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Human Medicines Development and Evaluation

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 022

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 (VX12-770-113) 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 VX12-770-113 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 the 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" highfat, 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 VX12-770-113, a Phase 2, randomized, double-blind, placebo-controlled, multiple within-subject crossover (n-of-1) study.

2.3.2. Clinical studies

Study VX10-770-113

Description

The purpose of this pilot study was to assess the effect of ivacaftor in patients 12 years and older with CF who have phenotypic or molecular evidence of residual CF transmembrane conductance regulator (CFTR) function.

Methods

- ***Objective(s)***

Primary Objective

To evaluate the effect of ivacaftor on lung function in subjects aged 12 years and older with cystic fibrosis (CF) who have phenotypic or molecular evidence of residual CF transmembrane conductance regulator (CFTR) function.

Secondary Objectives

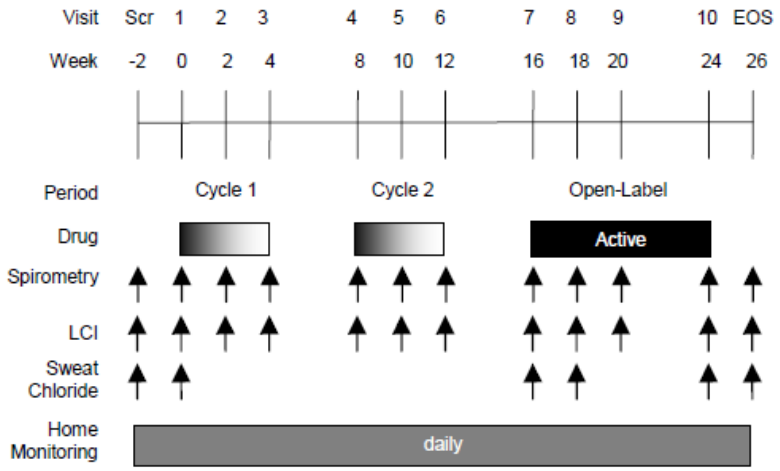
- To evaluate the utility of home spirometry as a clinical endpoint
- To evaluate the utility of a smart phone-based data collection

- ***Study design***

This was a Phase 2, randomized, double-blind, placebo-controlled, multiple within-subject crossover (n-of-1) study. The n-of-1 design was selected to evaluate the potential therapeutic benefit of ivacaftor in subjects with CF who did not have gating mutations but who may have benefited from ivacaftor treatment. This design enabled within subject comparison, while also allowing use of Bayesian meta-analysis for aggregation of multiple individual n-of-1 studies.

This study included a Screening Period (Day -14 to Day -1); a Crossover Period consisting of Cycle 1 (Day 1 to Day 29 [± 2 days]), Washout 1 (minimum of 4 weeks and did not exceed 8 weeks in duration), Cycle 2 (Day 1 to Day 29 [± 2 days]), Washout 2 (minimum of 4 weeks and did not exceed 8 weeks in duration); an Open-label Period (Day 1 to Day 57 [± 3 days]); and a Follow-up Visit (2 weeks [± 3 days] after last dose of study drug). The study design is presented in Figure 2-1.

Figure 2-1 Study Design



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

Male and female subjects with CF who were aged 12 years and older, had mild to moderate CF lung disease (FEV1 ≥ 40% of predicted), and had clinical evidence of residual CFTR function, as demonstrated by (1) residual exocrine pancreatic function, (2) sweat chloride values ≤80 mmol/L, or (3) age of diagnosis ≥12 years and at least 1 copy of CFTR mutation associated with residual CFTR function or mRNA splicing defect.

Enrolment was planned for a maximum of 40 subjects. The study sample size was primarily driven by operational considerations in this rare population.

- ***Treatments***

Ivacaftor-matched placebo were administered orally q12h. It was recommended to take ivacaftor with fat-containing food such as a standard "CF" high-fat, high calorie meal or snack. Placebo batch umber: 3091820R. Subjects were randomized to 1 of 4 treatment sequences (Table 2-1).

Table 2-1 Treatment Sequences

	Crossover Period				
Sequence	Cycle 1 Period 1 Day 1 to 14 (± 2 days)	Cycle 1 Period 2 Day 15 to 29 (± 2 days)	Cycle 2 Period 1 Day 1 to 14 (± 2 days)	Cycle 2 Period 2 Day 15 to 29 (± 2 days)	Open-label Period Day 1 to 57 (± 3 days)
1 (IPIP)	ivacaftor	placebo	ivacaftor	placebo	ivacaftor
2 (IPPI)	ivacaftor	placebo	placebo	ivacaftor	ivacaftor
3 (PIIP)	placebo	ivacaftor	ivacaftor	placebo	ivacaftor
4 (PIPI)	placebo	ivacaftor	placebo	ivacaftor	ivacaftor

The planned duration of study drug administration was 16 weeks. Excluding the 2-week Screening Period, each subject was planned to participate in the study for approximately 26 weeks (Day 1 through the Follow-up Visit).

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

- ***Outcomes/endpoints***

Efficacy Assessments:

The primary efficacy endpoint was the absolute change from baseline in percent predicted FEV1 after 2 weeks of treatment compared to placebo. This was assessed in 2 cross-over cycles (i.e., the Crossover Period), when ivacaftor was administered for 2 weeks either before or after 2 weeks of placebo.

The following were secondary efficacy endpoints:

- Change in LCI after 2 weeks of treatment during the Crossover Period;
- Changes from baseline during the 8-week Open-label Period in: percent predicted FEV1, LCI, Sweat chloride, Weight;
- Correlation between absolute change from baseline in percent predicted FEV1 and LCI after 2 and 8 weeks of treatment;
- Absolute change from baseline in percent predicted FEV1 collected by home spirometry after 2 and 8 weeks of treatment.

Safety Assessments: Adverse events (AEs), clinical laboratory values (serum chemistry, hematology, coagulation, and urinalysis), and vital signs, electrocardiograms (ECGs), and ophthalmologic examinations.

- ***Statistical Methods***

The Full Analysis Set (FAS), defined as all randomized subjects who received at least 1 dose of study drug, was used for all efficacy analyses. Safety Set (all randomized subjects) was used for all safety analyses.

Efficacy Analyses

The absolute change from cycle baseline in percent predicted FEV1 and LCI were analyzed using a Bayesian hierarchical model (BHM) as the primary analysis and a mixed effects model as a supportive analysis.

The results of the mixed effect model analyses are presented for the FAS as well as for the pre-defined mRNA splice site (Class V) mutation and residual CFTR function mutation subgroups. The mRNA splice site (Class V) mutation subgroup included all subjects with at least 1 allele having a mRNA splice site mutation, with the exception of Subject, who had the 1717-1G->A/R117H genotype. The mutation 1717-1G->A is not classified as mRNA splice site (Class V) mutation; therefore, this subject was assigned to the residual function mutation subgroup. Summary statistics for percent predicted FEV1, LCI, weight, BMI, and CFQ-R respiratory domain are presented by treatment within each cycle and during the Open-label Period, for the FAS and the genotype subgroups. Summary statistics for sweat chloride and fecal elastase-1 are presented during the Open-label Period only, for the FAS and the genotype subgroups.

Safety Analyses

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA; Version 15.0). The incidence of AEs that started or increased in severity after the initial study drug dosing was summarized by treatment group. The incidence of AEs was analyzed for the Safety Set and for the 2 genotype subgroups. Descriptive statistics (raw values) were summarized for clinical laboratory values, ECG parameters, vital signs, and ophthalmologic examinations.

Results

Recruitment/ Number analysed

A total of 24 subjects were randomized (Table 2-2); 21 (87.5%) subjects completed their assigned duration of dosing in the study. One subject (4.2%) in the PIPI treatment sequence group discontinued at the end of Cycle 1 (during the Washout Period) due to an adverse event (AE) of infective pulmonary exacerbation of CF, and 2 subjects, 1 in each of the IPPI and PIPI treatment sequence groups, discontinued after Cycle 2 due to non-compliance with study drug. Of the 24 FAS subjects, 10 were in the subgroup of subjects with mRNA splice site (Class V) mutations and 14 were in the subgroup of subjects with residual function mutations.

Table 2-2 Subject Disposition

Disposition Category	IPIP n (%)	IPPI n (%)	PIIP n (%)	PIPI n (%)	Overall n (%)
All Subjects	5	6	7	6	24
FAS[a]	5	6	7	6	24
Safety Set[b]	5	6	7	6	24
Completed Dosing	5 (100.0)	5 (83.3)	7 (100.0)	4 (66.7)	21 (87.5)
Failed to Complete Dosing	0	1 (16.7)	0	2 (33.3)	3 (12.5)
Reason for Failing to Complete Treatment Period:					
Adverse Event	0	0	0	1 (16.7)	1 (4.2)
Refused Further Dosing (Not Due to AE)	0	0	0	0	0
Non-compliance with Study Drug	0	1 (16.7)	0	1 (16.7)	2 (8.3)

Source: Table 14.1.1.1.

The FAS and Safety Set included both 24 subjects.

Baseline data

Demographic details were similar across mutation subgroups and treatment sequences. Overall, all subjects were White, 50% were male, and the mean age was 37.3 years (range 14 to 57 years). Mean baseline percent predicted FEV1 was approximately 67.8% (range 38% to 109%) with the majority having a percent predicted FEV1 of <70%. The mean baseline BMI was 24.15 kg/m2 and the mean LCI was 10.6351 $TO_{(N2.5)}$. The study population had a typical CF medical history profile, with the majority having sinus disorders and gastroesophageal reflux disease, and at least a third of FAS subjects reported a medical history of asthma and pancreatic insufficiency. All subjects were receiving at least 1 concomitant medication associated with the management of CF.

Efficacy results

Primary endpoint

The primary efficacy endpoint, absolute change from cycle baseline in percent predicted FEV1 after 2 weeks of treatment (i.e., the Crossover Period Cycle 1 and Cycle 2), was analyzed with the BHM. Table 11-1 presents the results of the model and demonstrates a treatment effect of 2.251 percentage points (SD 0.961; [95% CI 0.383, 4.144]) in favor of ivacaftor after 2 weeks of treatment.

Results are summarized for the primary efficacy endpoint, absolute change from cycle baseline in percent predicted FEV1 after 2 weeks treatment, in Table 11-3.

Table 11-3 Absolute Change From Cycle Baseline at Day 15 in Percent Predicted FEV1 (Percentage Points), Full Analysis Set

		Crossover Period			
		Cycle 1		Cycle 2	
Subjects Included	Statistic	Placebo N = 24	Ivacaftor N = 24	Placebo N = 23	Ivacaftor N = 23
Overall	n	24	24	23	23
	Mean	0.5828	2.0898	0.8495	3.6868
	SD	3.67326	4.63833	4.20641	6.13466
	Median	0.0155	2.0270	0.0980	3.2120
	Minimum	-5.075	-10.269	-6.713	-11.151
	Maximum	9.290	14.796	7.159	17.592
mRNA Splice Site (Class V) Mutations	n	10	10	9	9
	Mean	-0.5710	0.8196	1.7132	2.0640
	SD	3.39739	5.09161	3.80933	3.55493
	Median	-1.4835	2.0690	1.8170	3.2120
	Minimum	-5.075	-10.269	-3.732	-4.441
	Maximum	4.718	6.209	6.051	6.485
Residual Function Mutations	n	14	14	14	14
	Mean	1.4069	2.9971	0.2942	4.7300
	SD	3.75842	4.24124	4.49056	7.27436
	Median	0.3090	2.0270	-0.7840	3.2045
	Minimum	-3.192	-1.945	-6.713	-11.151
	Maximum	9.290	14.796	7.159	17.592

Sources: Table 14.2.1.1.1 and Table 14.2.1.1.2.

Secondary endpoints

Regarding, the absolute changes from cycle baseline in LCI after 2 weeks of treatment, the estimated treatment difference from the BHM analysis was -0.4230 TO $_{(N2.5)}$ with a posterior standard deviation of 0.22339.

Table 11-9 Absolute Change From Baseline at Day 15 in Lung Clearance Index ($TO_{(N2.5)}$), Full Analysis Set

		Crossover Period			
		Cycle 1		Cycle 2	
Subjects Included	Statistic	Placebo N = 24	Ivacaftor N = 24	Placebo N = 23	Ivacaftor N = 23
Overall	n	23	24	23	23
	Mean	0.4596	0.2822	0.4111	0.0770
	SD	1.97774	3.54741	2.39920	1.98188
	Median	0.2500	0.0240	0.3720	-0.0635
	Minimum	-4.147	-5.547	-7.285	-2.830
	Maximum	4.700	11.980	4.137	4.970
mRNA Splice Site (Class V) Mutations	n	10	10	9	9
	Mean	0.4321	-0.5306	1.0568	-0.3136
	SD	1.97140	1.91374	2.12093	1.89562
	Median	0.1390	0.0065	0.6800	-0.0700
	Minimum	-1.660	-3.340	-1.538	-2.830
	Maximum	4.700	1.887	4.137	3.790
Residual Function Mutations	n	13	14	14	13
	Mean	0.4808	0.8628	-0.0039	0.3475
	SD	2.06279	4.34252	2.54929	2.06990
	Median	0.2500	0.0240	0.1075	0.1170
	Minimum	-4.147	-5.547	-7.285	-2.432
	Maximum	3.710	11.980	3.865	4.970

Sources: Table 14.2.2.1.1 and Table 14.2.2.1.2.

Change From Baseline in Lung Clearance Index after 8 Weeks of Treatment:

For the FAS, the mean absolute change from baseline in LCI during the Open-label Period was -1.1344 TO(N2.5) after 2 weeks, -0.8129 $TO_{(N2.5)}$ after 4 weeks, and -1.5687 $TO_{(N2.5)}$ after 8 weeks of continuous ivacaftor treatment; after 2 weeks off-treatment at the Follow-up Visit, the LCI value was -2.0421 $TO_{(N2.5)}$.

After 8 weeks of open-label ivacaftor treatment, the mean LCI value was -1.3459 $TO_{(N2.5)}$ in the subgroup of subjects with mRNA splice site (Class V) mutations and -1.7358 $TO_{(N2.5)}$ in the subgroup of subjects with residual function mutations.

Change From Baseline in Sweat Chloride After 8 Weeks of Treatment:

For the FAS, the mean sweat chloride value at baseline was 64.69 mmol/L. At Day 1 of the Open-label Period, the mean absolute change in sweat chloride from study baseline was -9.14 mmol/L. The mean absolute change was -15.38 mmol/L at Day 15 and -15.74 mmol/L at Day 57. The baseline sweat chloride value was higher in the subgroup of subjects with mRNA splice site (Class V) mutations (72.50 mmol/L) than in the subgroup of subjects with residual function mutations (59.11 mmol/L).

Change From Baseline in Weight After 8 Weeks of Treatment

No relevant changes were seen in weight, height, or BMI during the Crossover Period.

Correlation Between Absolute Change From Baseline in Percent Predicted FEV1 and Lung Clearance Index After 2 and 8 Weeks of Treatment

Pearson correlation coefficients ranged from -0.372 (Crossover Cycle 2, ivacaftor treatment) to 0.168 (Open-label Period Day 15) (P = 0.9739 to P = 0.0881). There was no significant correlation between changes from baseline in percent predicted FEV1 and LCI at 2 and 8 weeks during the Crossover or Open-label Periods.

Absolute Change From Baseline in Percent Predicted FEV1 Collected by Home Spirometry After 2 and 8 Weeks of Treatment

For the FAS, the mean percent predicted FEV1 as collected by home spirometry was 57.6996% at the Open-label Period baseline and 58.0511% at Day 57 (mean absolute change from baseline: 2.8619 percentage points). For the subgroup of subjects with mRNA splice site (Class V) mutations, the mean percent predicted FEV1 was 63.2373% at the Open-label Period baseline and 61.9450% at Day 57. For the subgroup of subjects with residual function mutations, the mean percent predicted FEV1 was 53.1686% at the Open-label Period baseline and 55.4551% at Day 57.

Safety results

Overall Summary of Adverse Events

A total of 23 subjects (95.8%) had AEs during ivacaftor treatment. During the Crossover Period (Cycle 1 and Cycle 2), the incidence of AEs was similar during treatment with ivacaftor (75.0% subjects) and placebo (70.8% subjects). The overall incidence of AEs during the Open-label Period was 95.2%.

The SOC with the highest incidence of AEs during placebo or ivacaftor treatment was Respiratory, thoracic and mediastinal disorders. During the Crossover Period, AEs in this SOC occurred in 14 (58.3%) subjects during placebo treatment and 8 (33.3%) subjects during ivacaftor treatment. The most frequently reported AEs (occurring in at least 10% subjects during either the Crossover or Open-label Periods) within this SOC were cough, sputum increased, and dyspnea. During the Crossover Period, these AEs occurred in more subjects during placebo treatment compared with ivacaftor

treatment (cough: 6 subjects [25.0%] during placebo and 1 subject [4.2%] during ivacaftor treatment, sputum increased: 7 subjects [29.2%] during placebo and 1 subject [4.2%] during ivacaftor treatment, dyspnea: 4 subjects [16.7%] during placebo and 0 subjects during ivacaftor treatment). During the Open-label Period, cough occurred in 7 subjects (33.3%), while the incidence of sputum increased (2 subjects, 9.5%) and dyspnea (1 subject, 4.8%) were reduced compared with the placebo treatment of the Crossover Period of the study.

AE effecting the Infections and infestations SOC occurred in 7 subjects (29.2%) during the placebo treatment and in 11 subjects (45.8%) during ivacaftor treatment in the Crossover Period and in 7 subjects (33.3%) during the Open-label Period. The most frequently occurring AEs within this SOC were upper respiratory tract infection which occurred in 8 subjects (33.3%) overall during ivacaftor treatment. Infective pulmonary exacerbations of CF occurred in similar proportions of subjects during placebo and ivacaftor treatment in the Crossover Period and also during the Open-label Period of the study.

Other AEs that were reported in at least 10% subjects during either placebo or ivacaftor treatment were fatigue which occurred in 4 subjects overall (16.7%) during ivacaftor treatment and 3 subjects (12.5%) during placebo, and pyrexia which was reported in 3 subjects overall (12.5%) during ivacaftor treatment and 1 subject (4.2%) during placebo administration.

Table 12-3 Adverse Events Occurring in At Least 10% of Subjects in Either Group During the Crossover and Open-label Periods by System Organ Class and Preferred Term, Safety Set

	Crossover Period		Open-label Period	Overall
System Organ Class Preferred Term	Placebo (N = 24) n (%)	Ivacaftor (N = 24) n (%)	Ivacaftor (N = 21) n (%)	Ivacaftor (N = 24) n (%)
Subjects with any AEs	**17 (70.8)**	**18 (75.0)**	**20 (95.2)**	**23 (95.8)**
Respiratory, thoracic and mediastinal disorders	14 (58.3)	8 (33.3)	15 (71.4)	19 (79.2)
Cough	6 (25.0)	1 (4.2)	7 (33.3)	8 (33.3)
Sputum increased	7 (29.2)	1 (4.2)	2 (9.5)	3 (12.5)
Dyspnoea	4 (16.7)	0	1 (4.8)	1 (4.2)
Infections and infestations	**7 (29.2)**	**11 (45.8)**	**7 (33.3)**	**15 (62.5)**
Upper respiratory tract infection	0	5 (20.8)	4 (19.0)	8 (33.3)
Infective pulmonary exacerbation of CF	3 (12.5)	2 (8.3)	2 (9.5)	3 (12.5)
Oral candidiasis	3 (12.5)	0	0	0
General disorders and administration site conditions	**4 (16.7)**	**4 (16.7)**	**5 (23.8)**	**8 (33.3)**
Fatigue	3 (12.5)	0	4 (19.0)	4 (16.7)
Pyrexia	1 (4.2)	3 (12.5)	0	3 (12.5)

Source: Table 14.3.1.2.1.

AEs by severity

Most AEs were considered mild or moderate in severity for the majority of subjects. One subject (4.2%) had a severe SAE of infective pulmonary exacerbation of CF that occurred during ivacaftor treatment; this SAE occurred during the Crossover Period. One subject (4.2%) had a severe AE of infective pulmonary exacerbation of CF during placebo treatment. No subject had a life-threatening AE during either ivacaftor or placebo administration.

Table 12-4 Incidence and Severity of Adverse Events, Safety Set

	Crossover Period		Open-label Period	
System Organ Class Preferred Term	Placebo (N = 24) n (%)	Ivacaftor (N = 24) n (%)	Ivacaftor (N = 21) n (%)	Overall Ivacaftor (N = 24) n (%)
Subjects with any AEs	**17 (70.8)**	**18 (75.0)**	**20 (95.2)**	**23 (95.8)**
Mild	6 (25.0)	6 (25.0)	7 (33.3)	7 (29.2)
Moderate	10 (41.7)	11 (45.8)	13 (61.9)	15 (62.5)
Severe	1 (4.2)	1 (4.2)	0	1 (4.2)
Life-threatening	0	0	0	0

AEs Leading to Discontinuation

No AEs resulted in permanent discontinuation of study drug.

Adverse Events That Led to dose interruptions

One subject had a severe AE of infective pulmonary exacerbation of CF during placebo treatment that led to the interruption of ivacaftor treatment. The event resolved and was considered to be not related to study drug by the investigator. An additional subject had moderate AE of urticaria during open-label ivacaftor treatment that led the interruption of ivacaftor treatment. This event resolved was and considered possibly related to study drug.

Adverse Events by Relationship to Study Drug

In 19 of the 23 subjects with AEs, the AEs were considered not related or to study drug. AEs considered possibly related to study drug occurred in 3 subjects during ivacaftor treatment: one subject had headache and chest discomfort; another subject had paranasal sinus hypersecretion, sputum increased, cough, chest pain, and wheezing; and one last subject had urticaria). One additional subject had cough and sputum increased during placebo treatment that were considered treatment-related.

2.3.3. Discussion on clinical aspects

Cystic fibrosis is caused by mutations in the CF transmembrane conductance regulator gene (CFTR), which results in absent or deficient function of the CF transmembrane conductance regulator protein (CFTR) at the cell surface. CFTR is an epithelial chloride channel responsible for helping to regulate salt and water absorption and it's involved in the multi-system pathology associated with CF. Currently, increasing the level of chloride transport through the CFTR channels by using a potentiator, such as ivacaftor, is a strategy to treat CF.

Efficacy

Study VX12-770-113 was a Phase 2, randomized, double-blind, placebo-controlled, multiple within-subject crossover (n-of-1) study.

Design & conduct of the study

The study was conducted in a single centre in the USA and took place from September 2012 to April 2014.

Male and female subjects with CF, aged 12 years and older, with mild to moderate CF lung disease (FEV1 ≥40% of predicted), and had clinical evidence of residual CFTR function were allowed to enrol.

No formal sample size calculations were performed and the sample size was selected solely 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 objective of the study was to evaluate the effect of ivacaftor on lung function in subjects aged 12 years and older with CF who have phenotypic or molecular evidence of residual CFTR function. Secondary endpoints were: to evaluate the utility of home spirometry as a clinical endpoint and to evaluate the utility of a smart phone-based data collection.

Efficacy data & additional analyses
A total of 24 patients were included, of which only 1 was a pediatric patient (14 years of age).
Only global results have been provided and no separate results are available for the pediatric subject in this study. It is acknowledged that the number of pediatric patients included in the study was very small (n=1) and the applicability of the study results would probably be very limited as well and no further data is being requested from the MAH..

Safety
Most of the subjects (n=23, 95.8%) had AEs during ivacaftor treatment. During the Crossover Period, the incidence was similar during treatment with ivacaftor (75.0% subjects) and placebo (70.8% subjects). The overall incidence of AEs during the Open-label Period was 95.2%. The SOC with the highest incidence of AEs during placebo or ivacaftor treatment was Respiratory, thoracic and mediastinal disorders. The most frequently reported AEs (≥10%) within this SOC were cough, sputum increased, and dyspnea. Most of the AEs reported were of mild to moderate intensity.
No deaths or life threatening AEs occurred. No new or unexpected signals were identified in this study. Safety results have been presented globally, without separating paediatric and adult data. On the EMA cover letter accompanying the documentation supportive of this procedure, the MAH stated that the only paediatric patients included in the study did not experienced any AEs or SAEs, but no confirmation on this statement has been located in the clinical overview.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

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. Nevertheless, as only 1 adolescent was recruited into this trial requesting the pediatric data separately would not be add any relevant information to address the purpose of the article 44 of the Regulation (EC) No 1901/2006.

Recommendation

☒ **Fulfilled**

☐ **Not fulfilled**