventilation defect (%) by human reader versus percent predicted FEV1 (%) showed a moderate, negative correlation (-0.6172) for the duration of 48 weeks.

Similarly, the change from baseline in total ventilation defect (%) by human reader showed a moderate, negative correlation with the change from baseline in percent predicted FEV1 (%) for the duration of 48 weeks (-0.6679).

In Part A, the change from baseline in total ventilation defect (%) by human reader versus change from baseline in sweat chloride (mmol/L) values showed a weak, positive correlation during Day 15 to Day 43 (0.0240). In Part B, the change from baseline in total ventilation defect (%) by human reader versus change from baseline in sweat chloride (mmol/L) also showed a weak, positive correlation for the duration of 48 weeks (0.2293).

In Part A, the change from baseline in total ventilation defect (%) by human reader versus change from baseline in pooled CFQ-R respiratory domain score showed a weak, positive correlation during Day 15 to Day 43 (0.0976,). In Part B, the change from baseline in total ventilation defect (%) by human reader versus change from baseline in pooled CFQ-R respiratory domain score showed a weak, negative correlation for the duration of 48 weeks (-0.2048).

Safety results

Overall Summary of Adverse Events

Part A

Four (50.0%) subjects had 6 AEs: 3 events during the Placebo Run-in Period and 3 during the VX-770 Treatment Period. There were no SAEs, no deaths, and no discontinuation of study drug dosing due to an AE. None of the AEs reported were considered study drug-related.

Table 12-4 shows the incidence of all AEs by system organ class (SOC) and preferred term (PT) in Part A. the SOC with the highest incidence was the respiratory, thoracic, and mediastinal disorders SPC (2 [25.0%] subjects) in the Placebo Run-in Period; however all AEs by PT had an incidence of 1 (12.5%) subject.

Table 12-4 Adverse Events by System Organ Class and Preferred Term, Safety Set, Part A

System Organ Class Preferred Term	Placebo Run-in N = 8 n (%)	Placebo Wash-out N = 8 n (%)	Placebo Total N = 8 n (%)	VX-770 N = 8 n (%)	Total N = 8 n (%)
Number of AEs (Total), n	**3**	**0**	**3**	**3**	**6**
Subjects with any AEs	**2 (25.0)**	**0**	**2 (25.0)**	**3 (37.5)**	**4 (50.0)**
Respiratory, Thoracic, And Mediastinal Disorders	**2 (25.0)**	**0**	**2 (25.0)**	**0**	**2 (25.0)**
Dry Throat	1 (12.5)	0	1 (12.5)	0	1 (12.5)
Oropharyngeal Pain	1 (12.5)	0	1 (12.5)	0	1 (12.5)
Congenital, Familial, and Genetic Disorders	**0**	**0**	**0**	**1 (12.5)**	**1 (12.5)**
Cystic Fibrosis Lung	0	0	0	1 (12.5)	1 (12.5)
Gastrointestinal Disorders	**0**	**0**	**0**	**1 (12.5)**	**1 (12.5)**
Abdominal Distension	0	0	0	1 (12.5)	1 (12.5)
General Disorders and Administrative Site Condition	**1 (12.5)**	**0**	**1 (12.5)**	**0**	**1 (12.5)**
Pain	1 (12.5)	0	1 (12.5)	0	1 (12.5)
Nervous System Disorders	**0**	**0**	**0**	**1 (12.5)**	**1 (12.5)**
Headache	0	0	0	1 (12.5)	1 (12.5)

Sources: Table 14.3.1.2 and Listing 16.2.7.1

Part B

Six (66.7%) subjects had 32 AEs; 4 (44.4 %) subjects had AEs that were considered related or possibly related to the study drug. There was 1 (11.1%) subject with an SAE. There were no deaths and no discontinuation of study drug dosing due to an AE.

Table 12-5 shows the incidence of all AEs by SOC and PT in Part B. The SOCs with the highest incidences were infections and infestations (5 [55.6%] subjects) and investigations (4 [44.4%] subjects). The AEs by PT with the highest incidence were upper respiratory tract infection (44.4%), infective pulmonary exacerbation of CF (33.3%), BMI increased (22.2%), abnormal spirometry (22.2%), and pyrexia (22.2%). All other AEs had an incidence of 11.1% (1 subject).

Table 12-5 Adverse Events Occurring by System Organ Class and Preferred Term, Safety Set, Part B

System Organ Class Preferred Term	All Subjects N = 9 n (%)
Numbers of AEs (Total), n	**32**
Subjects with any AES	**6 (66.7)**
Infections and Infestations	**5 (55.6)**
Upper Respiratory Tract Infection	4 (44.4)
Infective Pulmonary Exacerbation of CF	3 (33.3)
Bronchitis	1 (11.1)
Cellulitis	1 (11.1)
Labyrinthitis	1 (11.1)
Nasopharyngitis	1 (11.1)
Pharyngitis Streptococcal	1 (11.1)
Vulvovaginal Mycotic Infection	1 (11.1)
Investigations	**4 (44.4)**
Body Mass Index Increased	2 (22.2)
Spirometry Abnormal	2 (22.2)
Bacterial Test Positive	1 (11.1)
Gastrointestinal Disorders	**2 (22.2)**
Abdominal Pain	1 (11.1)
Nausea	1 (11.1)
General Disorders and Administration Site Conditions	**2 (22.2)**
Pyrexia	2 (22.2)
Pain	1 (11.1)
Ear and Labyrinth Disorders	**1 (11.1)**
Cerumen Impaction	1 (11.1)
Injury, Poisoning, and Procedural Complications	**1 (11.1)**
Stress Fracture	1 (11.1)
Musculoskeletal And Connective Tissue Disorders	**1 (11.1)**
Tendonitis	1 (11.1)
Nervous System Disorders	**1 (11.1)**
Headache	1 (11.1)
Respiratory, Thoracic, And Mediastinal Disorders	**1 (11.1)**
Cough	1 (11.1)
Skin And Subcutaneous Tissue Disorders	**1 (11.1)**
Rash	1 (11.1)

Sources: Table 14.3.1.2.b and Listing 16.2.7.1.b

AEs by severity

There were no life-threatening AEs on either part of this study.

In part A, there was 1 AE of moderate severity (abdominal distension) and 5 AEs of mild severity that occurred in a total of 4 subjects. The 1 AE of moderate severity occurred during the VX-770 Treatment Period, it started 3 days after the first dose of VX-770, lasted for 10 days, and resolved after treatment with polycarbophil calcium.

In part B, There were 18 AEs of moderate severity in a total of 5 subjects (infective pulmonary exacerbation of CF [2 out of 9 subjects]; pyrexia [2 out of 9 subjects]; all other AEs [1 out of 9 subjects]). There was 1 AE that was severe in severity: a 48-year-old White male, had a severe infective pulmonary exacerbation of CF that started 249 days after the first dose of VX-770, lasted for 49 days, and resolved after intravenous administration of ceftazidime.

AEs Leading to Discontinuation

There were no AEs leading to study drug discontinuation on either part of the study.

Adverse Events by Relationship to Study Drug
In this study, there were 7 AEs in 4 subjects that were considered possibly related to the study drug (all of them occurred in Part B):

- Acute bronchitis of moderate severity that required treatment and was ongoing at the end of the study.
- Acute labyrinthitis of moderate severity that started 275 days after the first dose of VX-770, lasted for 5 days, and resolved without treatment.
- Increase in BMI (greater than 10%) of mild severity that was first measured 170 days after the first dose of VX-770, lasted for 192 days, and resolved without treatment.
- Increase in BMI (greater than 10%) of mild severity that was first measured 256 days after the first dose of VX-770, and was ongoing at the end of the study.
- Abnormal decrease in spirometry of mild severity that started 89 days after the first dose of VX-770, lasted for 85 days, and resolved without treatment.
- Upper respiratory tract infection of mild severity that started 344 days after the first dose of VX-770, lasted for 3 days, and resolved without any treatment.
- Abnormal decrease in spirometry of mild severity that started 83 days after the first dose of VX-770, lasted for 178 days, and resolved without any treatment.

2.3.3. Discussion on clinical aspects

In the clinical setting, FEV1 is currently the main marker of lung function, since the initial ventilation defect in CF is usually obstructive. This clinical parameter is also recognized in the regulatory setting as the recommended primary endpoint in CF trials. However, FEV1, which reflects total airways resistance, has some limitations in terms of a lower sensitivity to changes in small calibre airways, which contribute to less than 10% of the overall resistance (in healthy lungs). Additional difficulties can be identified to perform the lung function assessment of young children (especially those 5 years of age and younger), which require to be carried in specialised centres to promote standardised methods. In this context, it is agreed that new and adequately validated methods to measure lung function would be valuable.

Hyperpolarized noble gas magnetic resonance imaging (HG-MRI) is a method for assessing lung function by direct imaging of certain non-radioactive isotopes of an inert noble gas, usually helium or xenon. This imaging technique provides high-resolution, 3-dimensional images of lung ventilation that can be obtained in both pediatric and adult patients during a single short breath-hold following inhalation of the gas. In CF patients, HG-MRI images show a "ventilation defect" areas of the lung into which inhaled gas does not flow due to obstruction of the airway. This ventilation defect does not usually show in healthy subjects and it is thought to correlate with disease severity. It can be quantified using both manual and automated techniques. In addition, HG-MRI allows magnetic-resonance-specific measures (such as apparent diffusion coefficient) to be calculated from the data.

HG-MRI is a novel, yet experimental, method to assess lung function must be properly validated before being considered as a basis for the demonstration of efficacy in CF paediatric and adult patients.

Efficacy

Study VX10-770-107 was a phase 2, single-blind, placebo-controlled study which evaluated the short-term/long-term effect of ivacaftor on hyperpolarized helium-3 magnetic resonance imaging in subjects with cystic fibrosis (CF).

Design & conduct of the study

The study was conducted in a single centre in the USA and took place from October 2010 to February 2013.

Subjects aged ≥12 years with the G551D-cystic fibrosis transmembrane conductance regulator gene (CFTR) mutation (on at least 1 allele) were allowed to enrol. No formal sample size calculations were performed and the sample size was selected based on operational considerations. This approach can be accepted, considering the low prevalence of the disease and the selected CFTR mutation. However, the inherent limitations associated with small sample sizes need to be acknowledged.

The primary objectives of the study were to assess the short-term (28 days, part A) and long-term (48 weeks, part B) effects of ivacaftor on He-MRI, in order to explore the possibility of using this imaging technique as a potential biomarker of lung function in CF studies.

Efficacy data & additional analyses

A total of 17 patients were included (8 in phase A, and 9 in phase B), of which only 4 were pediatric patients (age range 12-16). In term of overall results, correlation between the changes in ventilation defect and clinical endpoints was considered modest.

Only global results, including all subjects (pediatric and adult) have been provided and no separate results are available for the pediatric subjects in this study. It is acknowledged that the number of pediatric patients included in the study was very small (n=4) and the applicability of the study results would probably be very limited as well. However, the lack of pediatric-specific data hampers from reaching any sort of conclusion. Therefore, the MAH is asked to provide pediatric data separately from the global study results. Efficacy as well as safety results should be provided.

Safety

In general, ivacaftor seemed to be well tolerated during study VX10-770-107. There were no life-threatening AEs or AEs leading to study drug discontinuation on either part of this study.

In part A, the SOC with the highest incidence of AEs was the respiratory, thoracic, and mediastinal disorders SOC (2 [25.0%] subjects). A total of 4 (50.0%) subjects had 6 AEs, none of them considered study drug-related.

In part B, the SOCs with the highest incidences were infections and infestations (5 [55.6%] subjects) and investigations (4 [44.4%] subjects). A total of 6 (66.7%) subjects had 32 AEs; 4 (44.4 %) subjects had AEs that were considered related or possibly related to the study drug (1 acute bronchitis AE, 1 acute labyrinthitis AE, 2 increased BMI AEs, 2 abnormal decrease in spirometry AEs, and one upper respiratory infection AE). There was 1 (11.1%) subject with an SAE.

The overall safety profile observed in study VX10-770-107was consistent with that observed in previous studies for CF subjects with G551D mutation on 1 allele. However, pediatric data has not been provided separately from the global study results. Therefore, no conclusion on pediatric safety can be reached and additional information is needed from the MAH.

3. CHMP's overall conclusion and recommendation

Overall conclusion

From the provided data, no conclusions can be reached on the effect of ivacaftor on hyperpolarized helium-3 magnetic resonance imaging in pediatric subjects with cystic fibrosis (CF). Considering that the aim of this procedure is to specifically assess pediatric data, the provided results (global results only) do not allow performing an adequate assessment. The MAH is asked to provide pediatric data separately from the global study results. Efficacy as well as safety results should be provided (see further details in the next section).

Recommendation

☐ **Fulfilled:**

☒ **Not fulfilled:**

Additional clarifications requested

Based on the data submitted, the MAH should provide the following information as part of this procedure.

1) **Efficacy**:
a. Separate efficacy results should be provided for the 4 paediatric subjects included in the study. Primary, secondary and exploratory endpoints data should be presented, using adequate descriptive statistics.

b. Potential differences between paediatric and adult results should also be discussed.

2) **Safety:**
a. An appropriate description of safety in the paediatric patients should be provided. An overall description as well as separate information for each part of the study should be provided.

b. Patients´ demographic and disease characteristics should also be provided separately for the paediatric patients.

c. Special attention should be paid to the one SAE and the drug-related AEs reported in the study. The MAH should clarify if these AEs occurred in paediatric patients, and should provide a brief description of the AEs, including demographic and disease characteristics of these patients.

4. Assessment of the responses to the Request for Supplementary Information.

<u>Question 1</u>

1a. Separate efficacy results should be provided for the 4 paediatric subjects included in study 107. Primary, secondary and exploratory endpoints data should be presented, using adequate descriptive statistics.
1b. Potential differences between paediatric and adult results should also be discussed.

MAH's response

1.a.
Study Part A

Primary Endpoint

The mean (standard deviation) (SD) change in total ventilation defect from Day 15 to Day 43 (for paediatric subjects) was -6.47% (6.478%) when analyzed by human reader. A similar change for these subjects -9.72% (4.804%) was observed when analyzed using the ventilation segmentation algorithm (Table 1). The mean change in total ventilation defect for paediatric subjects was slightly less than that determined for adult subjects (-9.23% [10.844%] by human reader and -14.67% [12.396] by ventilation segmentation algorithm. Over the 4 weeks of VX-770 treatment, the total ventilation defect as well as total defect volume, total lung volume, and total number of subjects showed a decrease in both paediatric and adult subjects (exception being the mean change from Day 15 to Day 29) in total ventilation defect and total defect volume for the paediatric subjects analyzed by ventilation segmentation algorithm. Following wash-out, the total ventilation defect values returned to pre-treatment levels in both paediatric and adult subjects. The changes from baseline for all parameters measured were not statistically significant, most likely because the analysis was limited by the sample sizes.

Table 1 Study 107 Within-subject Change from Baseline in Total Ventilation Defect (%) by Hyperpolarized 3He-MRI by Treatment Phase, Pediatric Subjects, Part A

		Placebo Run-in	VX-770 Treatment		Placebo Washout
Analysis Method	Statistics	Days 1 to 15	Days 15 to 29	Days 15 to 43	Days 43 to 57
Human reader	n	3	3	3	3
	Mean (SD)	7.16 (9.720)	-8.62 (11.870)	-6.47 (6.478)	2.67 (0.506)
	Median	3.68	-14.24	-7.67	2.52
	(min, max)	(-0.3, 18.1)	(-16.6, 5.0)	(-12.3, 0.5)	(2.3, 3.2)
	P value	0.5000	0.5000	0.5000	0.2500
Ventilation segmentation algorithm	n	3	3	3	3
	Mean (SD)	3.69 (6.303)	4.11 (23.258)	-9.72 (4.804)	6.25 (2.848)
	Median	3.49	-0.68	-8.84	7.33
	(min, max)	(-2.5, 10.1)	(-16.4, 29.4)	(-14.9, -5.4)	(3.0, 8.4)
	P value	0.5000	1.0000	0.2500	0.2500

Source: Table 14.2.1.1.1.ad and Table 14.2.5.1.1.ad.

^{3}He-MRI: helium-3 magnetic resonance imaging; n: size of subsample; SD: standard deviation.

Notes: Baseline is the most recent non-missing measurement collected prior to initial administration of study drug in each treatment phase (Day 1 to Day 15 on Placebo Run-in, Day 15 to Day 43 on VX-770, and Day 43 to Day 57 on Placebo Washout. *P* value was calculated using Wilcoxon signed rank test. Pediatric subjects were <18 years of age when enrolled in the study.

Secondary Endpoints

Total ventilation defect was further summarized by the forced expiratory volume in 1 second (FEV1) severity. Percent predicted FEV1 in paediatric subjects increased over the 4-week treatment period and returned to pre-treatment levels following placebo washout. Similar results were observed in the adult subjects.

Table 2 Study 107 Within-subject Absolute Change From Baseline in Percent Predicted FEV1 (%) by Treatment Phase, Paediatric Subjects, Part A

		Placebo Run-in	VX-770 Treatment		Placebo Washout
Endpoint	Statistics	Days 1 to 15	Days 15 to 29	Days 15 to 43	Days 43 to 57
Percent predicted FEV_1 (%)	n	3	3	3	3
	Mean (SD)	-5.52 (1.995)	2.28 (10.905)	8.24 (5.707)	-8.23 (2.560)
	Median	-4.49	4.84	7.82	-8.56
	(min, max)	(-7.8, -4.2)	(-9.7, 11.7)	(2.8, 14.2)	(-10.6, -5.5)
	P value	0.2500	0.7500	0.2500	0.2500

Source: Table 14.2.2.1.1.ad.

FEV_1: forced expiratory volume in 1 second; n: size of subsample; SD: standard deviation.

Notes: Baseline is the most recent non missing measurement collected prior to initial administration of study drug in each treatment phase (Day 1 to Day 15 on Placebo Run-in, Day 15 to Day 43 on VX 770, and Day 43 to Day 57 on Placebo Washout. *P* value was calculated using Wilcoxon signed rank test. Pediatric subjects were <18 years of age when enrolled in the study.

Sweat chloride values in pediatric subjects decreased over the 4-week treatment period and returned to pretreatment levels following placebo washout (Table 3). Results were similar to those observed for adult subjects.

Table 3 Study 107 Within-subject Absolute Change From Baseline in Sweat Chloride (mmol/L) by Treatment Phase, Pediatric Subjects, Part A

		Placebo Run-in	VX-770 Treatment		Placebo Washout
Endpoint	Statistics	Days 1 to 15	Days 15 to 29	Days 15 to 43	Days 43 to 57
Sweat chloride (mmol/L)	n	3	3	3	3
	Mean (SD)	2.67 (7.286)	-47.17 (13.769)	-53.50 (6.062)	58.83 (9.674)
	Median	5.00	-48.00	-57.00	53.50
	(min, max)	(-5.5, 8.5)	(-60.5, -33.0)	(-57.0, -46.5)	(53.0, 70.0)
	P value	0.7500	0.2500	0.2500	0.2500

Source: Table 14.2.3.1.ad.

n: size of subsample; SD: standard deviation.

Notes: Baseline is the most recent non missing measurement collected prior to initial administration of study drug in each treatment phase (Day 1 to Day 15 on Placebo Run-in, Day 15 to Day 43 on VX 770, and Day 43 to Day 57 on Placebo Washout. *P* value was calculated using Wilcoxon signed rank test. Pediatric subjects were <18 years of age when enrolled in the study.

The mean and median change from baseline in the Cystic Fibrosis Questionnaire - Revised (CFQ-R) respiratory domain scores did not change during the Placebo Run-in, indicating that subjects were stable during that phase (Table 4). During VX-770 treatment, the mean CFQ-R respiratory domain scores for pediatric subjects decreased through 4 weeks of treatment, while the mean CFQ-R scores for adult subjects did not change during VX-770 treatment. Interpretation of these results is confounded because the mean CFQ-R respiratory domain score during the VX-770 Treatment Period may have been influenced by a small number of outlying values and the small sample size.

Table 4 Study 107 Within-subject Absolute Change From Baseline in CFQ-R Respiratory Domain Score by Treatment Phase, Pediatric Subjects, Part A

		Placebo Run-in	VX-770 Treatment		Placebo Washout
Endpoint	Statistics	Days 1 to 15	Days 15 to 29	Days 15 to 43	Days 43 to 57
CFQ-R respiratory domain score	n	3	3	3	3
	Mean (SD)	0.00 (0.000)	-7.41 (12.830)	-20.37 (35.283)	16.67 (33.793)
	Median	0.00	0.00	0.00	0.00
	(min, max)	(0.0, 0.0)	(-22.2, 0.0)	(-61.1, 0.0)	(-5.6, 55.6)
	P value		1.0000	1.0000	1.0000

Source: Table 14.2.4.1.ad.

CFQ-R: Cystic Fibrosis Questionnaire – Revised; n: size of subsample; SD: standard deviation.

Notes: Baseline is the most recent non missing measurement collected prior to initial administration of study drug in each treatment phase (Day 1 to Day 15 on Placebo Run-in, Day 15 to Day 43 on VX 770, and Day 43 to Day 57 on Placebo Washout. *P* value was calculated using Wilcoxon signed rank test. Pediatric subjects were <18 years of age when enrolled in the study.

Study Part B

Primary Endpoint

The changes from baseline in total ventilation defect (Table 5) were generally greater in the pediatric subgroup than the adult subgroup, though they typically followed the same pattern as those observed in the adult subgroup and were consistent with those observed in Part A; however, analysis is limited by the sample size of the subgroups.

Table 5 Study 107 Within-subject Absolute Change From Baseline in Total Ventilation Defect (%) by Hyperpolarized 3He-MRI by Study Visit, Pediatric Subjects, Part B

		VX-770 Treatment					Week 52 (Safety Follow-up)
Analysis Method	Statistics	Day 15	Week 12	Week 24	Week 36	Week 48	
Human reader	n	2	2	2	2	2	1
	Mean	-6.26	-12.41	-20.03	-14.57	-18.41	-13.39
	(SD)	(2.394)	(2.156)	(15.789)	(8.611)	(11.062)	(-)
	Median	-6.26	-12.41	-20.03	-14.57	-18.41	-13.39
	(min, max)	(-8.0, -4.6)	(-13.9, -10.9)	(-31.2, -8.9)	(-20.7, -8.5)	(-26.2, -10.6)	(-13.4, -13.4)
	P value	0.5000	0.5000	0.5000	0.5000	0.5000	1.0000

Ventilation segmentation algorithm	n	2	2	2	2	2	1
	Mean	-2.97	-5.71	-20.55	-12.96	-19.10	-10.64
	(SD)	(4.380)	(7.242)	(21.025)	(11.088)	(18.156)	(-)
	Median	-2.97	-5.71	-20.55	-12.96	-19.10	-10.64
	(min, max)	(-6.1, 0.1)	(-10.8, -0.6)	(-35.4, -5.7)	(-20.8, -5.1)	(-31.9, -6.3)	(-10.6, -10.6)
	P value	1.0000	0.5000	0.5000	0.5000	0.5000	1.0000

Source: Tables 14.2.1.1.1b.ad and Table 14.2.5.1.1.b.ad.
^{3}He-MRI: helium-3 magnetic resonance imaging; n: size of subsample; SD: standard deviation.
Notes: Baseline is the most recent non-missing measurement collected prior to initial administration of study drug. *P* value was calculated using Wilcoxon signed rank test. Pediatric subjects were <18 years of age when enrolled in the study.

Secondary Endpoints

The mean percent predicted FEV1 increased from baseline and remained fairly constant throughout the 48-week treatment period for the pediatric subgroup as well as the adult subgroup (Table 6). In both subgroups, FEV1 values returned to baseline following completion of study treatment at the Week 52 Safety Follow-up Visit.

Table 6 Study 107 Within-Subject Absolute Change From Baseline in Percent Predicted FEV1 (%) by Study Visit, Pediatric Subjects, Part B

		VX-770 Treatment					Week 52 (Safety
Endpoint	**Statistics**	**Day 15**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**Follow-up)**
Percent predicted FEV_1 (%)	n	2	2	2	2	2	1
	Mean	9.87	9.12	9.86	11.36	15.19	1.39
	(SD)	(9.912)	(3.454)	(4.046)	(2.575)	(4.148)	(-)
	Median	9.87	9.12	9.86	11.36	15.19	1.39
	(min, max)	(2.9, 16.9)	(6.7, 11.6)	(7.0, 12.7)	(9.5, 13.2)	(12.3, 18.1)	(1.4, 1.4)
	P value	0.5000	0.5000	0.5000	0.5000	0.5000	1.0000

Source: Table 14.2.2.1.1.b.ad.
FEV_1: forced expiratory volume in 1 second; n: size of subsample; SD: standard deviation.
Notes: Baseline is the most recent non-missing measurement collected prior to initial administration of study drug. *P* value was calculated using Wilcoxon signed rank test. Pediatric subjects were <18 years of age when enrolled in the study.

The mean sweat chloride values (Table 7) decreased from baseline and remained constant throughout the 48-week treatment period for the pediatric subgroup as well as the adult subgroup. In both subgroups, sweat chloride values returned to baseline following completion of study treatment at the Week 52 Follow-up Visit.

Table 7 Study 107 Within-subject Absolute Change From Baseline in Sweat Chloride (mmol/L) by Study Visit, Pediatric Subjects, Part B

		VX-770 Treatment					Week 52 (Safety
Endpoint	**Statistics**	**Day 15**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**Follow-up)**
Sweat chloride (mmol/L)	n	2	2	2	2	2	1
	Mean	-56.75	-63.75	-67.50	-66.00	-67.25	-1.50
	(SD)	(1.061)	(2.475)	(11.314)	(17.678)	(3.182)	(-)
	Median	-56.75	-63.75	-67.50	-66.00	-67.25	-1.50
	(min, max)	(-57.5, -56.0)	(-65.5, -62.0)	(-75.5, -59.5)	(-78.5, -53.5)	(-69.5, -65.0)	(-1.5, -1.5)
	P value	0.5000	0.5000	0.5000	0.5000	0.5000	1.0000

Source: Table 14.2.3.1.b.ad.
n: size of subsample; SD: standard deviation.
Notes: Baseline is the most recent non-missing measurement collected prior to initial administration of study drug. *P* value was calculated using Wilcoxon signed rank test. Pediatric subjects were <18 years of age when enrolled in the study.

Mean CFQ-R score increased and remained constant throughout the 48-week VX-770 treatment period as well as at the Week 52 Safety Follow-up Visit (Table 8); scores at the Week 48 and Week 52 Visits were reported by a single pediatric subject. The mean CFQ-R score for the adult subjects was similarly increased from baseline and remained constant over the 48-week treatment period but returned to baseline levels at the Week 52 Follow-up Visit.

Table 8 Study 107 Within-Subject Absolute Change From Baseline in Pooled CFQ-R Respiratory Domain Score by Study Visit, Pediatric Subjects, Part B

		VX-770 Treatment					Week 52 (Safety
Endpoint	Statistics	Day 15	Week 12	Week 24	Week 36	Week 48	Follow-up)
CFQ-R respiratory domain score	n	2	2	2	2	1	1
	Mean	5.56	11.11	11.11	11.11	22.22	11.11
	(SD)	(7.857)	(15.713)	(15.713)	(15.713)	(-)	(-)
	Median	5.56	11.11	11.11	11.11	22.22	11.11
	(min, max)	(0.0, 11.1)	(0.0, 22.2)	(0.0, 22.2)	(0.0, 22.2)	(22.2, 22.2)	(11.1, 11.1)
	P value	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000

Source: Table 14.2.4.1.b.ad.

CFQ R: Cystic Fibrosis Questionnaire –Revised; n: size of subsample; SD: standard deviation.

Notes: *P* value was calculated using Wilcoxon signed rank test. Pooled across CFQ-R types, i.e., all self-response questionnaire versions are used: Adult/Adolescent and Child versions. Only the version of the questionnaire used at baseline for each subject was used in the analysis. Pediatric subjects were <18 years of age when enrolled in the study.

1.b.

For the most part, given the small sample size of the subgroups, the results for the paediatric subjects in this study are consistent with the results obtained for the adult subjects as well as the overall study population in both Part A (Table 9) and Part B (Table 10), indicating that the overall treatment effect of VX-770 was similar across the age groups.

Table 9 Study 107 Within-subject Absolute Change from Day 15 to the Day 29/Day 43 Average for Efficacy Endpoints for Pediatric, Adult, and All Subjects, Part A

Population Subgroup	Statistics	Total Ventilation Defect (%) by Human Reader	Percent Predicted FEV_1 (%)	Sweat Chloride (mmol/L)	CFQ-R Score
Pediatric	n	3	3	3	3
	Mean (SD)	-7.54 (9.102)	5.26 (7.038)	-50.33 (4.646)	-13.89 (24.056)
	Median	-10.95	3.80	-52.50	0.00
	(min, max)	(-14.4, 2.8)	(-0.9, 12.9)	(-53.5, -45.0)	(-41.7, 0.0)
	P value	0.5000	0.5000	0.2500	1.0000
Adult	n	5	5	5	5
	Mean (SD)	-8.83 (9.021)	14.72 (10.149)	-35.00 (12.133)	0.56 (26.889)
	Median	-7.69	12.41	-38.00	11.11
	(min, max)	(-22.1, 2.2)	(3.7, 29.4)	(-45.3, -14.0)	(-47.2, 16.7)
	P value	0.1250	0.0625	0.0625	0.6250
All subjects	n	8	8	8	8
	Mean (SD)	-8.35 (8.404)	11.17 (9.848)	-40.75 (12.380)	-4.86 (25.187)
	Median	-9.32	10.27	-42.63	4.17
	(min, max)	(-22.1, 2.8)	(-0.9, 29.4)	(-53.5, -14.0)	(-47.2, 16.7)
	P value	0.0391	0.0156	0.0078	1.0000

Source: Table 14.2.1.1.1.ad, Table 14.2.2.1.1.ad, Table 14.2.3.1.ad, and Table 14.2.4.1.ad.

CFQ R: Cystic Fibrosis Questionnaire – Revised; FEV_1: forced expiratory volume in 1 second; n: size of subsample; SD: standard deviation.

Notes: Baseline is the most recent non missing measurement collected prior to initial administration of study drug in each treatment phase (Day 1 to Day 15 on Placebo Run-in, Day 15 to Day 43 on VX 770, and Day 43 to Day 57 on Placebo Washout. *P* value was calculated using Wilcoxon signed rank test. Pediatric subjects were <18 years of age when enrolled in the study.

Table 10 Study 107 Within-subject Absolute Change From Baseline to the Week 48 for Efficacy Endpoints for Pediatric, Adult, and All Subjects, Part B

Population Subgroup	Statistics	Total Ventilation Defect (%) by Human Reader	Percent Predicted FEV_1 (%)	Sweat Chloride (mmol/L)	CFQ-R Score
Pediatric	n	2	2	2	1
	Mean (SD)	-18.41 (11.062)	15.19 (4.148)	-67.25 (3.182)	22.22 (-)
	Median	-18.41	15.19	-67.25	22.22
	(min, max)	(-26.2, -10.6)	(12.3, 18.1)	(-69.5, -65.0)	(22.2, 22.2)
	P value	0.5000	0.5000	0.5000	1.0000
Adult	n	6	6	6	6
	Mean (SD)	-2.30 (9.726)	1.83 (8.203)	-42.75 (22.633)	13.89 (7.658)
	Median	-1.72	0.24	-45.00	13.89
	(min, max)	(-13.6, 9.0)	(-7.1, 13.1)	(-74.5, -7.0)	(5.6, 22.2)
	P value	0.6875	0.6875	0.0313	0.0313
All subjects	n	8	8	8	7
	Mean (SD)	-6.33 (11.859)	7.04 (13.601)	-48.88 (22.271)	15.08 (7.667)
	Median	-8.15	9.55	-49.75	16.67
	(min, max)	(-26.2, 9.0)	(-10.3, 24.0)	(-74.5, -7.0)	(5.6, 22.2)
	P value	0.1953	0.1953	0.0078	0.0156

Source: Table 14.2.1.1.1.b.ad, Table 14.2.2.1.1.b.ad, Table 14.2.3.1.b.ad, and Table 14.2.4.1.b.ad.

CFQ R: Cystic Fibrosis Questionnaire – Revised; FEV_1: forced expiratory volume in 1 second; n: size of subsample; SD: standard deviation.

Notes: Baseline is the most recent non missing measurement collected prior to initial administration of study drug. *P* value was calculated using Wilcoxon signed rank test. Pooled across CFQ-R types, i.e., all self-response questionnaire versions are used: Adult/Adolescent and Child versions. Only the version of the questionnaire used at baseline for each subject was used in the analysis. Pediatric subjects were <18 years of age when enrolled in the study. Adults were 18 year of age or greater when enrolled in the study.

CHMP comments

Separate efficacy results for the 4 paediatric patients have been provided, as requested.
Changes from baseline for all the studied parameters were not statistically significant, and it can be agreed with the Applicant that this fact is likely due to the very small sample size. In addition, as previously noted for the overall results, the correlation between the changes in ventilation defect and clinical endpoints in paediatric patients seems to be very modest.
Paediatric results generally show the same trends that overall and adults results. In general, the sizes of the observed results varied from paediatric to adult patients; however, these differences are difficult to interpret due to the small number of paediatric patients. Overall, no large or worrisome differences are noted between paediatric and adult results. No additional information is being requested at this time.

In conclusion, the requested information has been provided. In that regard, the **issue can be considered solved.**

Question2

2a. An appropriate description of safety in the paediatric patients should be provided. An overall description as well as separate information for each part of the study should be provided.
2b. Patients' demographic and disease characteristics should also be provided separately for the paediatric patients.
2c. Special attention should be paid to the one SAE and the drug-related AEs reported in the study. The MAH should clarify if these AEs occurred in paediatric patients, and should provide a brief description of the AEs, including demographic and disease characteristics of these patients.

MAH's response

2.a.
A total of 4 paediatric subjects were enrolled in this study, 3 in Part A and 2 in Part B; 1 subject was enrolled in both Parts A and B (Part A as Subject; Part B as Subject). The overall safety profile was assessed in terms of the incidence of treatment-emergent adverse events (TEAE), clinical

laboratory values, electrocardiogram outcomes, and vital signs. These data were summarized using descriptive statistics and contingency tables. All individual paediatric subject data were presented in subject data listings.

Part A:

Of the 8 subjects enrolled in Part A, 3 were paediatric (<18 years of age). Only one of the 3 paediatric subjects had a TEAE (Subject; 14-year-old male), a non-serious event of mild CF lung, which was considered unlikely related to study drug. Of the remaining 2 paediatric subjects, neither had a TEAE; one (Subject ; 12-year-old male) did not have any adverse events (AEs) and the other (Subject ; 15-year-old female) had 2 pre-treatment AEs (events of pain [not related] and oropharyngeal pain [unlikely related]) during the Placebo Run-in.

Part B:

Of the 9 subjects enrolled in Part B, 2 were paediatric (Subjects and). Subject (13-year-old male) was also enrolled in Part A (as Subject) and did not have an AE in Part B of the study. Subject completed his Week 48 Visit, then withdrew consent, and did not complete the Safety Follow-up Visit.

Subject (16-year-old male) had 6 TEAEs in Part B (events of nausea, pain, pyrexia [2 events], pharyngitis streptococcal, and upper respiratory tract infection). All of the TEAEs were non serious, mild to moderate in severity, considered not related or unlikely related to study drug, and resolved. Subject completed the 48-week VX-770 treatment.

2.b.

Demographic data for the 4 paediatric subjects from Part A and Part B are provided in Table 11. Baseline disease characteristics and CF history for the 4 paediatric subjects from Part A and Part B are provided in Table 12.

Table 11 Study 107 Demographics, Pediatric Subjects

Subject Number	Study Part	Site Number/ Country	Sex	Race	Ethnicity	Age (years)	Genotype
[redacted]	A/B	[redacted]	M	White	Not Hispanic or Latino	12, 13	*G551D/F508del*
	A		F	White	Not Hispanic or Latino	15	*G551D/G542X*
	A		F	White	Not Hispanic or Latino	14	*G551D/F508del*
	B		M	White	Not Hispanic or Latino	16	*G551D/F508del*

Source: Module 5.3.5.4/Study VX10-770-107/Listing 16.2.4.1 and Listing 16.2.4.1b.

F: female; M: male.

[a] One pediatric subject was enrolled in both Part A (as Subject [redacted] and Part B (as Subject [redacted].

Table 12 Study 107 Baseline Disease Characteristics and Cystic Fibrosis History, Pediatric Subjects

Subject Number	Study Part	Weight (kg)[a]	BMI (kg/m^2)[a]	Percent predicted FEV_1 (%)[a]	Sweat Chloride mmol/L[b]	CF History
[redacted]	A/B	49.44/ 58.29	20.6/ 22.06	95.29/ 116.99	107.5/ 109	CF lung disease; pancreatic insufficiency
	A	58.06	22.67	113.97	102.5	CF lung disease; gastroesophageal reflux disease
	A	46.72	18.25	98.72	94.5	Atypical mycobacterial infection; CF lung disease; nasal polyps requiring surgery; pancreatic insufficiency; sinus disease (symptomatic)
	B	58.97	17.88	68.44	106.5	CF lung disease; nasal polyps requiring surgery; pancreatic insufficiency; sinus disease (symptomatic)

Source: Module 5.3.5.4/Study VX10-770-107/Listing 16.2.4.1, Listing 16.2.4.1b, Listing 16.2.4.4.2, Listing 16.2.4.4.2.b, Listing 16.2.6.2, Listing 16.2.6.2.b, Listing 16.2.6.3, Listing 16.2.6.3.b, Listing 16.2.8.9, and Listing 16.2.8.9.b.

BMI: body mass index; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second;

[a] Value recorded at screening for respective part of study.

[b] Value recorded at Day 1 for respective part of study.

[c] One pediatric subject was enrolled in both Part A (as Subject [redacted] and Part B (as Subject [redacted].

2.c.

One subject (Subject), a 48-year-old White male with G551D/ G551D, had an SAE of infective pulmonary exacerbation of CF in Part B of the study.

There were no AEs reported as related to study drug in Part A for any subject (pediatric or adult). In Part B, 4 subjects had 7 AEs that were considered possibly related to study drug, all were mild in severity unless noted and no events were considered related; none of these subjects were pediatric subjects.

- Subject (26-year-old white female) had 3 AEs that were assessed by the investigator as possibly related to study treatment (bronchitis, labyrinthitis, and body mass index [BMI] increased). The events of labyrinthitis and BMI increased, both moderate in severity, resolved during the study. The event of bronchitis occurred 344 days from first dose and had not resolved by the end of study.
- Subject (22-year-old white female) had 1 AE that was assessed by the investigator as possibly related to study treatment (spirometry abnormal). This event resolved while on study treatment.
- Subject (31-year-old white male) had 2 AEs that were assessed by the investigator as possibly related to study treatment (upper respiratory tract infection and spirometry abnormal). Both events resolved while on study treatment.
- Subject (48-year-old white male) had 1 AE that was assessed by the investigator as possibly related to study treatment (BMI increased). This event occurred 256 days from first dose and had not resolved by the end of study.

Demographic data for the 4 subjects from Part B who had an AE assessed by the investigator as possibly related to study treatment are provided in Table 13. Baseline disease characteristics and CF history for the 4 adult subjects from Part B who had an AE assessed by the investigator as possibly related to study treatment are provided in Table 14.

Table 13 Study 107 Demographics, Subjects Who Had an AE Possibly Related to Study Treatment

Subject Number	Study Part	Site Number/ Country	Sex	Race	Ethnicity	Age (years)	Genotype
[redacted]	B	[redacted]	F	White	Not Hispanic or Latino	26	*G551D*/unknown
	B		F	White	Not Hispanic or Latino	22	*G551D/F508del*
	B		M	White	Not Hispanic or Latino	31	*G551D/F508del*
	B		M	White	Not Hispanic or Latino	48	*G551D/G551D*

Source: Module 5.3.5.4/VX10-770-107/Listing 16.2.4.1.b.
F: female; M: male.

Table 14 Study 107 Baseline Characteristics and Cystic Fibrosis History, Subjects Who Had an Adverse Event Possibly Related to Study Treatment

Subject Number	Study Part	Weight (kg)[a]	BMI (kg/m^2)[a]	Percent predicted FEV_1 (%)[a]	Sweat Chloride (mmol/L)[b]	CF History
[redacted]	B	79.83	29.29	52.11	57.5	Allergic bronchial pulmonary aspergillosis; asthma; CF lung disease; depression; gallbladder disease requiring surgery; pancreatic insufficiency; pancreatitis; sinus disease (symptomatic)
	B	61.23	22.46	114.42	107	CF lung disease; gastroesophageal reflux disease; nasal polyps requiring surgery; pancreatic insufficiency
	B	67.59	22.0	66.35	104	CF lung disease; nasal polyps requiring surgery; pancreatic insufficiency; sinus disease (symptomatic)
	B	82.55	28.50	79.69	96	CF lung disease; CF related diabetes; hearing loss; hypertension; pancreatic insufficiency; sinus disease (symptomatic)

Source: Module 5.3.5.4/Study VX10-770-107/Listing 16.2.4.1.b, Listing 16.2.4.4.2.b, Listing 16.2.6.2.b, Listing 16.2.6.3.b, and Listing 16.2.8.9.b.
BMI: body mass index; CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second.
[a] Value recorded at screening for Part B.
[b] Value recorded at Day 1 for respective part of study.

CHMP comments:

2.a,
Of the 3 paediatric patients enrolled in part A, only one reported a treatment-related AE, which was mild in intensity and considered unlikely related with study treatment. In part B, one of the 2 paediatric patients included experienced a total of 6 treatment-related AEs, of mild-to-moderate intensity and considered not related-unlikely related to study treatment. The other patient did not experience any AEs or SAEs and did not complete the Safety follow-up visit.
In general, these data does not seem to differ with the overall population safety data and no new concerns have been identified.
2.b.
The requested information has been provided. Bearing in mind that the sample size is very small, the patients included can be considered representative of CF paediatric patients, in terms of baseline demographic and disease characteristics.
2.c.
No SAEs or treatment-related AEs were reported in paediatric patients on either part of the study. This is considered reassuring, although the limitations derived from the small sample size are acknowledged.

In conclusion, no new safety signals have been identified in paediatric patients included in study 107.
Issue considered solved.

5. CHMP's updated overall conclusion and recommendation

As a response to the CHMP´s request for additional information, the MAH has submitted separate data from paediatric patients included in study VX10-770-107, a phase 2, single-blind, placebo-controlled study which evaluated the short-term/long-term effect of ivacaftor on hyperpolarized helium-3 magnetic resonance imaging (HG-MRI) in subjects with cystic fibrosis (CF).

In terms of efficacy, changes from baseline for all the studied parameters were not statistically significant in paediatric patients, likely due to the very small sample size. In addition, as previously noted for the overall results, the correlation between the changes in ventilation defect and clinical endpoints in paediatric patients seems to be very modest.
Paediatric efficacy results generally showed the same trends that the overall and adults results. In general, the sizes of the observed effects varied from paediatric to adult patients; however, these differences are difficult to interpret due to the small number of paediatric patients. Overall, no large or worrisome differences in efficacy are noted between paediatric and adult results.

Regarding to safety, very few AEs reported in paediatric patients, most of them mild in intensity and considered not related/unlikely related to the study treatment. No SAEs or treatment-related AEs were reported in paediatric patients on either part of the study. This is considered reassuring, although the limitations derived from the small sample size are acknowledged.
In general, these data does not seem to differ with the overall population safety data and no new concerns or safety signals have been identified.

Overall conclusion

The number of paediatric patients included in study VX10-770-107 was very small. Results do not indicate large differences with those from the overall and adult population. As a result of the limited sample size, the applicability of the study results is considered very limited as well.

In conclusion, paediatric data from study VX10-770-107 does not change the B/R of Kalydeco (ivacaftor) in the currently approved indication. Therefore, further actions regarding the conditions of use and the product information are not required at this time.

Recommendation

☒ **Fulfilled:**

☐ **Not fulfilled:**

Additional clarifications requested

Not applicable