31 October 2018
EMA/716662/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Symkevi (1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropane-1-carboxamide and ivacaftor)
Treatment of cystic fibrosis
EU/3/17/1828 (EMA/OD/156/16)
Sponsor: Vertex Pharmaceuticals (Europe) Limited

Note

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

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1. Product and administrative information

Product	
Active substances	1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropane-1-carboxamide and ivacaftor
International Non-Proprietary Names	Tezacaftor and ivacaftor
Orphan indication	Treatment of cystic fibrosis
Pharmaceutical form	Film-coated tablets
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	R07AX31
Sponsor's details:	Vertex Pharmaceuticals (Europe) Limited 2 Kingdom Street London W2 6BD United Kingdom
Orphan medicinal product designation procedural history	
Sponsor/applicant	Vertex Pharmaceuticals (Europe) Limited
COMP opinion date	19 January 2017
EC decision date	27 February 2017
EC registration number	EU/3/17/1828
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	J.L. Hillege / N. Nagercoil
Applicant	Vertex Pharmaceuticals (Europe) Limited
Application submission date	25 July 2017
Procedure start date	17 August 2017
Procedure number	EMA/H/C/004682/0000
Invented name	Symkevi
Therapeutic indication	Symkevi is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T. Further information on Symkevi can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/European public assessment reports.
CHMP opinion date	26 July 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	I. Barisic / A. Magrelli
Sponsor's report submission date	14 July 2017 and 18 January 2018

COMP discussion and adoption of list of questions	19-21 June 2018
Oral explanation	17 July 2018
Adoption of second list of questions	6 August 2018
COMP opinion date	13 September 2018

2. Grounds for the COMP opinion at the time of designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2017 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropane-1-carboxamide and ivacaftor was considered justified based on preclinical data showing increased chloride transport across membranes of lung epithelial cells harbouring cystic fibrosis relevant mutations, and on preliminary clinical data showing improvement of lung function in patients affected by the condition;
- the condition is chronically debilitating and life threatening due to the recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure;
- the condition was estimated to be affecting less than 1 in 10,000 persons in the European Union, at the time the application was made;
- in addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropane-1-carboxamide and ivacaftor will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing improvement of lung function in patients heterozygous for the F508del and G551D mutations with the proposed product. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The therapeutic indication granted by the CHMP is "*Symkevi is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T*"

The authorised therapeutic indication falls within the scope of the designated orphan indication "treatment of cystic fibrosis".

Intention to diagnose, prevent or treat

Symkevi is a fixed dose combination of tezacaftor, a CFTR corrector that facilitates the cellular processing and trafficking of normal or multiple mutant forms of CFTR to increase the amount of functional CFTR protein delivered to the cell surface and ivacaftor, a CFTR potentiator that potentiates the channel-open probability (or gating) of CFTR at the cell surface. Symkevi is currently under assessment for being marketed with ivacaftor (Kalydeco) in a combination regimen (Symkevi in the morning and ivacaftor in the afternoon).

Based on the CHMP assessment, the intention to treat the condition has been justified.

Chronically debilitating and/or life-threatening nature

There have been no changes in the seriousness of cystic fibrosis since the time of orphan designation. The condition is chronically debilitating and life threatening due to the recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure.

Number of people affected or at risk

There have been no significant changes in the prevalence of the condition since the time of orphan designation. The sponsor provided a comprehensive overview of the prevalence of cystic fibrosis in Europe, based on the European Cystic Fibrosis Society Patient Registry (ECFSPR) 2014 report. Based on the registry data and relative to the whole population of the EU the estimated prevalence of CF in the EEA (including Iceland, Liechtenstein, and Norway) is 0.93 per 10,000 individuals, corresponding to 47,975 cases. This estimate is acceptable.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

A number of medicinal products are authorised in Europe for the treatment of cystic fibrosis, including antibiotics and mucolytics. The mucolytics include N-acetylcysteine, which acts as a mucolytic by breaking down disulfide bonds in mucus found in CF patients, RhDNAse, Pulmozyme, and inhaled mannitol (Bronchitol).

In addition bronchodilators and corticosteroids, both inhaled and systemic, are used as supportive treatment in patients with CF, even though they are not specifically authorised for this purpose and their efficacy in CF is very limited. Hypertonic saline solutions, administered as an aerosol, are also used to decrease mucus viscosity by changing the osmolarity of airway mucus.

Antibiotics approved for use in CF in Europe include: tobramycin, colistin, aztreonam lysine, and levofloxacin.

The CFTR potentiator Kalydeco is authorised in the European Union for the treatment of patients with CF due to gating (class III) mutation in the *CFTR* gene (*G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R*) and in patients aged 18 years and older who have the *R117H*

mutation. The combination of ivacaftor and lumacator (Orkambi) is authorized for patients homozygous for the F508del mutation.

Significant benefit

The sponsor based the discussion on significant benefit on a better efficacy of Symkevi (TEZ/IVA) plus Kalydeco (IVA) versus Orkambi (LUM/IVA) in patients homozygous of F508del, and on the clinical efficacy *versus* placebo on top of usual standard of care in F508del heterozygous patients with one of the mutations listed in the therapeutic indication (*P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T)*, for which no CFTR modulator was yet authorized. The sponsor defines the mutations listed in the therapeutic indication approved by the CHMP as 'residual function' (RF) mutations, based on the in vitro response to CFTR modulators, in this case TEZ/IVA. They encompass mutations belonging to different classes according to the current classification, and characterized by different severity and clinical course. *In vitro,* TEZ/IVA was considered effective when (1) a statistically significant increase in chloride transport over baseline normal; (2) a ≥10 pp increase in chloride transport over baseline as a percentage of normal CFTR; and (3) a statistically significant increase in chloride transport compared to treatment with ivacaftor alone were demonstrated.

The sponsor based the significant benefit discussion on three main studies:

- Study 106 of Symkevi plus Kalydeco *versus* placebo in patients homozygous for *F508del* and the indirect comparison of this study with the Orkambi clinical studies 103 and 104;
- Study 108 in patients heterozygous for *F508del* and a residual function mutation, a three arms cross-over study comparing tezacaftor/ivacaftor with ivacaftor alone and with placebo; and
- Study 114 of Symkevi plus Kalydeco in patients who had to discontinue Orkambi due to respiratory side effects such as persistent cough and bronchospasm.
- The sponsor also mentions study 110, a continuation of study 106 and 108, therefore enrolling both homozygous F508del/F508del and heterozygous F508del/residual function. Some data from this study are already available and the sponsor describes them but no conclusion from study 110 is yet available.

The whole significant benefit discussion is based on the use of Symkevi in combination with Kalydeco (here always mentioned as 'Symkevi plus Kalydeco') as this is the recommended treatment regimen and the regimen used in the pivotal studies for the approval of Symkevi and the MA extension of indication of Kalydeco to be used with Symkevi.

<u>Homozygous F508del</u>

Patients homozygous for F508 del (F/F) represent the largest CF patient population, and also the largest target population of the Symkevi plus Kalydeco MA application.

The sponsor claimed significant benefit in F/F patients (12 years of age and older, as per authorized indication) *versus* Orkambi (LUM/IVA), the only CFTR modulator authorized for this patient population, based on better efficacy from indirect comparison of the Symkevi plus Kalydeco and Orkambi studies, and on the establishment of efficacy in patients that cannot tolerate Orkambi due to respiratory side-effects in study 114 of Symkevi plus Klaydeco.

Efficacy of Symkevi plus Kalydeco in relation to authorized medicinal products for the treatment of CF:

The sponsor performed an indirect comparison between study 106 of the Symkevi development programme (the pivotal study supporting the MA in this indication; 248 patients) and two pooled Orkambi studies (LUM/IVA-103 and LUM/IVA-104; 369 patients).

Study 106 was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of tezacaftor/ivacaftor plus ivacaftor (100 mg TEZ/150 mg IVA daily for 24 weeks + 150 mg IVA daily for 24 weeks). The primary endpoint was the absolute change from baseline in percentage predicted FEV1 (ppFEV1) through Week 24, and secondary endpoints included: relative change in ppFEV1; number of pulmonary exacerbations; absolute change in BMI from baseline; and absolute change in CFQ-R Respiratory Domain Score. Studies LUM/IVA-103 and LUM/IVA-104 were Phase 3, randomized, double-blind, placebo-controlled, parallel-group studies to evaluate the efficacy and safety of Orkambi (LUM/IVA) versus placebo. The Orkambi dose chosen for the indirect comparison with study 106 was the current recommended therapeutic dose.

The results of the primary and secondary endpoints comparison between study 106 study and the Orkambi studies is reported in table 1 and table 2 respectively (from the sponsor's maintenance report).

Table 1. Absolute Change From Baseline in Percent Predicted FEV1 at Week 24, Full Analysis Set

	809-103 & 809-104		**661-106**	
	Placebo N = 371	**LUM/IVA N =369**	**Placebo N = 256**	**TEZ/IVA N = 248**
Mean (SD) at Baseline	60.4 (13.8)	60.5 (14.1)	60.4 (15.7)	59.6 (14.7)
LS Mean (SE)	-0.4 (0.4)	2.2 (0.4)	-1.3 (0.5)	3.5 (0.5)
P-value within Treatment	0.3494	<0.0001	0.0037	<0.0001
LS Mean Diff vs Placebo (SE) (95% CI)	-	2.6 (0.6) (1.4, 3.7)	-	4.8 (0.6) (3.6, 6.0)
P-value vs Placebo	-	<0.0001	-	<0.0001
LS Mean Diff vs Orkambi, 95% CI				2.3 (0.6, 3.9)
P-value vs Orkambi				0.0079

Source: based on original results Study VX-661 CSR, VX-809 CSR

Table 2. Indirect Treatment Comparison of Secondary Endpoints of TEZ/IVA Study 106 and Orkambi Studies 103 and 104, Full Analysis Set

		Orkambi 809-103 & 809-104		**TEZ/IVA 661-106**	
Analysis	**Statistic**	**Placebo N = 371**	**LUM/IVA N =369**	**Placebo N = 256**	**TEZ/IVA N = 248**
Relative change in $ppFEV_1$ from baseline at Week 24 (%)	Mean (SD) at Baseline	60.4 (13.8)	60.5 (14.1)	60.4 (15.7)	59.6 (14.7)
	LS Mean (SE)	-0.3 (0.7)	4.1 (0.7)	-1.6 (0.8)	6.4 (0.8)
	P-value within Treatment	0.6375	<0.0001	0.0441	<0.0001

		Orkambi 809-103 & 809-104		TEZ/IVA 661-106	
Analysis	**Statistic**	**Placebo N = 371**	**LUM/IVA N =369**	**Placebo N = 256**	**TEZ/IVA N = 248**
	LS Mean Diff vs Placebo (SE) (95% CI)	-	4.4 (1.0) (2.5,6.4)	-	8.0 (1.1) (5.9, 10.1)
	P-value vs Placebo	-	<0.0001	-	<0.0001
	LS Mean Diff vs Orkambi, 95% CI	-	-	-	3.5 (0.7, 6.4)
	P-value vs Orkambi	-	-	-	0.0146
Number of pulmonary exacerbations through Week 24	Number of Events (Estimated Event Rate per Year*)	251 (1.14)	152 (0.70)	122 (0.97)	78 (0.64)
	Rate Ratio vs Placebo, 95% CI*	-	0.61 (0.49, 0.76)	-	0.65 (0.48, 0.88)
	P-value vs Placebo*	-	< 0.0001	-	0.0054
	Rate Ratio vs Orkambi, 95% CI*	-	-	-	1.06 (0.72, 1.55)
	P-value vs Placebo*	-	-	-	0.7616
Absolute change in BMI from baseline at Week 24 (kg/m^2)	Mean (SD) at Baseline	21.02 (2.92)	21.50 (3.03)	21.12 (2.88)	20.96 (2.95)
	LS Mean (SE)	0.13 (0.05)	0.37 (0.05)	0.12 (0.05)	0.18 (0.05)
	P-value within Treatment	0.0066	<0.0001	0.0134	0.0004
	LS Mean Diff vs Placebo (SE) (95% CI)	-	0.24 (0.07) (0.11, 0.37)	-	0.06 (0.07) (-0.08, 0.19)
	P-value vs Placebo	-	0.0004	-	0.4127
	LS Mean Diff vs Orkambi, 95% CI	-	-	-	-0.18 (-0.37, 0.01)
	P-value vs Orkambi		-	-	0.0616
Absolute change in CFQ-R Respiratory Domain Score from baseline at Week 24 (points)[b]	Mean (SD) at Baseline	68.8 (17.3)	68.3 (18.0)	69.9 (16.6)	70.1 (16.8)
	LS Mean (SE)	1.9 (0.8)	4.1 (0.8)	0.1 (1.0)	5.5 (1.0)
	P-value within Treatment	0.0213	<0.0001	0.9283	<0.0001
	LS Mean Diff vs Placebo (SE) (95% CI)	-	2.2 (1.1) (0.0, 4.5)	-	5.4 (1.3) (2.9, 7.9)
	P-value vs Placebo	-	0.0512	-	<0.0001
	LS Mean Diff vs Orkambi, 95% CI	-	-	-	3.2 (-0.2, 6.5)

		Orkambi 809-103 & 809-104		TEZ/IVA 661-106	
Analysis	**Statistic**	**Placebo N = 371**	**LUM/IVA N =369**	**Placebo N = 256**	**TEZ/IVA N = 248**
	P-value vs Orkambi	-	-	-	0. 0661

Source: based on original results Study VX-661 CSR, VX-809 CSR
CI: Confidence interval; SE: Standard error;SD: Standard deviation
Pulmonary Exacerbation: new or change in antibiotic therapy for >=4 sinopulmonary signs/symptoms

The difference in percentage predicted FEV1 (ppFEV1) changes from baseline of Orkambi and Symkevi plus Kalydeco was established by the indirect comparison at 2.3 percentage points, as shown in table 1. The difference at week 24 (48 weeks of total treatment) extension visit was smaller with 0.7 percentage points [2.7 for Orkambi (95% CI 1.8, 3.6) and 3.4 for Symkevi/Kalydeco (95% CI 2.3, 4.5)] (data not shown). It was noted that the placebo groups of the two studies had a different ppFEV1 decline: -0.4 in the Orkambi placebo group vs. -1.3 in the Symkevi plus Kalydeco placebo group, which further reduces the actual difference between Symkevi and Orkambi. The placebo values used for the ppFEV1 comparison took into account the values measured at each visit (shown in table 3) in the MMRM analysis used for the indirect comparison.

Table 3. MMRM Analysis of the Absolute Change from Baseline LS Mean (SE) in $ppFEV_1$ at Each Visit, Full Analysis Sets (from sponsor's responses to second list of questions)

Visit	**TEZ/IVA (Study 661-106)**		**LUM/IVA (Pooled Studies 809-103/104)**	
	Placebo N=256	**TEZ/IVA N=248**	**Placebo N=371**	**LUM/IVA (Commercial Dose) N=369**
Absolute Change From Baseline at Each Study Visit				
Day 15	-0.4 (0.4)	3.0 (0.4)	-0.3 (0.4)	2.2 (0.3)
Week 4	-0.1 (0.4)	3.4 (0.4)	0.1 (0.4)	2.6 (0.4)
Week 8	-0.6 (0.4)	3.1 (0.4)	-0.1 (0.4)	3.1 (0.4)
Week 12	-1.0 (0.4)	3.5 (0.4)	NA[a]	NA[a]
Week 16	-0.3 (0.4)	3.7 (0.4)	-0.3 (0.4)	2.8 (0.4)
Week 24	-1.3 (0.5)	3.9 (0.5)	-0.4 (0.4)	2.2 (0.4)
Absolute Change From Baseline Through Week 24 (Primary Endpoint of Study 661-106)	-0.6 (0.3)	3.4 (0.3)	NA[b]	NA[b]

Sources: Study 661-106 CSR Tables 11-2 and 11-3; LUM/IVA ISE Table 3.2.2.1.2.
IVA: ivacaftor; LS: least squares; LUM: lumacaftor; MMRM: mixed-effects model for repeated measures; NA: not applicable; ppFEV1: percent predicted forced expiratory volume in 1 second; SE: standard error; TEZ: tezacaftor
Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug. All measurements up to Week 24, both on-treatment measurements and measurements after treatment discontinuation, were included. ppFEV1 was measured in percentage points.
[a] Data not collected
[b] Analysis not done per Statistical Analysis Plan

The MMRM methodology in the table above allows correcting for inter-visit variability in FEV1 values in the active and placebo group, therefore increasing the robustness of the comparison. Nevertheless the difference between the placebo groups remain and the final difference of 2.3% in FEV1 is difficult to interpret from a point of view of clinical relevance. This is because the available literature describes that yearly decline in ppFEV1 levels are influenced by a number of factors, including age cohort and clinical factors such as pancreatic insufficiency, baseline FEV1, exacerbations, and Pseudomonas aeruginosa infection/colonization among others, and there is no consensus regarding a minimally clinically relevant difference in FEV1 decline for clinical trials and more in general for therapeutic response purposes.

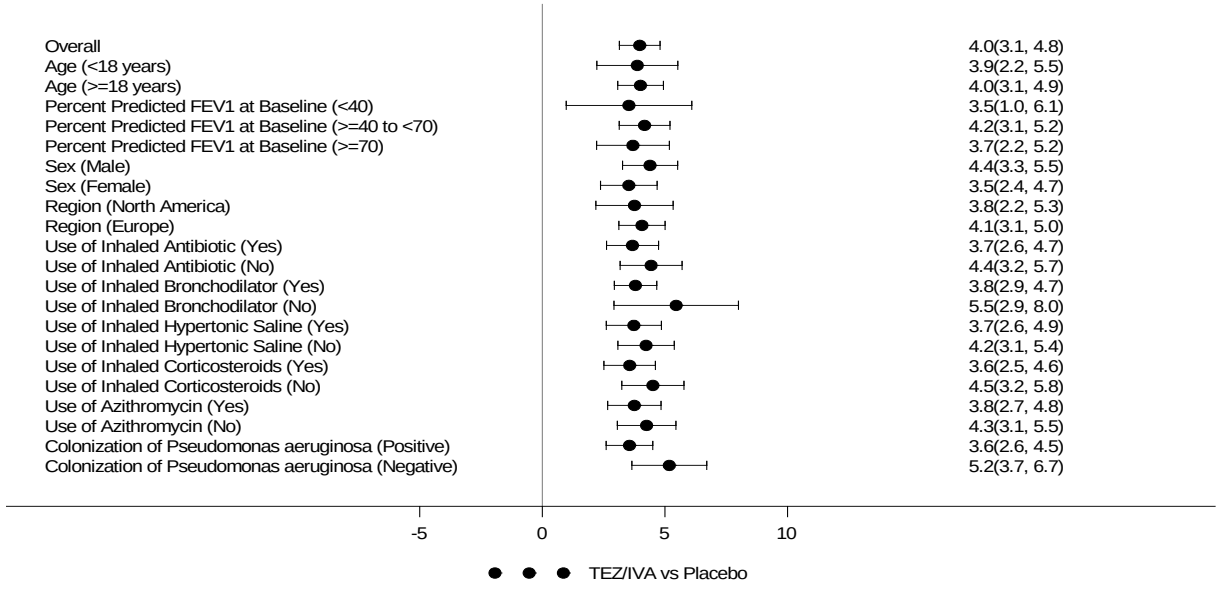
From the available literature, rates of FEV1 decline in young adults with CF have been indeed shown to diminish with successive birth cohorts, and patients infected with Pseudomonas traditionally had a greater average decline in FEV(1) (-1.6% v -1.1%) (Que, 2006). Konstan et al (2010) report mean rates of FEV1 change in a population of CF > 6 years and with baseline FEV1 above 70%. Median age specific year to year changes in FEV1 % predicted (Liou, 2010) vary from close to 0% up to 4% during adolescence and young adulthood. One important aspect when considering yearly FEV1 changes is also the rather large short-term variability identified by most authors. In a Danish registry study (Taylor-Robinson 2012) short-term variability of FEV1 was 6.3%, and during an EMA expert workshop on endpoints for CF, held in 2012, it was stated that although the median changes are low, the variability of ppFEV1 is high, with 5 to 20% of the population having changes more than 10% predicted. A mean (SD) year to year change in FEV1 of only -1.22 (9.17) was reported in the Belgian population (De Boeck, 2011). The MMRM analysis of the applicant of the different FEV1 time points is expected to correct for variability, and this was acknowledged.

Because of all these reasons, in the EMA workshop report it was concluded, besides on the lack of consensus on the minimally clinical important difference in FEV1 in cystic fibrosis, that long-term stability of FEV1 is a relevant aspect when looking at treatment effect size. Since the observation period compared in the Orkambi and Symkevi plus Kalydeco studies is of 24 weeks only, the sponsor modelled the gain in median predicted survival based on the Symkevi plus Kalydeco trial data and compared it to that of Orkambi, showing an estimated gain of median predicted survival) of additional 0.83 years with Symkevi plus Kalydeco versus, Orkambi. It was noted however that in the model the treatment effect of Symkevi plus Kalydeco was assumed to impact three out of the 9 factors influencing survival in CF, therefore uncertainty remains around the interpretation of the results. The COMP also noted that there were no relevant differences between Orkambi and the combination Symkevi plus Kalydeco in most secondary endpoints, including exacerbations, as shown in table 2.

Considering all the above, the COMP acknowledged that there are slightly better results in FEV1 with Symkevi plus Kalydeco than with Orkambi but this was not considered to be a significant benefit. This because the effect size of the difference in ppFEV1 decline between Symkevi plus Kalydeco and Orkambi was small and considered not clinically relevant, taking into account the different FEV1 decline described in different studies (including different placebo response), the lack of consensus in the scientific community on the minimum clinically relevant difference in FEV1 in CF studies, and the lack of difference in clinically relevant secondary endpoints such as exacerbations.

The significant benefit versus the current non-CFTR modulator standard of care (SoC), including bronchodilators, mucolytics and antibiotics, was considered justified based on the fact that all Symkevi plus Kalydeco study arms, including placebo, continued to receive their existing SoC non-modulator therapies and that subgroup analyses showed improvement in $ppFEV_1$ in all subgroups regardless of concomitant CF medication use, as shown in Figure 1

Figure 1. Study 106 Subgroup Analysis for Absolute Change From Baseline in ppFEV$_1$, Full Analysis Set



Efficacy and tolerability of Symkevi plus Kalydeco in patients who cannot tolerate Orkambi:

The sponsor also claimed that Symkevi was better tolerated than Orkambi and to support this they presented new data from study 114 as a response to the list of questions. This was a study of Symkevi plus Kalydeco in patients who had to discontinue Orkambi due to respiratory side effects such aschest discomfort, dyspnea, and respiration abnormal (chest tightness) . In the SmPC, the use of Orkambi is associated with increased risk of transient respiratory events such as chest discomfort, dyspnoea and respiration abnormal (chest tightness) at the start of dosing, more frequently in patients with a ppFEV1 less than 40 %, i.e. in the most severe patients, based on the results from the clinical trials. In real-life, routine safety reporting systems (spontaneous and solicited reports), and recent published literature (2016 to date) have shown discontinuation rates of Orkambi in range between 17 to 40% due to the same side-effects reported in the clinical studies, mainly respiratory AEs (chest discomfort, dyspnoea, and respiration abnormal (chest tightness), and mainly in patients with low FEV1 (below 40% predicted).

Study 114 was a phase 3b, randomized, double-blind, placebo-controlled, parallel group trial to assess the safety and efficacy of Symkevi plus Kalydeco (TEZ/IVA) in patients who discontinued Orkambi due to a Respiratory adverse event of Special Interest (RAESI). Target sample size was 90 subjects with ppFEV1 at screening visit ≥25% and ≤90%. The primary safety endpoint was the incidence of respiratory adverse events and the key secondary efficacy endpoints included the absolute change in ppFEV1 from baseline to the average of Day 28 and 56. Table 4 shows the rates of respiratory adverse events in the placebo and treated group in study 114.

Table 4. Rates of respiratory adverse events in the placebo and treated group in study 114.

Preferred Term (PT)	Placebo N=47, n (%)	TEZ/IVA N=50, n (%)
Subjects with any RAESI	10 (21.3)	7 (14.0)
Chest discomfort	1 (2.1)	0 (0.0)
Dyspnoea	5 (10.6)	5 (10.0)
Respiration abnormal	1 (2.1)	3 (6.0)
Asthma	1 (2.1)	0 (0.0)
Bronchial hyperreactivity	0 (0.0)	0 (0.0)
Bronchospasm	2 (4.3)	0 (0.0)
Wheezing	2 (4.3)	0 (0.0)
Subjects with related RAESI	4 (8.5)	1 (2.0)
Subjects with serious RAESI	0 (0.0)	0 (0.0)
Subjects with RAESI leading to treatment discontinuation	0 (0.0)	0 (0.0)

The results presented at table 4 showed that Symkevi plus Kalydeco was well tolerated in patients who discontinued Orkambi, with a rate of respiratory adverse events comparable to that of the placebo group (table 4). The ppFEV1 improvement was similar to the one described in the Orkambi studies, as shown in table 5; therefore based on the results from the available studies Symkevi plus Kalydeco appears better tolerated than Orkambi, with comparable efficacy.

Table 5. ppFEV2 results of study 114

Key Secondary Efficacy Endpoint – Percent Predicted FEV_1	Placebo N = 47	TEZ/IVA N = 50
Baseline, Mean (SD)	48.0 (18.1)	44.6 (16.1)
Absolute Change at the Average of Day 28 and Day 56, Mean (SD)	-0.6 (3.4)	2.2 (4.8)
\\\\\\\\\		
Observed Mean Diff (TEZ/IVA vs Placebo), 95% Confidence Interval	2.7 (1.0, 4.4)	
Bayesian Posterior Probability for Mean Diff > 0 was >99%		

Heterozygous F508del and homozygous F508del/residual function (F/RF)

The group of Heterozygous F508del/RF mutations approved by the CHMP included the following mutations: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T. No CFTR modulator medicinal product is authorized in the European Union for these mutations (Kalydeco is approved in the US).

The significant benefit in F/RF mutations was based on the efficacy results of study 108, three arms cross-over study comparing TEZ/IVA with IVA alone and with placebo. The study was performed on a larger number of residual function mutations than those authorized by the CHMP. The efficacy results of ppFEV1 of the single mutations included in the authorized indication are shown in table 6 below.

Table 6. Effect of TEZ/IVA for Efficacy Variables in CFTR Mutation Subgroups (Results shown as difference in mean (min, max) change from study baseline for TEZ/IVA)

Mutation (n)	Absolute Change in Percent Predicted FEV_1 *†	Absolute Change in CFQ-R Respiratory Domain Score (Points) *§	Absolute Change in Sweat Chloride (mmol/L) *§
2789+5G→A (25)	8.6 (-1.5, 23.4)	12.0 (-8.3, 38.9)	-3.2 (-16.5, 9.0)
3272-26A→G (23)	5.7 (-2.1, 25.9)	5.7 (-22.2, 44.4)	-3.8 (-22.3, 16.5)
3849+10kBc→T (43)	5.8 (-7.2, 22.3)	8.2 (-25.0, 47.2)	-5.6 (-27.0, 8.5)
711+3A→G (2)	4.3 (2.0, 6.7)	-4.2 (-5.6, -2.8)	-15.4 (-21.0, -9.8)
D579G (2)	8.1 (-0.2, 16.4)	11.1 (5.6, 16.7)	-23.1 (-24.8, -21.5)
D1152H (21)	3.8 (-2.5, 12.5)	15.2 (-8.3, 55.6)	-4.1 (-15.0, 11.5)
A455E (11)	8.5 (2.6, 16.1)	11.6 (-11.1, 44.4)	-0.3 (-8.8, 14.0)
L206W (4)	3.0 (-4.5, 10.2)	12.5 (-2.8, 38.9)	-36.1 (-44.5, -27.5)
P67L (11)	9.4 (0.0, 31.9)	11.7 (-12.5, 72.2)	-29.3 (-50.0, 0.8)
R1070W (2)	6.1 (2.0, 10.1)	29.2 (16.7, 41.7)	-13.8 (-26.8, -0.8)
R117C (1)	2.9 (2.9, 2.9)	16.7 (16.7, 16.7)	-38.8 (-38.8, -38.8)
R352Q (2)	4.9 (2.6, 7.1)	8.3 (8.3, 8.3)	-43.3 (-49.8, -36.8)
S945L (7)	9.6 (0.7, 19.5)	11.3 (-4.2, 25.0)	-29.0 (-42.5, -8.0)
S977F (2)	10.1 (5.5, 14.7)	-1.4 (-8.3, 5.6)	-13.9 (-22.3, -5.5)

Sources: Study 661-108 Ad hoc Tables 14.2.1.11, 14.2.2.6, and 14.2.3.7
*Average of Week 4 and 8 values
†Absolute change in $ppFEV_1$ by individual mutations is an ad hoc analysis.
§Absolute change in CFQ-R Respiratory Domain Score and absolute change in sweat chloride by mutation subgroups and by individual mutations are ad hoc analyses.
(n) = subject numbers
Note: CHMP considers there to be a lack of clinical evidence for 2 of the mutations enrolled in Study 661-108: E831X and D110H; therefore, these mutations are not included in this table. The 1 subject with E831X was not randomized to the TEZ/IVA arm, and the 1 subject with *D110H* did not have $ppFEV_1$ improvement during TEZ/IVA treatment.

In general, most mutations included in the therapeutic indications of Symkevi plus Kalydeco are rare, therefore their phenotype is not very well known. Nevertheless from the data in the table above it can be seen that, in spite of the variability of effect within these mutations, the overall FEV1 results appear favourable for all mutations, ranging from of 2.9 to 10.1% improvement in ppFEV1. These results were on top of the usual standard of care treatment and it was considered that the improvement in ppFEV1 in these mutations (6.9% on average), as well as the efficacy on the secondary endpoints were sufficient to support a significant benefit based on efficacy.

Conclusions

The COMP expressed a positive opinion based on a majority vote, on the grounds that study 114 showed that patients who had to discontinue Orkambi due to respiratory adverse events could be treated with Symkevi plus Kalydeco. Based on literature and post-marketing data, approximately 17 to 40% of patients have to discontinue Orkambi due to respiratory adverse events. In study 114 in patients who discontinued Orkambi, the combination of Symkevi plus Kalydeco was well tolerated, with a frequency of respiratory adverse events similar to placebo, and a ppFEV1 improvement similar to the one described in the Orkambi studies. The COMP therefore was of the opinion that Symkevi plus Kalydeco can be considered of significant benefit for the homozygous F508del patient population that cannot tolerate Orkambi.

Regarding the claim of better efficacy of Symkevi plus Kalydeco versus Orkambi in the F508del homozygous population, although a trend towards a better ppFEV1 was noted in the indirect comparison provided by the sponsor, the COMP considered that the difference of 2.3% ppFEV1 between Symkevi plus Kalydeco versus Orkambi could not be considered clinically relevant. This is because of lack of consensus in the scientific community on the minimum clinically relevant difference in FEV1, as well as the variability in FEV1 measurements in CF reported in the literature. The indirect comparison also did not show difference in key secondary endpoints such as exacerbations. The COMP was of the opinion that the results of the indirect comparison showed comparable efficacy of Symkevi plus Kalydeco with Orkambi, therefore a claim of superior efficacy was not considered justified.

The significant benefit in the patients heterozygous for F508del and the residual function mutations listed in the approved therapeutic indication was considered justified based on clinical trial 108 showing efficacy in these CF patients, for which so far no specific CFTR modulator treatments was authorized. In study 108, patients were treated with Symkevi plus Kalydeco on top of the current standard of care, including antibiotics, bronchodilators and mucolytics, and the results in the primary endpoint of ppFEV1, showing an average 6.9% improvement on top of the current treatment, were considered to justify the significant benefit in this patient population.

Three Committee members expressed a divergent opinion, appended in this report.

4. COMP position adopted on 13 September 2018

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of cystic fibrosis (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be less than 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Symkevi will be of significant benefit to those affected by the orphan condition is confirmed. This is based on clinical data showing the better tolerability of Symkevi in combination with Kalydeco in patients with homozygous F508del mutation who had to discontinue treatment with Orkambi, with comparable efficacy. The significant benefit of Symkevi in combination with Kalydeco in patients heterozygous for F508del and one of the residual function mutations included in the authorized therapeutic indication, for whom no specific CFTR modulator treatment is authorized, was considered justified based on clinical data showing improved efficacy versus placebo.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Symkevi, 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropane-1-carboxamide and ivacaftor, tezacaftor and ivacaftor, EU/3/17/1828 for treatment of cystic fibrosis is not removed from the Community Register of Orphan Medicinal Products.

Annex

Divergent position expressed by some members of the COMP

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Symkevi may be of potential significant benefit to those affected by the orphan condition does not hold.

- The members were of the opinion that the clinical data in the homozygous F508del patient population, which represents the majority of the population covered by the therapeutic indication of this application, were not sufficient to demonstrate the significant benefit versus Orkambi, already authorised for the same patient population.
- In particular, it was considered that the sponsor did not sufficiently demonstrate that the difference of 2.3 in percentage predicted Forced Expiratory Volume in 1 second (FEV1) from the indirect comparison between Orkambi and the combination of Symkevi and Kalydeco is clinically relevant. This conclusion took into account the higher decline in the placebo group in the Symkevi plus Kalydeco studies compared to the Orkambi data presented by the applicant, not allowing to conclude on the true treatment difference of Symkevi and Kalydeco versus Orkambi. The conclusion is supported by the lack of significant difference in the secondary endpoints of exacerbations and symptoms score.
- In relation to the claimed better safety of the combination of Symkevi and Kalydeco versus Orkambi, the members were of the opinion that the data presented by the sponsor were not sufficient to justify that the respiratory side-effects of Orkambi would be clinically relevant and persistent.

B. Bloechl-Daum, Austria

N. Sypsas, Greece

V. Stoyanova-Beninska, Netherland