▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Symkevi 50 mg/75 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of tezacaftor and 75 mg of ivacaftor.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Symkevi 50 mg/75 mg film coated tablets

White, capsule-shaped tablet debossed with "V50" on one side and plain on the other (dimensions 12.70 mm x 6.78 mm)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symkevi is indicated in a combination regimen with ivacaftor tablets for the treatment of patients with cystic fibrosis (CF) aged 6 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.*

4.2 Posology and method of administration

Symkevi should only be prescribed by physicians with experience in the treatment of CF. If the patient's genotype is unknown, an accurate and validated genotyping method should be performed to confirm the presence of an indicated mutation using a genotyping assay.

Posology

Adults, adolescents and children aged 6 years and older should be dosed according to Table 1.

Table 1: Dosing recommendations for patients aged 6 years and older		
Age	**Morning (1 tablet)**	**Evening (1 tablet)**
6 to < 12 years weighing < 30 kg	tezacaftor 50 mg/ivacaftor 75 mg	ivacaftor 75 mg
6 to < 12 years weighing ≥ 30 kg	tezacaftor 100 mg/ivacaftor 150 mg	ivacaftor 150 mg
≥ 12 years	tezacaftor 100 mg/ivacaftor 150 mg	ivacaftor 150 mg

The morning and evening dose should be taken approximately 12 hours apart with fat-containing food (see Method of administration).

Missed dose

If 6 hours or less have passed since the missed morning or evening dose, the patient should take the missed dose as soon as possible and continue on the original schedule.

If more than 6 hours have passed since the missed morning or evening dose, the patient should not take the missed dose. The next scheduled dose can be taken at the usual time.

More than one dose of either tablet should not be taken at the same time.

Concomitant use of CYP3A inhibitors

The dose of Symkevi and ivacaftor should be adjusted when co-administered with moderate and strong CYP3A inhibitors.

When co-administered with moderate CYP3A inhibitors (*e.g.*, fluconazole, erythromycin, verapamil), or strong CYP3A inhibitors (*e.g.*, ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin), the dose should be reduced according to Table 2 (see sections 4.4 and 4.5).

Table 2: Dosing recommendations for concomitant use with moderate or strong CYP3A inhibitors		
	Moderate CYP3A inhibitors	**Strong CYP3A inhibitors**
6 years to < 12 years, < 30 kg	Alternate each morning: - one tablet of tezacaftor 50 mg/ivacaftor 75 mg on the first day - one tablet of ivacaftor 75 mg on the next day. Continue alternating tablets each day. No evening dose.	One morning tablet of tezacaftor 50 mg/ivacaftor 75 mg twice a week, approximately 3 to 4 days apart. No evening dose.
6 years < 12 years, ≥ 30 kg	Alternate each morning: - one tablet of tezacaftor 100 mg/ivacaftor 150 mg	One morning tablet of tezacaftor 100 mg/ivacaftor 150 mg twice a week, approximately 3 to 4 days apart. No evening dose.

Table 2: Dosing recommendations for concomitant use with moderate or strong CYP3A inhibitors		
	Moderate CYP3A inhibitors	**Strong CYP3A inhibitors**
	once daily on the first day - one tablet of ivacaftor 150 mg on the next day. Continue alternating each day. No evening dose.	
12 years and older	Alternate each morning: - one tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily on the first day - one tablet of ivacaftor 150 mg on the next day. Continue alternating each day. No evening dose.	One morning tablet of tezacaftor 100 mg/ivacaftor 150 mg twice a week, approximately 3 to 4 days apart. No evening dose.

Special populations

Elderly people

The safety, efficacy and pharmacokinetics of Symkevi have been examined in a limited number of elderly patients. No dose adjustment specific to this patient population is required (see section 5.2).

Renal impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment. Caution is recommended in patients with severe renal impairment or end-stage renal disease (see sections 4.4 and 5.2).

Hepatic impairment

For dose adjustment for patients with hepatic impairment, see Table 3. There is no experience of the use of Symkevi in patients with severe hepatic impairment (Child-Pugh Class C); therefore, its use is not recommended unless the benefits outweigh the risks. In such cases, Symkevi should be used at a reduced dose (see sections 4.4 and 5.2). No dose adjustment is necessary for Symkevi in patients with mild hepatic impairment (Child-Pugh Class A).

Table 3: Dosing recommendations for use in patients with hepatic impairment		
	Moderate (Child-Pugh Class B)	**Severe (Child-Pugh Class C)**
6 years to < 12 years, < 30 kg	One morning tablet of tezacaftor 50 mg/ivacaftor 75 mg once daily. No evening dose.	One morning tablet of tezacaftor 50 mg/ivacaftor 75 mg once daily or less frequently.

Table 3: Dosing recommendations for use in patients with hepatic impairment		
	Moderate (Child-Pugh Class B)	**Severe (Child-Pugh Class C)**
		Dosing intervals should be modified according to clinical response and tolerability. No evening dose.
6 years to < 12 years, ≥ 30 kg	One morning tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily. No evening dose.	One morning tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily or less frequently. Dosing intervals should be modified according to clinical response and tolerability. No evening dose.
12 years and older	One morning tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily. No evening dose.	One morning tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily or less frequently. Dosing intervals should be modified according to clinical response and tolerability. No evening dose.

Paediatric population

The safety and efficacy of Symkevi in children aged less than 6 years has not yet been established. No data are available (see sections 4.8 and 5.1).

Method of administration

For oral use. Patients should be instructed to swallow the tablets whole. The tablets should not be chewed, crushed, or broken before swallowing because there are no clinical data currently available to support other methods of administration.

Both Symkevi and ivacaftor tablets should be taken with fat-containing food, such as food recommended in standard nutritional guidelines (see section 5.2).

Food or drink containing grapefruit should be avoided during treatment (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Symkevi should not be prescribed in patients with CF who are heterozygous for the *F508del* mutation and have a second *CFTR* mutation not listed in section 4.1.

Effect on liver function tests

Elevated transaminases are common in patients with CF, and have been observed in some patients treated with Symkevi in combination with ivacaftor, as well as with ivacaftor monotherapy. Therefore, liver functions tests are recommended for all patients prior to initiating treatment, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring of liver function tests should be considered. In the event of significant elevations of transaminases (*e.g.*, patients with ALT or AST >5 x the upper limit of normal (ULN), or ALT or AST >3 x ULN with bilirubin >2 x ULN), dosing should be interrupted and laboratory tests closely followed until the abnormalities resolve. Following resolution of transaminase elevations, the benefits and risks of resuming treatment should be considered (see section 4.8).

Hepatic impairment

The use of Symkevi is not recommended in patients with severe hepatic impairment unless the benefits are expected to outweigh the risks (see sections 4.2 and 5.2).

Renal impairment

Caution is recommended in patients with severe renal impairment or end-stage renal disease (see sections 4.2 and 5.2).

Patients after organ transplantation

Symkevi in combination with ivacaftor has not been studied in patients with CF who have undergone organ transplantation. Therefore, use in transplanted patients is not recommended. See section 4.5 for interactions with ciclosporin or tacrolimus.

Interactions with medicinal products

CYP3A inducers

Exposure to tezacaftor and ivacaftor may be reduced by the concomitant use of CYP3A inducers, potentially resulting in reduced efficacy of Symkevi and ivacaftor. Therefore, co-administration with strong CYP3A inducers is not recommended (see section 4.5).

CYP3A inhibitors

The dose of Symkevi and ivacaftor should be adjusted when used concomitantly with strong or moderate CYP3A inhibitors (see section 4.5 and Tables 2 and 3 in section 4.2).

Paediatric population

Cataracts

Cases of non-congenital lens opacities without impact on vision have been reported in paediatric patients treated with ivacaftor-containing regimens. Although other risk factors were present in some cases (such as corticosteroid use and exposure to radiation), a possible risk attributable to treatment cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in paediatric patients initiating treatment with Symkevi in combination with ivacaftor (see section 5.3).

Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products affecting the pharmacokinetics of tezacaftor and ivacaftor

CYP3A inducers

Tezacaftor and ivacaftor are substrates of CYP3A (ivacaftor is a sensitive substrate of CYP3A). Concomitant use of CYP3A inducers may result in reduced exposures and thus reduced efficacy of Symkevi and ivacaftor. Co-administration of ivacaftor with rifampicin, a strong CYP3A inducer, significantly decreased ivacaftor exposure [area under the curve (AUC)] by 89%. Tezacaftor exposures can also be expected to decrease significantly during co-administration with strong CYP3A inducers; therefore, co-administration with strong CYP3A inducers is not recommended.

Examples of strong CYP3A inducers include rifampicin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort (*Hypericum perforatum*).

CYP3A inhibitors

Co-administration with itraconazole, a strong CYP3A inhibitor, increased tezacaftor exposure (measured as AUC) by 4-fold and increased ivacaftor AUC by 15.6-fold. The dose of Symkevi should be adjusted when co-administered with strong CYP3A inhibitors (see Table 3 in section 4.2).

Examples of strong CYP3A inhibitors include ketoconazole, itraconazole, posaconazole, and voriconazole, telithromycin and clarithromycin.

Physiologically based pharmacokinetic modeling suggested co-administration with fluconazole, a moderate CYP3A inhibitor, may increase tezacaftor exposure (AUC) by approximately 2-fold. Co-administration of fluconazole increased ivacaftor AUC by 3-fold. The dose of Symkevi and ivacaftor should be adjusted when co-administered with moderate CYP3A inhibitors (see Table 3 in section 4.2).

Examples of moderate CYP3A inhibitors include fluconazole, erythromycin and verapamil.

Co-administration with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of ivacaftor and tezacaftor; therefore, food or drink containing grapefruit should be avoided during treatment (see section 4.2).

Potential for tezacaftor/ivacaftor to interact with transporters

In vitro studies showed that tezacaftor is a substrate for the uptake transporter OATP1B1, and efflux transporters P-gp and Breast Cancer Resistance Protein (BCRP). Tezacaftor is not a substrate for OATP1B3. Exposure to tezacaftor is not expected to be affected significantly by concomitant inhibitors of OATP1B1, P-gp, or BCRP due to its high intrinsic permeability and low likelihood of being excreted intact. However, exposure to M2-TEZ (tezacaftor metabolite) may be increased by inhibitors of P-gp. Therefore, caution should be used when P-gp inhibitors are used with Symkevi.

In vitro studies showed that ivacaftor is not a substrate for OATP1B1, OATP1B3, or P-gp. Ivacaftor and its metabolites are substrates of BCRP *in vitro*. Due to its high intrinsic permeability and low likelihood of being excreted intact, co-administration of BCRP inhibitors is not expected to alter exposure of ivacaftor and M1-IVA, while any potential changes in M6-IVA exposures are not expected to be clinically relevant.

Ciprofloxacin

Co-administration of ciprofloxacin did not affect the exposure of ivacaftor or tezacaftor. No dose adjustment is required when Symkevi is co-administered with ciprofloxacin.

<u>Medicinal products affected by tezacaftor and ivacaftor</u>

CYP2C9 substrates

Ivacaftor may inhibit CYP2C9; therefore, monitoring of the international normalized ratio (INR) is recommended during co-administration of warfarin with Symkevi given in combination with ivacaftor. Other medicinal products for which exposure may be increased include glimepiride and glipizide; these medicinal products should be used with caution.

CYP3A, digoxin and other P-gp Substrates

<u>*CYP3A substrates*</u>

Co-administration with (oral) midazolam, a sensitive CYP3A substrate, did not affect midazolam exposure. No dose adjustment of CYP3A substrates is required when co-administered with Symkevi in combination with ivacaftor.

<u>*Digoxin and other P-gp substrates*</u>

Co-administration with digoxin, a sensitive P-gp substrate, increased digoxin exposure by 1.3-fold, consistent with weak inhibition of P-gp by ivacaftor. Administration of Symkevi in combination with ivacaftor may increase systemic exposure of medicinal products that are sensitive substrates of P-gp, which may increase or prolong their therapeutic effect and adverse reactions. When used concomitantly with digoxin or other substrates of P-gp with a narrow therapeutic index, such as ciclosporin, everolimus, sirolimus, and tacrolimus, caution and appropriate monitoring should be used.

Hormonal contraceptives

Symkevi in combination with ivacaftor has been studied with an estrogen/progesterone oral contraceptive and was found to have no significant effect on the exposures of the hormonal contraceptive. Symkevi and ivacaftor are not expected to modify the efficacy of hormonal contraceptives.

OATP1B1 substrates

Symkevi in combination with ivacaftor has been studied with pitavastatin, an OATP1B1 substrate, and was found to have no clinically relevant effect on the exposure of pitavastatin (1.24-fold increased exposure based on AUC). No dose adjustment of OATP1B1 substrates is required when co-administered with Symkevi.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of tezacaftor or ivacaftor in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure**,** it is preferable to avoid the use of therapy during pregnancy.

Breast-feeding

It is unknown whether tezacaftor, ivacaftor, or their metabolites are excreted in human milk. Available pharmacokinetic/toxicological data in animals have shown excretion of tezacaftor and ivacaftor into the milk of lactating female rats (see section 5.3). A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Tezacaftor

There are no data available on the effect of tezacaftor on fertility in humans. Tezacaftor had no effects on fertility and reproductive performance indices in male and female rats at doses up to 100 mg/kg/day.

Ivacaftor

There are no data available on the effect of ivacaftor on fertility in humans. Ivacaftor had an effect on fertility in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Symkevi in combination with ivacaftor has a minor influence on the ability to drive and use machines. Dizziness has been reported in patients receiving Symkevi in combination with ivacaftor, as well as ivacaftor monotherapy (see section 4.8). Patients experiencing dizziness should be advised not to drive or use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions experienced by patients aged 12 years and older who received Symkevi in combination with ivacaftor in Phase 3 clinical studies were headache (14% versus 11% on placebo) and nasopharyngitis (12% versus 10% on placebo).

Tabulated list of adverse reactions

Table 4 reflects adverse reaction observed with Symkevi in combination with ivacaftor and with ivacaftor monotherapy in clinical studies. Adverse reactions are listed by MedDRA system organ class and frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 4: Adverse reactions

MedDRA System Organ Class	Adverse reactions	Frequency
Infections and infestations	Upper respiratory tract infection, Nasopharyngitis*	very common
	Rhinitis	common
Nervous system disorders	Headache*, Dizziness*	very common
Ear and labyrinth disorders	Ear pain, Ear discomfort, Tinnitus, Tympanic membrane hyperaemia, Vestibular disorder	common
	Ear congestion	uncommon
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain, Nasal congestion	very common
	Sinus congestion*, Pharyngeal erythema	common
Gastrointestinal disorders	Abdominal pain, Diarrhoea	very common
	Nausea*	common
Hepatobiliary disorders	Transaminase elevations	very common
Skin and subcutaneous tissue disorders	Rash	very common
Reproductive system and breast disorders	Breast mass	common
	Breast inflammation, Gynaecomastia, Nipple disorder, Nipple pain	uncommon
Investigations	Bacteria in sputum	very common

*Adverse reactions observed during clinical studies with IVA/TEZ in combination with ivacaftor.

The safety data from 1042 patients 12 years and older treated with Symkevi in combination with ivacaftor for up to an additional 96 weeks in a long-term safety and efficacy rollover study (study 3) were consistent with the safety data from the placebo-controlled Phase 3 studies.

Description of selected adverse reactions

Transaminase elevations

During the placebo-controlled Phase 3 studies (up to 24 weeks), the incidence of maximum transaminase (ALT or AST) >8, >5, or >3 x ULN were similar between Symkevi- and placebo-treated patients; 0.2%, 1.0%, and 3.4% in Symkevi-treated patients, and 0.4%, 1.0%, and 3.4% in placebo-treated patients. One patient (0.2%) on therapy and two patients (0.4%) on placebo permanently discontinued treatment for elevated transaminases. No patients treated with Symkevi experienced a transaminase elevation >3 x ULN associated with elevated total bilirubin >2 x ULN.

<u>Paediatric population</u>

The safety of Symkevi in combination with ivacaftor was evaluated in 124 patients between 6 to less than 12 years of age. The tezacaftor 100 mg/ivacaftor 150 mg and ivacaftor 150 mg dose has not been investigated in clinical trials in children aged 6 to less than 12 years weighing 30 to < 40 kg.

The safety profile is generally consistent among children and adolescents, and is also consistent with adult patients.

During the 24-week, open-label Phase 3 study in patients aged 6 to less than 12 years (study 5, n=70), the incidence of maximum transaminase (ALT or AST) >8, >5, and >3 x ULN were 1.4%, 4.3%, and 10.0%, respectively. No Symkevi-treated patients experienced a transaminase elevation >3 x ULN associated with elevated total bilirubin >2 x ULN or discontinued Symkevi treatment due to transaminase elevations. One patient interrupted treatment due to elevated transaminases, and subsequently resumed Symkevi treatment successfully. (see section 4.4 for management of elevated transaminases).

<u>Other special populations</u>

The safety profile of Symkevi in combination with ivacaftor, including respiratory events (*e.g.*, chest discomfort, dyspnea, and respiration abnormal), was generally similar across all subgroups of patients, including analysis by age, gender, and baseline percent predicted FEV_1 ($ppFEV_1$).

<u>Reporting of suspected adverse reactions</u>

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There are no known risks due to overdose with Symkevi and there is no specific antidote available in the event of overdose. Treatment of overdose consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other respiratory system products; ATC code: R07AX31

<u>Mechanism of action</u>

Tezacaftor is a selective CFTR corrector that binds to the first Membrane Spanning Domain (MSD-1) of CFTR. Tezacaftor facilitates the cellular processing and trafficking of normal or multiple mutant forms of CFTR (including F508del-CFTR) to increase the amount of CFTR protein delivered to the cell surface, resulting in increased chloride transport *in vitro*.

Ivacaftor is a CFTR potentiator that potentiates the channel-open probability (or gating) of CFTR at the cell surface to increase chloride transport. For ivacaftor to function CFTR protein must be present at the cell surface. Ivacaftor can potentiate the CFTR protein delivered to the cell surface by tezacaftor, leading to a further enhancement of chloride transport than either active substance alone. The combination targets the abnormal CFTR protein by increasing the quantity and function of CFTR at the cell surface and subsequently increasing airway surface liquid height, and ciliary beat frequency *in vitro* in human bronchial epithelial (HBE) cells from homozygous F508del CF patients. The exact mechanisms by which tezacaftor improves cellular processing and trafficking of F508del-CFTR and ivacaftor potentiates F508del-CFTR are not known.

<u>Pharmacodynamic effects</u>

Effects on sweat chloride

In study 1 (patients homozygous for the *F508del* mutation), the treatment difference between Symkevi in combination with ivacaftor and placebo in mean absolute change from baseline in sweat chloride through week 24, was -10.1 mmol/L (95% CI: -11.4, -8.8; nominal *P*<0.0001*).

In study 2 (patients heterozygous for the *F508del* mutation and a second mutation associated with residual CFTR activity), the treatment difference in mean absolute change from baseline in sweat chloride through week 8 was -9.5 mmol/L (95% CI: -11.7, -7.3; nominal *P*<0.0001*) between Symkevi in combination with ivacaftor and placebo, and -4.5 mmol/L (95% CI: -6.7, -2.3; nominal *P*<0.0001*) between ivacaftor and placebo.

In study 4 (patients aged 6 to less than 12 years who were homozygous or heterozygous for the *F508del* mutation and a second mutation associated with residual CFTR activity), the within treatment mean absolute change in sweat chloride from baseline at week 8 was -12.3 mmol/L (95% CI: -15.3, -9.3; nominal *P* <0.0001). In subgroup analyses the mean absolute change was -12.9 mmol/L (95% CI: -16.0, -9.9) for patients with F/F and for patients with F/RF the mean absolute change was -10.9 mmol/L (95% CI: -20.8, -0.9).
*Nominal p-value, based on hierarchical testing procedure.

ECG evaluation

Neither tezacaftor nor ivacaftor prolong the QTcF interval in healthy subjects at 3 times the therapeutic dose.

<u>Clinical efficacy and safety</u>

The efficacy of Symkevi in combination with ivacaftor 150 mg tablet in adult and adolescent patients with CF was demonstrated in two Phase 3, double-blind, controlled studies (study 1 and study 2), and one Phase 3, open-label extension study (study 3).

Study 1 was a 24-week, randomised, double-blind, placebo-controlled study. A total of 504 patients aged 12 years and older (mean age 26.3 years) who were homozygous for the *F508del* mutation in the *CFTR* gene were randomised (1:1 randomization: 248 Symkevi in combination with ivacaftor, 256 placebo). Patients had a percent predicted forced expiratory volume in one second ($ppFEV_1$) at screening between 40 to 90%. The mean $ppFEV_1$ at baseline was 60.0% (range: 27.8% to 96.2%).

Study 2 was a randomised, double-blind, placebo-controlled, 2-period, 3-treatment, 8-week crossover study. A total of 244 patients aged 12 years and older (mean age 34.8 years) who were heterozygous for the *F508del* mutation and a second mutation associated with residual CFTR activity were randomised to and received sequences of treatment that included Symkevi in combination with ivacaftor, ivacaftor, and placebo. Patients had a $ppFEV_1$ at screening between 40 to 90%. The mean $ppFEV_1$ at baseline was 62.3% (range: 34.6% to 93.5%).

Patients in studies 1 and 2 continued on their standard-of-care CF therapies during the studies (*e.g.*, bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline), and were eligible to roll over into a 96-week open-label extension study (study 3). Patients had a confirmed genotype of a protocol-specified *CFTR* mutation, and a confirmed diagnosis of CF.

Patients with a history of colonization with organisms associated with a more rapid decline in pulmonary status such as *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*, or who had two or more abnormal liver function tests at screening (ALT, AST, AP, GGT ≥3 x ULN or total bilirubin ≥2 x ULN) or AST or ALT ≥5 x ULN, were excluded from both studies.

Study 1

In study 1 treatment with Symkevi in combination with ivacaftor resulted in a statistically significant improvement in $ppFEV_1$ (Table 5). The treatment difference between Symkevi (in combination with ivacaftor) and placebo for the primary endpoint of mean absolute change (95% CI) in $ppFEV_1$ from baseline through week 24 was 4.0 percentage points (95% CI: 3.1, 4.8; *P*<0.0001). Mean improvement in $ppFEV_1$ was observed at the first assessment on day 15 and sustained throughout the 24-week treatment period. Improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$, colonization with *Pseudomonas*, concomitant use of standard-of-care medications for CF, and geographic region. See Table 5 for a summary of primary and key secondary outcomes.

Table 5: Primary and key secondary efficacy analyses, full analysis set (study 1)			
Analysis	**Statistic**	**Placebo N=256**	**Symkevi in combination with Ivacaftor N=248**
Primary			
$ppFEV_1$ Baseline value	n/N Mean (SD)	256/256 60.4 (15.7)	247/248 59.6 (14.7)
	n/N Within-group change LS mean (95% CI)	256/256 -0.6 (-1.3, 0.0)	245/248 3.4 (2.7, 4.0)
Average absolute change from baseline through week 24 (percentage points)**	Treatment difference LS mean (95% CI) *P* value	4.0 (3.1, 4.8) *P*<0.0001*	
Key Secondary			

Table 5: Primary and key secondary efficacy analyses, full analysis set (study 1)			
Analysis	**Statistic**	**Placebo N=256**	**Symkevi in combination with Ivacaftor N=248**
$ppFEV_1$ Baseline value	n/N Mean (SD)	256/256 60.4 (15.7)	247/248 59.6 (14.7)
	n/N Within-group change LS mean (95% CI)	256/256 -0.5 (-1.7, 0.6)	245/248 6.3 (5.1, 7.4)
Relative change from baseline through week 24 (%)**	Treatment difference LS mean (95% CI) *P* value	6.8 (5.3, 8.3) *P*<0.0001*	
Pulmonary exacerbations	Number of subjects with events (n)/N Number of events (estimated event rate per year†)	88/256 122 (0.99)	62/248 78 (0.64)
Number of pulmonary exacerbations from baseline through week 24	Rate ratio (RR) (95% CI) *P* value	0.65 (0.48, 0.88) *P*=0.0054*	
BMI Baseline value	n/N Mean (SD)	256/256 21.12 (2.88)	248/248 20.96 (2.95)
	n/N Within-group change LS mean (95% CI)	245/256 0.12 (0.03, 0.22)	237/248 0.18 (0.08, 0.28)
Absolute change from baseline at week 24 (kg/m^2)**	Treatment difference LS mean (95% CI) *P* value	0.06 (-0.08, 0.19) *P*=0.4127#	
CFQ-R respiratory domain score Baseline value	n/N Mean (SD)	256/256 69.9 (16.6)	248/248 70.1 (16.8)
	n/N Within-group change LS mean (95% CI)	256/256 -0.1 (-1.6, 1.4)	246/248 5.0 (3.5, 6.5)
Absolute change from baseline through week 24 (points)**	Treatment difference LS mean (95% CI) *P* value	5.1 (3.2, 7.0) nominal *P*<0.0001±	

$ppFEV_1$: percent predicted forced expiratory volume in 1 second; SD: Standard Deviation; LS mean: least squares mean; CI: confidence interval; BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire-Revised.
**Mixed Effect model for repeated measures with treatment, visit, treatment-by-visit interaction, sex, age group (<18, >=18 years) at screening, baseline value, and baseline value-by-visit interaction as fixed effect.
*Indicates statistical significance confirmed in the hierarchical testing procedure.
†Estimated event rate per year calculated using 48 weeks per year.
#P value not statistically significant.
±Nominal p value, based on hierarchical testing procedure.

Symkevi in combination with ivacaftor was associated with a lower event rate per year of severe pulmonary exacerbations requiring hospitalization or IV antibiotic therapy (0.29) compared to placebo (0.54). The rate ratio versus placebo was 0.53 (95% CI: 0.34, 0.82; nominal *P*= 0.0042). Pulmonary exacerbations requiring IV antibiotic therapy were lower in the treatment group compared to placebo (RR: 0.53 [95% CI: 0.34, 0.82]; nominal *P*=0.0042). Pulmonary exacerbations requiring hospitalizations were similar between treatment groups (RR: 0.78 [95% CI: 0.44, 1.36]; *P*=0.3801).

BMI increased in both treatment groups (Symkevi in combination with ivacaftor: 0.18 kg/m^2, placebo: 0.12 kg/m^2). The treatment difference of 0.06 kg/m^2 for mean change in BMI from baseline to week 24 (95% CI: -0.08, 0.19) was not statistically significant (*P*=0.4127).

For CFQ-R respiratory domain score (a measure of respiratory symptoms relevant to patients with CF including cough, sputum production, and difficulty breathing) the percentage of subjects with at least a 4 point-increase from baseline (minimal clinically important difference) was 51.1% for Symkevi and 35.7% for placebo at week 24.

Study 2

Of the 244 patients enrolled in study 2 the following indicated mutations associated with residual CFTR activity were represented: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G,* and *3849+10kbC→T.*

In study 2 treatment with Symkevi in combination with ivacaftor resulted in a statistically significant improvement in $ppFEV_1$ (Table 6). The treatment difference between Symkevi in combination with ivacaftor- and placebo-treated patients for the primary endpoint of mean absolute change in $ppFEV_1$ from study baseline to the average of week 4 and week 8 was 6.8 percentage points (95% CI: 5.7, 7.8; *P*<0.0001). The treatment difference between ivacaftor alone- and placebo-treated patients was 4.7 percentage points (95% CI: 3.7, 5.8; *P*<0.0001) and 2.1 percentage points (95% CI: 1.2, 2.9) between Symkevi in combination with ivacaftor- and ivacaftor alone-treated patients. Mean improvement in $ppFEV_1$ was observed at the first assessment on Day 15 and sustained throughout the 8-week treatment period. Improvements in $ppFEV_1$ were observed regardless of age, disease severity, sex, mutation class, colonization with *Pseudomonas*, concomitant use of standard-of-care medications for CF, and geographic region. See Table 6 for a summary of primary and key secondary outcomes.

Table 6: Primary and key secondary efficacy analyses, full analysis set (study 2)				
Analysis	**Statistic**	**Placebo N=161**	**Ivacaftor N=156**	**Symkevi in Combination with Ivacaftor N=161**
$ppFEV_1$ Baseline value	n/N Mean (SD)	161/161 62.2 (14.3)	156/156 62.1 (14.6)	161/161 62.1 (14.7)
Absolute change from baseline to the average of week 4 and week 8 (percentage points)**	n/N Within-group change LS mean (95% CI)	160/161 -0.3 (-1.2, 0.6)	156/156 4.4 (3.5, 5.3)	159/161 6.5 (5.6, 7.3)
	Treatment difference versus placebo LS mean (95% CI) *P* value	NA NA	4.7 (3.7, 5.8) *P*<0.0001*	6.8 (5.7, 7.8) *P*<0.0001*
	Treatment difference versus IVA LS mean (95% CI)	NA	NA	2.1 (1.2, 2.9)
CFQ-R respiratory domain score Baseline value	n/N Mean (SD)	161/161 68.7 (18.3)	156/156 67.9 (16.9)	161/161 68.2 (17.5)
Absolute change from baseline to the average of week 4 and week 8 (points)**	n/N Within-group change LS mean (95% CI)	160/161 -1.0 (-2.9, 1.0)	156/156 8.7 (6.8, 10.7)	161/161 10.1 (8.2, 12.1)
	Treatment difference versus placebo LS mean (95% CI) *P* value	NA NA	9.7 (7.2, 12.2) *P*<0.0001*	11.1 (8.7, 13.6) *P*<0.0001*
	Treatment difference versus IVA LS mean (95% CI)	NA	NA	1.4 (-1.0, 3.9)
$ppFEV_1$: percent predicted forced expiratory volume in 1 second; SD: Standard Deviation; LS mean: least squares mean; CI: confidence interval; NA: not applicable; IVA: ivacaftor; CFQ-R: Cystic Fibrosis Questionnaire-Revised. **Linear Mixed Effects model with treatment, period, and study baseline $ppFEV_1$ as fixed effects and subject as a random effect. *Indicates statistical significance confirmed in the hierarchical testing procedure.				

Subgroup analysis of patients with severe lung dysfunction ($ppFEV_1$ <40)

Study 1 and study 2 included a total of 39 patients treated with Symkevi in combination with ivacaftor with $ppFEV_1$ <40. There were 23 patients with $ppFEV_1$ <40 at baseline receiving Symkevi and 24 patients receiving placebo in study 1. The mean treatment difference between Symkevi and placebo-treated patients for absolute change in $ppFEV_1$ through week 24 in this subgroup was 3.5 percentage points (95% CI: 1.0, 6.1). There were 16 patients with $ppFEV_1$ <40 at baseline receiving Symkevi, 13 receiving ivacaftor and 15 receiving placebo in study 2. The mean treatment difference between Symkevi and placebo-treated patients for absolute change in $ppFEV_1$ through the average of week 4 and week 8 was 4.4 percentage points (95% CI: 1.1, 7.8). The mean treatment difference between ivacaftor and placebo-treated patients was 4.4 percentage points (95% CI: 0.9, 7.9).

Study 3

Study 3 was a Phase 3, open-label, multicenter, rollover, 96-week study to evaluate the safety and efficacy of long-term treatment with Symkevi in combination with ivacaftor in patients from studies 1 (n=462) and 2 (n=227). Efficacy was a secondary objective for study 3 and the efficacy endpoints were not adjusted for multiplicity.

Patients who received placebo in both study 1 and study 2 demonstrated improvements in $ppFEV_1$ when treated with Symkevi in combination with ivacaftor in study 3 [Study 1: within-group change=2.1(95% CI: 0.8, 3.3) percentage points, study 2: within-group change=4.1 (95% CI: 2.2, 6.0)) percentage points]. Patients who received Symkevi in combination with ivacaftor in the parent studies and continued on treatment, showed a slight attenuation in $ppFEV_1$ in the extension study, however the overall treatment effect was still positive through 120 weeks and 104 weeks for study 1 and study 2, respectively.

Similar trends were observed for CFQ-R respiratory domain score, pulmonary exacerbation rate and BMI.

<u>Paediatric population</u>

Adolescents aged 12 years and older

Adolescents were included together with adults in the trials.

<u>*Adolescent patients with CF who were homozygous for the* F508del *mutation in the* CFTR *gene*</u>

The mean absolute change (SE) from baseline in $ppFEV_1$ was 3.5 (0.6) percentage points in the Symkevi in combination with ivacaftor group and -0.4 (0.6) percentage points in the placebo group in study 1. Patients who received Symkevi in combination with ivacaftor in study 1 and continued on treatment showed sustained improvements in $ppFEV_1$ through 96 weeks in study 3 [within-group change=1.5 (1.6) percentage points]. Patients who were previously treated with placebo and received Symkevi in combination with ivacaftor in study 3 showed an increase of 0.9 (1.7) percentage points.

The mean absolute change (SE) from baseline in BMI z-value was -0.01(0.05) kg/m^2 in the Symkevi in combination with ivacaftor group and 0.00 (0.05) kg/m^2 in the placebo group in study 1. In study 3, the change in BMI z-value in the Symkevi in combination with ivacaftor group was maintained and patients previously treated with placebo showed an increase of 0.12 (0.07) kg/m^2.

<u>*Adolescent patients with CF who were heterozygous for the* F508del *mutation and a second mutation associated with residual CFTR activity*</u>

The mean absolute change (SE) from baseline in $ppFEV_1$ was 11.7 (1.2) percentage points in the Symkevi in combination with ivacaftor group, 7.6 (1.2) percentage points in the ivacaftor group and -0.4 (1.2) percentage points in the placebo group in study 2. Patients who received Symkevi in combination with ivacaftor in study 2 and continued on treatment showed sustained improvements in $ppFEV_1$ through 96 weeks in study 3 [within-group change=16.9 (4.0) percentage points]. Patients who were previously treated with ivacaftor or placebo and received Symkevi in combination with ivacaftor in study 3 showed an increase of 4.1 (4.5) percentage points and 6.0 (3.5) percentage points, respectively.

The mean absolute change (SE) from baseline in BMI z-value was 0.24 (0.07) kg/m^2 in the Symkevi in combination with ivacaftor group, 0.20 (0.07) kg/m^2 in the ivacaftor group and 0.04 (0.07) kg/m^2 in the placebo group in study 2. In study 3, the change in BMI z-value were maintained in the Symkevi in combination with ivacaftor group (0.29 (0.22) kg/m^2, in the ivacaftor group 0.23 (0.27) kg/m^2, and in the placebo group 0.23 (0.19) kg/m^2.

Paediatric patients aged 6 to <12 years

<u>Study 4</u>

Study 4 was an 8-week, double-blind, Phase 3 trial in 67 patients aged 6 to less than 12 years (mean age 8.6 years) who were randomised 4:1 to either Symkevi or a blinding group. The Symkevi group included patients who were homozygous for the *F508del* mutation (F/F) (n=42) or heterozygous for the *F508del* mutation and a second mutation associated with residual CFTR activity (F/RF) (n=12). Blinding groups were placebo if homozygous F/F *(n=10),* or ivacaftor if heterozygous F/RF (n=3). Fifty-four patients received either tezacaftor 50 mg/ivacaftor 75 mg and ivacaftor 75 mg (patients weighing < 40 kg at baseline) or tezacaftor 100 mg/ivacaftor 150 mg and ivacaftor 150 mg (patients weighing ≥ 40 kg at baseline), 12 hours apart. Patients receiving tezacaftor/ivacaftor had a screening $ppFEV_1 \geq 70\%$ [mean baseline $ppFEV_1$ of 86.5% (range: 57.9, 124.1%)], baseline $LCI_{2.5}$ of 9.56 (range: 6.95, 15.52), and weight ≥15 kg. Patients with abnormal hepatic or renal function were excluded from the study. Abnormal hepatic impairment was defined as any two or more of ≥ 3 x ULN AST, ALT, GGT, ALP; ≥ 2 x ULN total bilirubin; or ≥ 5 x ULN ALT or AST. Abnormal renal function was defined as GFR ≤ 45 mL/min/1.73 m^2 calculated by the Counahan-Barratt equation.

In study 4, treatment with Symkevi in combination with ivacaftor resulted in a statistically significant within-group reduction from baseline in $LCI_{2.5}$ through week 8. Reduction in $LCI_{2.5}$ was observed at week 2 and was sustained through week 8. See Table 7 for a summary of primary and key secondary endpoints. Growth parameters, which were exploratory endpoints, remained stable over 8 weeks of Symkevi treatment.

Table 7: Effect of Symkevi on efficacy parameters (study 4)

Parameter	Baseline Mean (SD) N=54	Absolute change through week 8* Mean (95% CI) N=54
Primary endpoint		
$LCI_{2.5}$	9.56 (2.06)	-0.51 (-0.74, -0.29) P <0.0001
Secondary and other key endpoints		
CFQ-R respiratory domain scores (points)	84.6 (11.4)	2.3 (-0.1, 4.6)
$ppFEV_1$	86.5 (12.9)	2.8 (1.0, 4.6)
SD: standard deviation; CI: confidence interval; CFQ-R: Cystic Fibrosis Questionnaire-Revised; FEV_1: forced expiratory volume in 1 second * within-group change		

In subgroup analyses of F/F and F/RF patients, the within group mean absolute change in $LCI_{2.5}$ was -0.39 (95% CI: -0.67, -0.10) and -0.92 (95% CI: -1.65, -0.20), respectively. The within group mean change in CFQ-R respiratory domain scores in F/F and F/RF patients was 1.4 points (95% CI: -1.9, 4.7) and 5.6 points (95% CI: -2.8, 13.9), respectively.

The tezacaftor 100 mg/ivacaftor 150 mg and ivacaftor 150 mg dose has not been investigated in clinical trials in children aged 6 to less than 12 years weighing 30 to < 40 kg.

Children aged less than 6 years

The European Medicines Agency has deferred the obligation to submit the results of studies with Symkevi in combination with ivacaftor in one or more subsets of the paediatric population in cystic fibrosis. See 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

The pharmacokinetics of tezacaftor and ivacaftor are similar between healthy adult volunteers and patients with CF. Following once daily dosing of tezacaftor and twice-daily dosing of ivacaftor in patients with CF, plasma concentrations of tezacaftor and ivacaftor reach steady-state within 8 days and within 3 to 5 days, respectively, after starting treatment. At steady-state, the accumulation ratio is approximately 2.3 for tezacaftor and 3.0 for ivacaftor. Exposures of tezacaftor (administered alone or in combination with ivacaftor) increase in an approximately dose-proportional manner with increasing doses from 10 mg to 300 mg once daily. Key pharmacokinetic parameters for tezacaftor and ivacaftor at steady-state are shown in Table 8.

Table 8: Mean (SD) pharmacokinetic parameters of tezacaftor and ivacaftor at steady state in patients with CF

	Drug	C_{max} (mcg/mL)	$t_{½}$ (h)	AUC_{0-24h} or AUC_{0-12h} (mcg·h/mL)*
Tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours	Tezacaftor	6.52 (1.83)	156 (52.7)	82.7 (23.3)
	Ivacaftor	1.28 (0.440)	9.3 (1.7)	10.9 (3.89)

*AUC_{0-24h} for tezacaftor and AUC_{0-12h} for ivacaftor

Absorption

After a single dose in healthy subjects in the fed state, tezacaftor was absorbed with a median (range) time to maximum concentration (t_{max}) of approximately 4 hours (2 to 6 hours). The median (range) t_{max} of ivacaftor was approximately 6 hours (3 to 10 hours) in the fed state. The AUC of tezacaftor did not change when given with fat-containing food relative to fasted conditions. The AUC of ivacaftor when given in combination with tezacaftor increased approximately 3-fold when given with fat-containing food; therefore, Symkevi and ivacaftor should be administered with fat-containing food.

Distribution

Tezacaftor is approximately 99% bound to plasma proteins, primarily to albumin. Ivacaftor is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein and albumin. After oral administration of tezacaftor 100 mg once daily in combination with ivacaftor 150 mg every 12 hours in patients with CF in the fed state, the mean (±SD) for apparent volume of distribution of tezacaftor and ivacaftor was 271 (157) L and 206 (82.9) L, respectively. Neither tezacaftor nor ivacaftor partition preferentially into human red blood cells.

Biotransformation

Tezacaftor is metabolized extensively in humans. *In vitro* data suggested that tezacaftor is metabolized mainly by CYP3A4 and CYP3A5. Following oral administration of a single dose of 100 mg ^{14}C-tezacaftor to healthy male subjects, M1-TEZ, M2-TEZ, and M5-TEZ were the three major circulating metabolites of tezacaftor in humans, contributing to 15%, 31%, and 33% of total radioactivity, respectively. Under steady-state, for each of the metabolites, exposure to M1-TEZ, M2-TEZ and M5-TEZ is approximately 1.5-fold higher than for tezacaftor. M1-TEZ has similar potency to that of tezacaftor and is considered pharmacologically active. M2-TEZ is much less pharmacologically active than tezacaftor or M1-TEZ, and M5-TEZ is not considered pharmacologically active. Another minor circulating metabolite, M3-TEZ, is formed by direct glucuronidation of tezacaftor.

Ivacaftor is also metabolized extensively in humans. *In vitro* and *in vivo* data indicate that ivacaftor is metabolized primarily by CYP3A4 and CYP3A5. M1-IVA and M6-IVA are the two major metabolites of ivacaftor in humans. M1-IVA has approximately one-sixth the potency of ivacaftor and is considered pharmacologically active. M6-IVA is not considered pharmacologically active.

The effect of the CYP3A4*22 heterozygous genotype on tezacaftor and ivacaftor exposure is consistent with the effect of co-administration of a weak CYP3A4 inhibitor, which is not clinically relevant. No dose-adjustment of tezacaftor and ivacaftor is considered necessary. No data are available for CYP3A4*22 homozygous genotype patients.

Elimination

After oral administration of tezacaftor 100 mg once daily in combination with ivacaftor 150 mg every 12 hours in patients with CF in the fed state, the mean (±SD) for apparent clearance values of tezacaftor and ivacaftor were 1.31 (0.41) and 15.7 (6.38) L/h, respectively. After steady-state dosing of tezacaftor in combination with ivacaftor in CF patients, the mean (SD) terminal half-lives of tezacaftor and ivacaftor were approximately 156 (52.7) and 9.3 (1.7) hours, respectively. The mean (SD) elimination half-lives for M1-TEZ, M2-TEZ and M5-TEZ were similar to that of the parent compound. The mean (SD) elimination half-lives for M1-IVA and M6-IVA were 11.3 (2.12) h and 14.4 (6.14) h, respectively.

Following oral administration of ^{14}C-tezacaftor, the majority of the dose (72%) was excreted in the faeces (unchanged or as the M2-TEZ metabolite) and about 14% was recovered in urine (mostly as M2-TEZ metabolite), resulting in a mean overall recovery of 86% up to 21 days after the dose. Less than 1% of the administered dose was excreted in urine as unchanged tezacaftor, showing that renal excretion is not the major pathway of tezacaftor elimination in humans.

Following oral administration of ivacaftor alone, the majority of ivacaftor (87.8%) is eliminated in the faeces after metabolic conversion. There was negligible urinary excretion of ivacaftor as unchanged drug.

Hepatic impairment

Following multiple doses of tezacaftor and ivacaftor for 10 days, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had an approximately 36% increase in AUC and a 10% increase in C_{max} for tezacaftor, and a 50% increase in ivacaftor AUC compared with healthy subjects matched for demographics. Based on these results, a modified regimen of Symkevi is recommended for patients with moderate hepatic impairment (see Table 2 in section 4.2).

The impact of severe hepatic impairment (Child-Pugh Class C, score 10 to 15) on the pharmacokinetics of tezacaftor and ivacaftor has not been studied. The magnitude of increase in exposure in these patients is unknown but is expected to be higher than that observed in patients with moderate hepatic impairment. The use of Symkevi in patients with severe hepatic impairment is therefore not recommended unless the benefits outweigh the risks (see Table 2 in section 4.2).

No dose adjustment is considered necessary for patients with mild hepatic impairment.

Renal impairment

Tezacaftor alone or in combination with ivacaftor has not been studied in patients with moderate or severe renal impairment (creatinine clearance ≤30 mL/min) or in patients with end-stage renal disease. In a human pharmacokinetic study with tezacaftor alone, there was minimal elimination of tezacaftor and its metabolites in urine (only 13.7% of total radioactivity was recovered in the urine with 0.79% as unchanged medicinal product).

In a human pharmacokinetic study with ivacaftor alone, there was minimal elimination of ivacaftor and its metabolites in urine (only 6.6% of total radioactivity was recovered in the urine).

In population pharmacokinetic analysis, data from 147 patients on tezacaftor or tezacaftor in combination with ivacaftor in Phase 2/3 clinical studies indicated that mild renal impairment (estimated glomerular filtration rate, estimated by the modification of diet in renal disease method, 60 to ≤89 mL/min/1.73 m^2) did not affect the clearance of tezacaftor significantly. No dose adjustment is recommended for mild and moderate renal impairment. Caution is recommended when administering Symkevi in combination with ivacaftor to patients with severe renal impairment or end-stage renal disease.

Gender

The pharmacokinetic parameters of tezacaftor and ivacaftor are similar in males and females.

Race

Very limited PK data indicate comparable exposure to tezacaftor in white (n=652) and non-white (n=8) patients. Race had no clinically meaningful effect on the PK of ivacaftor in white (n=379) and non-white (n=29) patients based on a population PK analysis.

Elderly

Clinical trials of Symkevi in combination with ivacaftor did not include patients over 75 years of age. The pharmacokinetic parameters of tezacaftor in combination with ivacaftor in the elderly patients (65 to 72 years) are comparable to those in younger adults.

Paediatric population

The pharmacokinetic parameters of tezacaftor and ivacaftor are presented in Table 9. The pharmacokinetics of tezacaftor/ivacaftor in children below 6 years of age has not been investigated.

Table 9. Mean (SD) tezacaftor and ivacaftor exposure by age group				
Age group	**Dose**	**Tezacaftor Mean (SD) $AUC_{0\text{-}24h}$ (mcg·h/mL)**	**Ivacaftor Mean (SD) $AUC_{0\text{-}12h}$ (mcg·h/mL)**	**M1-TEZ Mean (SD) $AUC_{0\text{-}24h}$ (mcg·h/mL)**
6 to < 12 < 30 kg	TEZ 50 mg qd/ IVA 75 mg q12h	58.9 (17.5)	7.1 (1.95)	126 (30.0)
6 to < 12 ≥ 30 kg*	TEZ 100 mg qd/ IVA 150 mg q12h	107 (30.1)	11.8 (3.89)	193 (45.8)
Adolescents	TEZ 100 mg qd/ IVA 150 mg q12h	97.1 (35.8)	11.4 (5.5)	146 (35.7)
Adults	TEZ 100 mg qd/ IVA 150 mg q12h	85.9 (28.0)	11.4 (4.14)	126 (34.9)
*Exposures in ≥ 30 kg to < 40 kg weight range are predictions derived from the population PK model.				

5.3 Preclinical safety data

Tezacaftor

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development. Placental transfer of tezacaftor was observed in pregnant rats.

Ivacaftor

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Ivacaftor was associated with slight decreases of the seminal vesicle weights, a decrease of overall fertility index and number of pregnancies in females mated with treated males and significant reductions in number of corpora lutea and implantation sites with subsequent reductions in the average litter size and average number of viable embryos per litter in treated females. The No Observed Adverse Effect Level (NOAEL) for fertility findings provides an exposure level of approximately 5 times the systemic exposure of ivacaftor and its metabolites when administered as tezacaftor/ivacaftor in adult humans at the maximum recommended human dose (MRHD).

In the pre- and post-natal study ivacaftor decreased survival and lactation indices and caused a reduction in pup body weights. The NOAEL for viability and growth in the offspring provides an exposure level of approximately 4 times the systemic exposure of ivacaftor and its metabolites when administered as tezacaftor/ivacaftor in adult humans at the MRHD. Placental transfer of ivacaftor was observed in pregnant rats and rabbits.

Findings of cataracts were observed in juvenile rats dosed from postnatal day 7 through 35 at ivacaftor exposure levels of 0.25 times the MRHD based on systemic exposure of ivacaftor and its metabolites when administered as tezacaftor/ivacaftor. This finding has not been observed in fetuses derived from rat dams treated with ivacaftor on gestation days 7 to 17, in rat pups exposed to ivacaftor through milk ingestion up to postnatal day 20, in 7-week-old rats, nor in 3.5- to 5-month-old dogs treated with ivacaftor. The potential relevance of these findings in humans is unknown.

Tezacaftor/ivacaftor

Combination repeat-dose toxicity studies in rats and dogs involving the co-administration of tezacaftor and ivacaftor to assess the potential for additive and/or synergistic toxicity did not produce any unexpected toxicities or interactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hypromellose acetate succinate
Sodium laurilsulfate (E487)
Hypromellose 2910 (E464)
Microcrystalline cellulose (E460(i))
Croscarmellose sodium (E468)
Magnesium stearate (E470b)

Tablet film coat (Symkevi 50 mg/75 mg film-coated tablets)

Hypromellose 2910 (E464)
Hydroxypropyl cellulose (E463)
Titanium dioxide (E171)
Talc (E553b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister consisting of PCTFE (polychlorotrifluoroethylene)/PVC (polyvinyl chloride) with a paper-backed aluminum foil lidding.

Pack size of 28 tablets (4 blister cards of 7 tablets each).

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Europe) Limited
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United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

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