



Australian Government  
Department of Health  
Therapeutic Goods Administration

# Australian Public Assessment Report for Tezacaftor/Ivacaftor and Ivacaftor

Proprietary Product Name: Symdeko

Sponsor: Vertex Pharmaceuticals Australia Pty  
Ltd

**October 2019**

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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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## Common abbreviations

Abbreviation	Meaning
$\geq$	Greater than or equal to
$\leq$	Less than or equal to
~	Approximately
<	Less than
>	Greater than
ABC	Adenosine triphosphate binding cassette
ACM	Advisory Committee on Medicines
AE	Adverse event
ALT	Alanine transaminase
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
AST	Aspartate transaminase
AUC	Area under the concentration versus time curve
$AUC_{0-\infty}$	AUC from the time of dosing extrapolated to infinity
$AUC_{0-t}$	AUC from the time of dosing to time t
BCRP	Breast cancer resistance protein
BID	Two times a day (Latin: <i>Bis in die</i> )
BMI	Body mass index
BP/Ph. Eur	British Pharmacopoeia /European Pharmacopoeia
CF	Cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	Cystic fibrosis transmembrane conductance regulator
CFTRm	CFTR modulator
CI	Confidence interval
$C_{max}$	Maximum observed concentration

Abbreviation	Meaning
CMI	Consumer Medicine Information
CNS	Central nervous system
CPK	Creatine phosphokinase
CSR	Clinical Study Report
CYP	Cytochrome P450
DIOS	Distal intestinal obstruction syndrome
DLP	Data lock point
EC <sub>50</sub>	Concentration resulting in 50% of the maximum inhibition
ECG	Electrocardiogram
EMA	European Medicines Agency (EU)
EU	European Union
EU-RMP	EU-Risk Management Plan
F/F	Subjects homozygous for the F508del CFTR mutation
F/G551D	F508del/G551D mutation
F/RF	Subjects heterozygous for the F508del CFTR mutation and a second mutation that results in residual CFTR function
F508del	CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FDA	Food and Drug Administration (USA)
FDC	Fixed dose combination
FEV1	Forced expiratory volume in 1 second
FRT	Fischer rat thyroid
FSH	Follicle-stimulating hormone
G551D	CFTR missense gene mutation that results in the replacement of a glycine residue at position 551 of CFTR with an aspartic acid residue
GCP	Good Clinical Practice
GI	Gastrointestinal

Abbreviation	Meaning
GLP	Good Laboratory Practice
GVP	Good Pharmacovigilance Practice
HBE	Human bronchial epithelia cells
hERG	Human ether-à-go-go related gene
IC <sub>50</sub>	Concentration resulting in 50% of the maximum inhibition
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IR	Infrared
IVA	Ivacaftor
L	Litre
LFT	Liver function test
LH	Luteinizing hormone
LS	Least squares
LUM	Lumacaftor
M1	Tezacaftor metabolite 1
M2	Tezacaftor metabolite 2
M5	Tezacaftor metabolite 5
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Millilitre
mRNA	Messenger ribonucleic acid
MSD1	Membrane spanning domain 1
NOAEL	No observed adverse effect level
OATP	Organic anion transporter protein
OCT	Organic cation transporter

Abbreviation	Meaning
OLE	Open label extension
PASS	Post Authorisation Safety Study
PD	Pharmacodynamic(s)
PEx	Pulmonary exacerbations
P-gp	P-glycoprotein
PI	Product Information
PK	Pharmacokinetic(s)
PO	By mouth (Latin: <i>Per os</i> )
popPK	Population pharmacokinetic(s)
ppFEV1	Percent predicted FEV1
PSUR	Periodic safety update report
q12h	12 hourly
qd	Once daily
QT	QT interval
QTc	QT interval corrected
RF	Residual function
RMP	Risk management plan
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SDD	Spray dried dispersions
SOC	System Organ Class
TEAEs	Treatment emergent adverse events
TEZ	Tezacaftor
TGA	Therapeutic Goods Administration
t <sub>max</sub>	Time of maximum concentration

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Abbreviation	Meaning
ULN	Upper limit of normal
US	United States(of America)
USP	United States Pharmacopeia
VX-661	Tezacaftor (drug development code name)
µg	Microgram

## I. Introduction to product submission

### Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	1 March 2019
<i>Date of entry onto ARTG:</i>	5 March 2019
<i>ARTG number:</i>	298329
<i>, Black Triangle Scheme</i>	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
<i>Active ingredients:</i>	Tezacaftor/ivacaftor and ivacaftor
<i>Product name:</i>	Symdeko
<i>Sponsor's name and address:</i>	Vertex Pharmaceuticals Australia Pty Ltd Suite 3 Level 3/601 Pacific Highway St Leonards NSW 2065
<i>Dose form:</i>	Film coated tablets, composite pack
<i>Strengths:</i>	Tezacaftor 100 mg/ivacaftor 150 mg fixed dose combination and ivacaftor 150 mg
<i>Container:</i>	Blister pack
<i>Pack size:</i>	56 tablets
<i>Approved therapeutic use:</i>	<i>Symdeko is indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence. Refer to Table 1 for a list of responsive mutations.</i>
<i>Route of administration:</i>	Oral
<i>Dosage:</i>	The recommended dose is one tablet (tezacaftor 100 mg/ivacaftor 150 mg) taken in the morning and one tablet (ivacaftor 150 mg) taken in the evening, approximately 12 hours apart. For further details please see the Product Information (PI).

## Product background

This AusPAR describes the application by Vertex Pharmaceuticals Australia Pty Ltd (the sponsor) to register Symdeko (tezacaftor/ivacaftor fixed dose combination and ivacaftor) for the following indication:

*Symdeko is indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence. See details of responsive mutations in section 5.1.*

Cystic fibrosis (CF) is caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein.

The inheritance of CF is autosomal recessive. There are over 1700 mutations in the CFTR gene that causes CF.<sup>1</sup> F508del is the most common cystic fibrosis causing mutation. This results in minimal or no functional expression of CFTR protein and leads to the most severe CF disease. Other mutations generally lead to some CFTR function and are often associated with milder disease.

In Australia, patients who are homozygous for the F508del mutation represent 49.3% of patients with cystic fibrosis, followed by gating mutations (G551D) and residual function mutations (R117H) affecting approximately 8% and 3.7% patients respectively.<sup>2,3</sup>

Currently, there is no cure for CF. The majority of CF therapies target the symptoms of the disease. Responsiveness to CFTR modulators will vary according to the phenotype. Ivacaftor, a CFTR potentiator, increases the probability of channel opening which works for gating mutations. CFTR correctors (tezacaftor and lumacaftor) improve intracellular trafficking of normal and mutated CFTR protein to the cell surface; increasing the amount of functional CFTR available at the cell surface for ivacaftor to act on. At the time of this submission tezacaftor was not currently approved in Australia.

Ivacaftor is approved in Australia for the treatment of CF patients with certain gating mutations. These include G551D, along with other gating mutations and R117H, which is one of the residual function mutations. At the time of this submission there was no current application for ivacaftor to extend use for other residual function mutations.

Orkambi (lumacaftor/ivacaftor) is approved for treatment of patients with CF and who are homozygous for F508del mutation.

At the time of this submission, there were no TGA approved CFTR modulators for the majority of residual function CF mutations.

## Regulatory status

Symdeko (tezacaftor/ivacaftor fixed dose combination and ivacaftor) is a new chemical entity for Australian regulatory purposes.

At the time the TGA considered this application, similar applications had been approved in European Union (EU), under the centralised procedure on 31 October 2018, in the United

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<sup>1</sup>Elborn, J.S. (2016), Cystic fibrosis. *Lancet*, 2016; 388: 2519-2531

<sup>2</sup>Cystic Fibrosis Standards of Care, Australia (2008). Bell, S.C. and Robinson, P.J. (Steering Committee Co-Chairs) Fitzgerald, D.A. (Editor). Accessed from the website of the Thoracic Society of Australia and New Zealand 20 June 2019.

<sup>3</sup> Australian cystic fibrosis data registry annual report (2016). Ruseckaite et al. Accessed from the website of Cystic Fibrosis Australia 20 June 2019

States (US) on 12 February 2018 and in Canada on 27 June 2018 for the indications as shown in Table 1.

**Table 1: Approved indications for similar drug products as of 20 November 2018**

Region	Approval Date	Product Name	Indication
EU, centralised procedure	31 October 2018	Symkevi	<i>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.</i>
USA	12 February 2018	Symdeko	<i>Symdeko is a combination of tezacaftor and ivacaftor, indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence. (12.1, 14).  If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.</i>
Canada	27 June 2018	Symdeko	<i>Symdeko (tezacaftor/ivacaftor and ivacaftor) is indicated 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, D110H, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.</i>

Symdeko (tezacaftor/ivacaftor fixed dose combination and ivacaftor) was designated an orphan drug by the TGA on 14 December 2017 for the treatment of patients with cystic fibrosis aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.

## Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

## II. Registration time line

Table 2 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

**Table 2: Timeline for Submission PM-2017-04765-1-5**

Description	Date
Submission dossier accepted and first round evaluation commenced	31 January 2018
First round evaluation completed	3 July 2018
Sponsor provides responses on questions raised in first round evaluation	3 August 2018
Second round evaluation completed	12 October 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	1 November 2018
Sponsor's pre-Advisory Committee response	20 November 2018
Advisory Committee meeting	7 December 2018
Registration decision (Outcome)	1 March 2019
Completion of administrative activities and registration on ARTG	5 March 2019
Number of working days from submission dossier acceptance to registration decision*	228

\*Statutory timeframe for standard applications is 255 working days

Evaluations included under quality findings and nonclinical findings incorporate both the first and second round evaluations.

TGA guidance at pre-submission meetings is nonbinding and without prejudice.

## III. Quality findings

### Introduction

The sponsor has submitted an application for a composite pack product, to register Symdeko film coated tablets containing one new active substance (tezacaftor) and one previously registered active substance (ivacaftor) in a film coated tablet 100/150 mg, co packaged with ivacaftor film coated tablets 150 mg.

The primary container closure system is the same for both the tezacaftor/ivacaftor fixed dose combination (FDC) and the co packaged ivacaftor tablet. The FDC tablets (100 mg/150 mg) are co packaged in a 7 tablet weekly blister card that also contains 7 times 150 mg ivacaftor tablets. Four cards are then packaged in a secondary carton to

contain a total of 56 tablets (28 of each). The proposed shelf life is 30 months, stored below 30°C.

Tezacaftor is a broad acting CFTR corrector that facilitates the cellular processing and trafficking of normal or multiple mutant forms of CFTR (including F508del CFTR) to increase the amount of functional CFTR protein delivered to the cell surface, resulting in increased chloride transport.

Ivacaftor is a CFTR potentiator that potentiates the channel open probability (or gating) of CFTR at the cell surface to increase chloride transport.

The combined effect of tezacaftor and ivacaftor is increased quantity and function of CFTR at the cell surface, resulting in increases in chloride transport, airway surface liquid height, and ciliary beat frequency. In patients who are homozygous for the F508del mutation or who have at least one tezacaftor/ivacaftor-responsive mutation in the CFTR gene, Symdeko targets the underlying cause of CF and modifies the course of the disease.

The indication proposed for the product is:

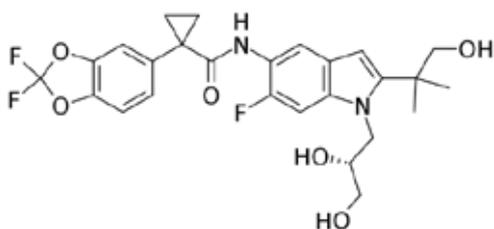
*Treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence.*

The recommended daily dose is one FDC tablet (100 mg tezacaftor/150 mg ivacaftor) in the morning and one 150 mg ivacaftor tablet in the evening, approximately 12 hours apart. This equates to a maximum daily dose of 100 mg for tezacaftor and 300 mg of ivacaftor. Patients are instructed to swallow the tablets whole and Symdeko is to be administered with fat containing food.

There are no British Pharmacopoeia /European Pharmacopoeia (BP/Ph. Eur.) or United States Pharmacopeia (USP) monographs for the drug substances or drug products relevant to the proposed product.

## Drug substance (active ingredient)

**Figure 1: Chemical structure of tezacaftor**



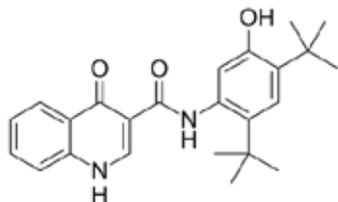
Tezacaftor is a crystalline substance which is practically insoluble in water and buffer solutions from pH 1.0 to pH 9.0. In fasted state simulated intestinal fluid, tezacaftor drug substance is practically insoluble and very slightly soluble in fed state simulated intestinal fluid at room temperature and 37°C.

Tezacaftor is produced by chemical synthesis using a convergent synthetic route. Physical characterization of tezacaftor was conducted by X-ray powder diffraction, differential scanning calorimetry, thermal gravimetric analysis and dynamic vapour sorption. The physical form of tezacaftor active substance manufactured by the proposed commercial process has been confirmed. To understand the polymorph landscape of tezacaftor, a comprehensive polymorph screening was conducted.

The drug substance is appropriately controlled by acceptable tests and limits for appearance, identity infrared (IR), assay, organic impurities, residual solvents and

palladium content. Residual solvents and heavy metals have been controlled according to the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use guidelines. Organic impurities at levels above ICH guidelines have been justified based on toxicological data.

**Figure 2: Chemical structure of ivacaftor**



The manufacture, quality control and stability of the drug substance, ivacaftor, has previously been assessed by the TGA in association with the registration of Kalydeco (ivacaftor) 150 mg film coated tablets in bottles and blisters (AUST R 198654 and 198655), and Orkambi 200/125 (lumacaftor/ivacaftor) 200/125 mg film coated tablets (AUST R 235759).

## Drug product

The immediate release ivacaftor 150 mg film coated tablet to be co packaged with the new fixed dose combination, has previously been reviewed by the TGA and approved under Kalydeco ivacaftor 150 mg film coated Tablets (AUST R 198655, PM-2012-01491-3). They are light blue, capsule shaped tablets (16.5 mm by 8.4 mm in modified caplet shape) with V150 printed on one side in black ink.

The tezacaftor/ivacaftor FDC tablets are yellow, capsule shaped tablet debossed with V100 on one side and plain on the other (15.9 mm by 8.5 mm).

The tablets are packaged in a thermoform blister. The FDC tablets are co packaged in a weekly blister card that also contains 150mg ivacaftor tablets. Four cards are then packaged in a secondary carton to contain a total of 56 tablets (28 of each).

The tezacaftor/ivacaftor FDC tablets are manufactured using tezacaftor and ivacaftor spray dried dispersions (SDD).

The tezacaftor SDD is manufactured by dissolution of the tezacaftor drug substance and then mixed with excipients, followed by spray drying, and then drying until the residual solvents meets specifications.

The ivacaftor SDD intermediate has previously been evaluated and approved in submission PM-2012-01491-3-5 under the trade name Kalydeco (AUST R 198654 and 198655).

The finished product is appropriately controlled using the finished product specifications. The specifications include acceptable tests and limits for appearance, identity (IR), assay, degradation products, uniformity of dosage, dissolution, water content, absence of crystalline drug substance and microbial purity. No degradation impurities have been identified in the finished product and all individual degradation products are controlled according to the ICH identification threshold.

A shelf life of 30 months when stored below 30°C is recommended in the proposed container closure.

Chemistry and quality control aspects are considered acceptable.

## Quality summary and conclusions

Registration of the product with respect to chemistry and quality control is recommended.

## IV. Nonclinical findings

### Introduction

The sponsor has applied to register Symdeko, a new fixed dose combination product containing tezacaftor (a new chemical entity) and ivacaftor (an existing agent, approved for monotherapy as Kalydeco).<sup>4</sup> Tezacaftor belongs to the same pharmacological class as lumacaftor, which is approved in combination with ivacaftor as Orkambi.<sup>5</sup>

Symdeko is proposed to be used for the:

*Treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence.*

The proposed PI document identifies the following mutations as responsive as shown in Table 3.

**Table 3: Mutations listed as responsive to Symdeko in the proposed PI**

<b>E56K</b>	R117C	F508del	S977F	<b>F1074L</b>	3849+10kbC→T
P67L	<b>E193K</b>	D579G	<b>F1052V</b>	D1152H	
<b>R74W</b>	L206W	711+3A→G	<b>K1060T</b>	<b>D1270N</b>	
<b>D110E</b>	R352Q	E831X	<b>A1067T</b>	2789+5G→A	
D110H	A455E	S945L	R1070W	3272-26A→G	

A patient must have two copies of the F508del mutation or at least one copy of a responsive mutation to be indicated. Evidence for responsiveness relies solely on *in vitro* data for the mutations shown in bold in the list above, while clinical data are available for the others.

Treatment involves oral administration of 100 mg tezacaftor and 150 mg ivacaftor (as a combined tablet) in the morning, and 150 mg ivacaftor in the evening, approximately 12 hours apart. This yields a maximum recommended human dose of 100 mg tezacaftor and 300 mg ivacaftor per day. The dose of ivacaftor obtained with Symdeko therapy is the same as that approved for Kalydeco and lower than that approved for Orkambi (500 mg/day). Clinical exposure to ivacaftor and its major metabolites is slightly lower with Symdeko compared with Kalydeco.

### General comments

The nonclinical dossier contained studies with tezacaftor and ivacaftor as single agents, and with the two drugs in combination. The data for ivacaftor as a single agent had been previously submitted and evaluated, and is not discussed here.

The nonclinical dossier was of high quality. All pivotal safety related studies were conducted according to Good Laboratory Practice (GLP).

<sup>4</sup>At the time of this submission the current approved indications for Kalydeco were for: treatment of cystic fibrosis (CF) in patients aged 2 years and older who have a G551D or other gating (class III) mutation in the CFTR gene, and in patients aged 6 years and older who have an R117H mutation in the CFTR gene.

<sup>5</sup>At the time of this submission the current approved indication for Orkambi were for: treatment of cystic fibrosis (CF) in patients age 6 years and older who are homozygous for the F508del mutation in the CFTR gene.

## Pharmacology

### Primary pharmacology

Tezacaftor is a CFTR corrector (increasing the amount of CFTR delivered to the cell surface) and ivacaftor is a CFTR potentiator (increasing channel open probability); both act to enhance chloride transport.

[Information redacted]

Tezacaftor was shown to act as a CFTR corrector *in vitro* in experiments with primary human and transfected rat cells.

In experiments with human bronchial epithelial cells from F508del homozygous subjects, treatment with tezacaftor:

- Produced a multi fold increase in appearance of mature glycosylated CFTR (concentration resulting in 50% of the maximum inhibition ( $EC_{50}$ ), 100 to 300 nM);
- Increased cell surface stability (from a half-life of 1.7 hours untreated to 9.0 hours (compared with 10 to 16 hours for wildtype CFTR));
- Increased chloride transport (by up to approximately (~) 7 fold, with an  $EC_{50}$  of 139 nM and a concentration of 279 nM required to increase CFTR activity to 10% of wildtype); and
- Increased airway surface liquid height.

Consistent with an effect on cellular processing and trafficking of CFTR, acute addition of tezacaftor did not increase F508del CFTR mediated chloride secretion; the maximum effect of tezacaftor was obtained after ~ 24 hours treatment (that is, enough time for de novo protein synthesis, processing and trafficking). No significant decrease in efficacy was observed following 30 days of sustained cellular treatment.

Additional increases in chloride transport and airway surface liquid height were obtained with tezacaftor and ivacaftor in combination. As well, co treatment (but neither single agent) produced a significant increase in ciliary beat frequency.

Pharmacological activity was seen for two of the three major human circulating metabolites of tezacaftor (M1, M2 and M5). M1 showed similar apparent potency and maximum efficacy compared with tezacaftor; M2 (formed by sequential oxidation of M1) was less potent (5 fold) and less efficacious (2.7 fold) than tezacaftor; M5 was pharmacologically inactive.

The effect of tezacaftor on a large number of other mutant CFTR forms was studied in assays with transfected Fischer rat thyroid (FRT) cells. Statistically significant increases in processing and trafficking were observed with tezacaftor (alone and in combination with ivacaftor) for most mutant CFTR forms examined. Chloride transport was also statistically significantly increased by tezacaftor for most tested mutants, and tezacaftor/ivacaftor combination treatment was mostly significantly more efficacious than monotherapy. The criteria for tezacaftor/ivacaftor responsiveness used in the main nonclinical efficacy study (M078) were:

- A statistically significant increase in chloride transport over baseline;
- A  $\geq 10$  percentage point increase in chloride transport over baseline as a percentage of normal CFTR; and
- A statistically significant increase in chloride transport compared to treatment with ivacaftor alone.

In the nonclinical overview in the description of responsiveness, the first criterion is omitted. In the proposed PI, the first and third criteria are omitted.

The sponsor wrote that a  $\geq 10$  percentage point increase was chosen 'because it is predictive or reasonably expected to predict clinical benefit based on extensive natural history studies and previous interventional clinical studies with CFTR modulators shown to provide clinical benefit in people with CF'. No further explanation was given, but this is consistent with clinical data compiled by the sponsor and cited in the application to register Orkambi where the mean amount of mutant CFTR mediated chloride secretion in CF patients with severe, moderate and mild lung disease was  $< 1\%$ ,  $9\%$  and  $68\%$  that of wildtype CFTR, respectively. Accordingly, increasing mutant CFTR activity to  $\geq 10\%$  of the wildtype level is expected to improve lung function in patients with severe disease to a level associated with moderate lung disease.

The increase in chloride transport considered by the sponsor is for the maximum effect obtained. So as not to over predict responsiveness, it is more appropriate to consider the level of activity specifically obtained at clinically relevant drug concentrations. While tezacaftor and ivacaftor were tested at nominal concentrations of up to  $10 \mu\text{M}$  and  $3 \mu\text{M}$ , respectively, in the assay system, lower nominal concentrations of the agents,  $3 \mu\text{M}$  and  $1 \mu\text{M}$ ; are associated with free drug levels in the assay medium ( $148 \text{ nM}$  and  $5.2 \text{ nM}$ ) more closely resembling that in patient plasma (considering the extent of protein binding and some additional contribution by pharmacologically active metabolites). The sponsor's criteria for defining responsiveness should be refined to consider  $\geq 10$  percentage point increases in chloride transport obtained with the drugs at therapeutically relevant concentrations (that is, nominal concentrations of  $3 \mu\text{M}$  for tezacaftor and  $1 \mu\text{M}$  for ivacaftor), in addition to statistically significant enhancement with the combination compared with baseline and single agent ivacaftor. In this case, the *in vitro* data supports tezacaftor/ivacaftor responsiveness for the following mutant CFTR forms as shown in Table 4.

**Table 4: Mutant CFTR forms which are responsive to tezacaftor/ivacaftor according to *in vitro* data**

E56K	<u>R117H</u>	A455E	D579G	F1074L	<u>G1349D</u>
P67L	<u>G178R</u>	<u>S549N</u>	S945L	<u>G1244E</u>	
R74W	E193K	<u>S549R</u>	K1060T	<u>S1251N</u>	
D110H	L206W	<u>G551D</u>	A1067T	<u>S1255P</u>	
R117C	R352Q	<u>G551S</u>	R1070W	D1270N	

Of these, clinical data relating to efficacy are additionally available for P67L, D110H, R117C, L206W, R352Q, A455E, D579G, S945L and R1070W.

Four mutant CFTR forms that are proposed to be included in the indication; D110E, S977F, F1052V and D1152H, did not show appropriate *in vitro* responsiveness to tezacaftor/ivacaftor under the revised criteria. While statistically significant  $\geq 10$  percentage point increases in chloride transport over Baseline as a percentage of normal CFTR *in vitro* were shown, the level of enhancement obtained with the combination at  $3/1 \mu\text{M}$  was not significantly greater than that seen with ivacaftor alone. Statistical significance was only attained when the maximum effect (compared with the effect predicted at clinically relevant concentrations) was considered. While tezacaftor is broadly acting, its potency (and the extent to which it improves processing and trafficking) varies considerably with mutation. Importantly, the *in vitro* data does predict clinically relevant enhancement of CFTR activity for Symdeko for these four CFTR mutants (and clinical efficacy data are available for S977F and D1152H); it is just that this is not predicted to be significantly greater than would be obtained with ivacaftor monotherapy.

The set of CFTR mutants for which responsiveness is seen to be adequately established from *in vitro* data is larger than identified by the sponsor in the draft PI. These additional responsive mutants are underlined in the list above. Of note, applications for approval of Symdeko made in the USA, Canada and EU included these additional mutations.

No *in vivo* pharmacodynamic studies were conducted due to the lack of an adequate disease model.

### Secondary pharmacodynamics and safety pharmacology

Tezacaftor did not rescue the processing and trafficking of two closely related misfolded mutant proteins; G601S human ether à-go-go related gene (hERG; a cardiac potassium channel, which uses similar trafficking pathways as CFTR) and G268V P-glycoprotein (P-gp, which belongs to the same superfamily of ATP binding cassette (ABC) transporters as CFTR), suggesting a level of specificity for CFTR.

The only notable secondary target identified for tezacaftor from screening assays involving an extensive panel of receptors, enzymes, transporters and ion channels was site 2 of the sodium channel. The potency for inhibition of reference ligand binding by tezacaftor was 6.64  $\mu\text{M}$  (> 50 times higher than the peak unbound concentration of tezacaftor in plasma in patients). Functional experiments using cells expressing various voltage gated sodium channel subtypes revealed no or only very weak inhibitory activity (concentration resulting in 50% of the maximum inhibition ( $\text{IC}_{50}$ ),  $\geq 17 \mu\text{M}$ ). No relevant inhibition of sodium channels is predicted in patients.

Specialised safety pharmacology studies with tezacaftor covered the central nervous system (CNS), cardiovascular, respiratory and gastrointestinal systems. Single oral administration of tezacaftor did not affect CNS function, cause adverse effects on respiration, or affect gastrointestinal motility in rats at  $\leq 200 \text{ mg/kg}$ . Inhibition of stomach emptying was seen in rats at  $\geq 100 \text{ mg/kg}$  by mouth (PO), no effect at  $30 \text{ mg/kg}$ . Tezacaftor inhibited the hERG  $\text{K}^+$  channel in transfected mammalian cells, but only very weakly (by  $< 17\%$  at  $10 \mu\text{M}$ ); M2 was also tested, with negligible hERG  $\text{K}^+$  channel inhibitory activity seen (4.5% inhibition at  $300 \mu\text{M}$ ). Heart rate was unaffected by tezacaftor in dogs ( $\leq 250 \text{ mg/kg}$  PO). Moderate increases in arterial blood pressure (17 to 25%) were observed in 2 out of 4 dogs 6 to 14 hours after dosing at  $250 \text{ mg/kg}$ , but this did not coincide with peak plasma levels and the relationship to treatment is unclear. No effect on blood pressure was seen in dogs at  $75 \text{ mg/kg}$  PO. Electrocardiogram (ECG) parameters were unaffected by tezacaftor in dogs in the specialised safety pharmacology study ( $\leq 250 \text{ mg/kg}$ ) and in general repeat dose toxicity studies ( $\leq 450 \text{ mg/kg/day}$  PO).

### Pharmacokinetics

Absorption of tezacaftor after oral administration was rapid in mice (plasma time of maximum concentration ( $T_{\text{max}}$ ) typically  $\leq 1$  hours), and slower in rats ( $T_{\text{max}}$  typically 2 to 8 hours) and dogs ( $T_{\text{max}}$  typically 2 to 4 hours), similar to humans ( $T_{\text{max}}$ , 3 hours in patients at the proposed dose). Oral bioavailability of tezacaftor was moderate in rats and dogs ( $\sim 40$  to  $50\%$ ) [not determined in humans]. Peak and overall exposure to tezacaftor (maximum observed concentration ( $C_{\text{max}}$ ) and area under the concentration versus time curve (AUC)) were generally less than dose proportional in mice, rats and dogs. Tezacaftor's plasma half-life was  $\sim 6$  to 9 hours in rats and 8 to 11 hours in dogs.

Plasma protein binding by tezacaftor was very high in humans (99.1% at  $1 \mu\text{M}$  and 99.0% at  $10 \mu\text{M}$ ), and similar in laboratory animal species (97.9 to 98.5% in mouse, rat, dog and monkey). Human serum albumin was the plasma component chiefly responsible for binding tezacaftor, with the contribution of  $\alpha_1$ -acid glycoprotein low. The major circulating metabolites of tezacaftor (M1, M2 and M5) showed similar plasma protein binding profiles

as the parent drug. Tissue distribution of tezacaftor and/or its metabolites was rapid and wide following oral administration of  $^{14}\text{C}$  tezacaftor or unlabelled drug in rats. Outside of the gastrointestinal (GI) tract, highest drug or radioactivity levels were observed in the liver, adrenal glands, kidney, pancreas and lung. Penetration of the blood: brain barrier was very low ( $C_{\text{max}}$  for tezacaftor in brain being almost 30 times lower than the plasma  $C_{\text{max}}$ ). The peak tezacaftor lung concentration was around double that in plasma, and tezacaftor was detected in the epithelial lining fluid of rats at 1.2 to 1.7 times the plasma concentration at 2 hours post dose. No melanin binding was apparent for tezacaftor.

Tezacaftor is extensively metabolised. The main metabolic pathways are dehydrogenation and subsequent intramolecular cyclisation (to form M1), glucuronidation (M3), oxidation of M1 (M2) and phosphorylation of M1 (M5). Circulating levels of M1, M2 and M5 exceeded tezacaftor in humans. M1 was also a major plasma metabolite in mice, rats and dogs, but M2 was only a minor circulating metabolite in laboratory animal species, in contrast to humans. M5 was demonstrated to be a major circulating metabolite in the rat. M1 and M2, but not M5, are seen to contribute to tezacaftor efficacy. Experiments with recombinant human cytochrome P450 (CYPs) indicated roles for CYP3A4 and CYP3A5 in the metabolism of tezacaftor. Excretion was predominantly via the faeces in rats, dogs and humans. Biliary excretion was demonstrated in the two laboratory animal species.

Comparisons of the pharmacokinetic profiles of tezacaftor in the laboratory animal species used in the pivotal repeat dose toxicity studies (rats and dogs) indicate that sufficient similarities exist to allow them to serve as appropriate models for the assessment of tezacaftor toxicity in humans except with regard to toxicity associated with M2 (due to insufficient plasma levels). Studies involving direct administration of M2 have been conducted to overcome this.

### Pharmacokinetic drug interactions

Tezacaftor, M1, M2 and M5 were investigated for inhibition of CYPs; 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 in experiments with human liver microsomes. Lowest  $\text{IC}_{50}$  values were 25  $\mu\text{M}$  for tezacaftor (against CYP3A4) and 12.1  $\mu\text{M}$  for M1 (against CYP2C8);  $\text{IC}_{50}$  values for M2 and M5 were all > 75  $\mu\text{M}$ . The  $\text{IC}_{50}$  values for the tezacaftor and M1 at the most sensitive CYPs are around 200 times the assumed peak free concentrations in patient plasma. Accordingly, no relevant CYP inhibition by tezacaftor is expected in patients.

Induction of CYP3A4 was observed with tezacaftor at  $\geq 30 \mu\text{M}$  in cultured human hepatocytes. M1 and M5 showed weak induction of CYP3A4 messenger ribonucleic acid (mRNA) too. The effect was modest, and the tested concentrations are very much higher than the peak free concentrations in plasma in patients. More significant CYP induction potential was seen with lumacaftor previously. No significant induction of CYP3A4 by tezacaftor is expected in the clinic.

Transport studies identified tezacaftor and M1 as substrates of P-glycoprotein (P-gp). Tezacaftor is also a substrate of breast cancer resistance protein (BCRP), and of organic anion transporting polypeptide 1B1 (OATP1B1). M2 is a substrate of OATP1B1 as well, and of OATP1B3. Tezacaftor and its three major human metabolites weakly inhibited P-gp, OATP1B1, OATP1B3, BCRP, OAT1, organic cation transporter 2 (OCT2) and OAT3. Of these, the most potent effect was inhibition of OATP1B1 by tezacaftor ( $\text{IC}_{50}$ , 3.2  $\mu\text{M}$ ). Assessment based on the European Medicines Agency (EMA) guidelines;<sup>6</sup> is unable to exclude interactions caused by inhibition of OATP1B1 by tezacaftor *in vivo*; the ratio of the  $\text{IC}_{50}$  to the maximum unbound drug concentration in the portal vein is 16 (where a figure of > 25 is required for no interaction to be predicted).

<sup>6</sup> European Medicines Agency (EMA) Committee for Proprietary Medicinal Products (CPMP), 6 July 2012, Guidelines on the investigation of drug interactions, CPMP/EWP/560/95/Rev.1 Corr.2

## Toxicology

### Acute toxicity

In accordance with guideline,<sup>7</sup> no single dose toxicity studies were conducted with tezacaftor. Maximum non-lethal doses of 750 mg/kg/day in mice, 150 mg/kg/day in rats and 450 mg/kg/day in dogs are evident for tezacaftor by the oral route in repeat dose toxicity studies of  $\geq 2$  weeks duration.

### Repeat dose toxicity

Studies of up to 4 weeks duration were conducted with tezacaftor in mice, 6 months in rats and 12 months in dogs. Studies with tezacaftor and ivacaftor in combination were conducted in rats (up to 3 months) and dogs (4 weeks). All studies involved once daily oral dosing, which is consistent with the clinical route and frequency of administration. The toxicity of M2 (administered subcutaneously (SC) due to poor oral bioavailability) was examined in a 4 week study in dogs. The pivotal studies were appropriately designed and conducted in terms of the species used (rats and dogs), duration (6 and 12 months), group size and range of end points examined, consistent with the relevant TGA adopted guideline.<sup>7</sup>

Animal: human exposure multiples achieved in the key toxicity studies with single agent tezacaftor are calculated in Table 5 based on comparison of plasma  $AUC_{0-24 \text{ hours}}$  for tezacaftor and M1. Relative exposure to tezacaftor at the upper dose levels tested was low in rodents and moderate in dogs. Exposure multiples for M1 were modest in rodents and low in dogs. Exposure to M2 (data not shown in the Table 5) was subclinical in all species/studies with tezacaftor. Exposure to M2 in a 4 week study in dogs that utilised direct administration of the metabolite was 2.3 times that of patients in males and 1.8 times in females at the highest dose level tested (20 mg/kg/day SC) (compared with a human  $AUC_{0-24 \text{ hours}}$  value for M2 of 121  $\mu\text{g hours/mL}$  in Study VX13-661-103). Adequate exposure multiples for tezacaftor and its pharmacologically active major metabolites have been achieved.

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<sup>7</sup> European Medicines Agency (EMA) Committee for Proprietary Medicinal Products (CPMP), 11 February 2013, Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals, ICH M3 (R2).

**Table 5: Relative tezacaftor exposure in selected repeat dose toxicity and carcinogenicity studies**

Species	Study duration [Study no.]	Dose (mg/kg /day); PO	AUC <sub>0-24 hours</sub> (µg·hours/mL)				Exposure ratio <sup>#</sup>				
			tezacaftor		M1		tezacaftor		M1		
			M	F	M	F	M	F	M	F	
<b>Mouse</b> (TgrasH2)	6 months (carcinogenicity) [VX-661-TX-019]	30	17.4	15.1	90.6	72.2	0.20	0.18	0.71	0.57	
		100	40.1	54.1	214	212	0.47	0.63	1.7	1.7	
		500	92.6	154	467	424	1.1	1.8	3.7	3.3	
<b>Rat</b> (Sprague dawley)	6 months (pivotal) [VX-661-TX-012]	25	86.7	113	133	165	1.0	1.3	1.0	1.3	
		50	174	236	290	318	2.0	2.7	2.3	2.5	
		100	226	337	449	520	2.6	3.9	3.5	4.1	
	2 years (carcinogenicity) [VX-661-TX-020]	5	19.2	28.3	34.7	34.2	0.22	0.33	0.27	0.27	
		15	73.8	-	106	-	0.86	-	0.83	-	
		20	-	109	-	139	-	1.3	-	1.1	
		50	180	-	288	-	2.1	-	2.3	-	
75	-	337	-	479	-	3.9	-	3.8			
<b>Dog</b> (Beagle)	3 months [VX-661-TX-016]	5	30.3	39.5	3.12	6.93	0.35	0.46	0.025	0.055	
		25	142	207	10.3	21.2	1.7	2.4	0.081	0.17	
		50	426	497	36.0	46.1	5.0	5.8	0.28	0.36	
	3 months [VX-661-TX-011]	50	273	323	22.0	23.1	3.2	3.8	0.17	0.18	
		150	775	559	60.9	31.9	9.0	6.5	0.48	0.25	
		450	1440	1430	75.4	79.6	17	17	0.59	0.63	
	12 months (pivotal) [VX-661-TX-013]	2	9.34	8.84	1.13	1.17	0.11	0.10	0.009	0.009	
		10	59.8	58.2	6.36	6.21	0.70	0.68	0.050	0.049	
		100	852	983	44.1	75.6	10	11	0.35	0.60	
		200	1450	2080	88.8	173	17	24	0.70	1.4	
	<b>Human</b> (patients)	Steady state [VX13-661-103]	[100 mg tezacaftor or qd + 150 mg ivacaftor BID]	85.9		127		-		-	

# = animal: human plasma AUC<sub>0-24 hours</sub>; - = not determined/not applicable; M = males; F = females; animal AUC values are for the last sampling occasion. qd = once daily, BID = two times a day.

### Major toxicities; tezacaftor

No clear target organs for toxicity for tezacaftor (or M2) were identified in the repeat dose toxicity program. Notable effects comprised inhibition of body weight gain or body weight loss, mild anaemia, and microscopic changes in the small intestine.

Marked inhibition of body weight gain was seen in rats treated with tezacaftor at 100 mg/kg/day and at all dose levels in dogs ( $\geq 2$  mg/kg/day) in the pivotal 6 and 12 month studies. This generally occurred in the absence of decreased food consumption. Mucoid/soft/watery faeces and emesis/vomitus were observed in dogs at  $\geq 100$  mg/kg/day. Watery faeces may be related to the pharmacology of tezacaftor, with CFTR involved in the regulation of water content in the GI tract, and overstimulation of CFTR (for example, because of activation of protein kinases by bacterial enterotoxins)

recognised to cause diarrhoea.<sup>8 9 10</sup> These effects are considered unlikely to be clinically relevant, with tezacaftor treatment in CF patients producing increased normalisation of CFTR activity rather than overstimulation.

Dilated lymphatics were observed in the small intestine (duodenum, jejunum and/or ileum) in rats (150 mg/kg/day for 4 weeks;  $\geq$  25 mg/kg/day for 3 months and 6 months) and dogs ( $\geq$  60 mg/kg/day for 4 weeks,  $\geq$  25 mg/kg/day for 3 months,  $\geq$  100 mg/kg/day for 6 months and  $\geq$  10 mg/kg/day for 12 months). The severity was minimal or mild in all instances except in some dogs at 250 mg/kg/day in a 4 week study, where the finding was graded up to moderate. Of particular note is the limited severity at the high dose level in the pivotal dog study, where systemic exposure to tezacaftor was  $\geq$  17 times higher than in patients and the local exposure ratio in the intestinal tract is 80 (based on comparison of mg/kg doses [assuming 40 kg body weight for a 12 year old patient]). The findings persisted in rats in the pivotal study after 4 weeks of recovery and showed slow reversibility in dogs (over 12 months following 4 weeks treatment at 100 mg/kg/day). While decreased serum albumin without decreased food consumption, to suggest a protein losing enteropathy, was seen at  $\geq$  100 mg/kg/day in the pivotal 12 month dog study, serum protein levels were unaffected despite similar microscopic changes in the other studies/dose groups, or reduced but in association with decreased food consumption. Dilated lymphatics in the small intestine were not observed with lumacaftor in studies evaluated for the registration of Orkambi (Submission PM-2015-00424-1-5), but were previously seen in rats (but not dogs) in studies with ivacaftor (at  $\geq$  200 mg/kg/day PO; Submission PM-2012-01491-3-5).

Treatment with tezacaftor was associated with small reductions in red blood cell count in rats (by 5 to 12% at 50 to 200 mg/kg/day) accompanied by a regenerative response (reticulocytes increased by up to 72%). There were no similar findings in dogs despite higher tezacaftor exposure.

#### ***Major toxicities; tezacaftor and ivacaftor in combination***

Repeat dose studies with tezacaftor and ivacaftor in combination did not identify novel or exacerbated toxicity. Dose ratios used in the combination studies were varied, but dosing at 80/20 mg/kg/day tezacaftor/ivacaftor in the pivotal 3 month study in rats produced exposure to tezacaftor, M1 and ivacaftor that reasonably paralleled the relative contribution of these components to overall exposure in patients (that is, exposure multiples of  $\sim$  3 to 4 times for all three compounds, as shown in Table 6, below).

<sup>8</sup> Field M. and Semrad C.E. (1993), Toxigenic diarrheas, congenital diarrheas, and cystic fibrosis: disorders of intestinal ion transport. *Annual Rev. Physiol*, 1993; 55: 631–655.

<sup>9</sup> Hansen M.B. and Skadhauge E. (1995), New aspects of the pathophysiology and treatment of secretory diarrhoea. *Physiol. Res*, 1995; 44: 61–78.

<sup>10</sup> Moon, C. et al. (2015) Drug-induced secretory diarrhea: A role for CFTR, *Pharmacol. Res*, 2015, 102: 107–112.

**Table 6: Relative exposure in tezacaftor/ivacaftor combination repeat dose toxicity studies**

Species	Study duration [Study no.]	Dose (mg/kg/day); PO [TEZ/IVA]	AUC <sub>0-24 hours</sub> (µg·hours/mL)			Exposure ratio <sup>#</sup>		
			TEZ	M1	IVA	TEZ	M1	IVA
<b>Rat</b> (Sprague dawley)	4 weeks [VX-661-TX- 004]	40/5	143	166	9.4	1.7	1.3	0.43
		60/10	198	212	17.6	2.3	1.7	0.81
		80/10	227	304	17.6	2.6	2.4	0.81
		100/100	160	308	350	1.9	2.4	16
	3 months (pivotal) [VX-661-TX- 014]	20/80	52.9	91.2	425	0.62	0.72	19
		40/40	177	199	218	2.1	1.6	10
80/20		335	394	62.4	3.9	3.1	2.9	
<b>Dog</b> (Beagle)	4 weeks [VX-661-TX- 003]	25/2.5	145	13.5	28.2	1.7	0.11	1.3
		25/5	123	9.1	45.4	1.4	0.07	2.1
		50/5	336	21.8	50.7	3.9	0.17	2.3
		100/60	436	15.2	411	5.1	0.12	19
<b>Human</b> (patients)	Steady state [VX13-661- 103]	[100 mg tezacaftor qd + 150 mg ivacaftor BID]	85.9	127	21.8	-	-	-

# = animal: human plasma AUC<sub>0-24 hours</sub>; - = not determined/not applicable; animal AUC values are for sexes combined at the last sampling occasion. qd = once daily, BID = two times a day. TEZ = tezacaftor, IVA = ivacaftor.

Notable findings in the combination studies comprised minimally dilated lymphatics, observed in both species (chiefly attributable to tezacaftor and not considered adverse given the severity), and decreased bone marrow cellularity (chiefly attributable to ivacaftor) with small decreases in red blood cell count and moderately increased reticulocytes (chiefly attributable to tezacaftor), seen in rats but not dogs.

### Genotoxicity

The potential genotoxicity of tezacaftor was investigated in the standard battery of tests: a bacterial reverse mutation assay, an *in vitro* chromosomal aberration assay (in Chinese hamster ovary cells) and the mouse bone marrow micronucleus test. Concentration/doses used were appropriate (up to maximum recommended levels or limited by cytotoxicity), a suitable set of *S. typhimurium* and *E. coli* strains was used in the bacterial mutagenicity assay, and the assays were appropriately validated. Negative results were returned for tezacaftor in all assays. *In vitro* assays for mutagenicity and clastogenicity were additionally performed with M2, and were also negative.

### Carcinogenicity

The carcinogenic potential of tezacaftor was investigated in a 6 month study in transgenic mice (Tg.rasH2) and a conventional 2 year study in rats. Administration was by the clinical route (oral). The design and conduct of the studies was consistent with relevant TGA adopted guidelines.<sup>11</sup> Appropriate dose levels were used, with the drug tested up to

<sup>11</sup> European Medicines Agency (EMA) Committee for Proprietary Medicinal Products (CPMP), 25 July 2002, Guideline on carcinogenic potential, ICH S1A; CPMP/SWP/2877/00.

maximally tolerated doses, but high multiples of the clinical exposure were not obtained. No tezacaftor related increase in tumours was observed in either species up to the highest doses tested; 500 mg/kg/day in transgenic mice (relative exposure to tezacaftor, 1.1 for males and 1.8 for females), 50 mg/kg/day in male rats (relative exposure, 2.1) and 75 mg/kg/day in female rats (relative exposure, 3.9). Exposure multiples for M1 were higher compared with tezacaftor in mice (3.3 to 3.7 fold) and similar compared to the parent molecule in rats. The absence of hyperplastic/pre-neoplastic lesions in the general repeat dose toxicity studies, most notably the 12 month dog study where substantial exposure to tezacaftor was obtained (exposure ratios of 17 to 24), offer further for the lack of carcinogenic potential for tezacaftor.

### Reproductive toxicity

Reproductive toxicity studies conducted with tezacaftor covered all stages (fertility, early embryonic development, embryofetal development, and pre and postnatal development). An embryofetal development study involving direct administration of M2 was also performed. Numbers of animals, species selection, dose selection, and the timing/duration of treatment were appropriate. All tezacaftor studies involved oral administration, and the M2 study involved SC administration (due to low oral bioavailability of the metabolite).

### Relative exposure

At most, low multiples (~ 2 to 3 fold) of the clinical plasma AUC were obtained for tezacaftor, M1 and M2 in embryofetal development studies in rats and rabbits (see Table 7). Doses were limited by maternotoxicity.

**Table 7: Relative exposure to tezacaftor and its major metabolites in embryofetal development studies**

Species	Study no.	Dose (mg/kg/day)	AUC <sub>0-24 hours</sub> (µg·hours/mL)			Exposure ratio <sup>#</sup>			
			TEZ	M1	M2	TEZ	M1	M2	
Rat (Sprague Dawley)	VX-661-TX- 008	Tezacaftor (PO)	25	80.4	74.5	-	0.94	0.59	-
			50	165	168	-	1.9	1.3	-
			100	276	354	-	3.2	2.8	-
Rabbit (New Zealand White)	VX-661-TX- 009		10	4.52	9.99	-	0.053	0.08	-
			25	17.4	33.1	-	0.20	0.26	-
			50	107	144	-	1.2	1.1	-
	[Information redacted]	M2 (SC)	20	-	-	78.0	-	-	0.64
			60	-	-	213	-	-	1.8
Human (patients)	VX13-661- 103	[100 mg tezacaftor QD + 150 mg ivacaftor BID]	85.9	127	121	-	-	-	

# = animal: human plasma AUC<sub>0-24 hours</sub>; - = not determined/not applicable; Animal AUC values are for the last day of dosing (Gestation Day 17 in rats and Day 20 in rabbits), TEZ = tezacaftor.

Tezacaftor and/or its metabolites were shown to cross the placenta in rats. The peak concentration of <sup>14</sup>C tezacaftor derived radioactivity in the fetus was almost half the maternal plasma C<sub>max</sub> in late pregnancy. Transfer of tezacaftor and/or its metabolites in milk was also shown in rats, with levels of <sup>14</sup>C tezacaftor derived radioactivity in milk higher than in plasma.

Fertility indices were unaffected by tezacaftor in male and female rats, although increases in the percentage of abnormal sperm and decreased corpora lutea were observed at the highest dose tested (100 mg/kg/day PO; estimated relative exposure, ~ 3). This dose exceeded the maximum tolerated dose, producing substantial inhibition of body weight gain and clinical signs in both sexes.

No teratogenicity was observed with tezacaftor in rats ( $\leq 100$  mg/kg/day PO; relative exposure to tezacaftor and M1,  $\sim 3$ ) or rabbits ( $\leq 50$  mg/kg/day PO; relative exposure, 1.1 to 1.2). M2 was also shown not to be teratogenic in rabbits ( $\leq 60$  mg/kg/day SC; relative exposure, 1.8).<sup>12</sup> The only effect on embryofetal development observed was decreased fetal weight with tezacaftor in rabbits at 50 mg/kg/day PO. This finding is attributable to concomitant maternotoxicity (evident as maternal body weight loss) and is not considered to indicate a direct effect of the drug on the developing fetus.

Pup birth weight, body weight gain and perinatal and/or pre-weaning survival were reduced, and postnatal development delayed (age of reflex attainment, pinna detachment, eye opening and sexual maturation) in rats with maternal treatment with tezacaftor at  $\geq 50$  mg/kg/day during gestation and lactation (relative exposure to tezacaftor,  $\sim 2$ ). Impaired reproductive performance was observed in the offspring of mothers dosed at 100 mg/kg/day. These effects occurred in conjunction with significant maternotoxicity and are mostly seen to be secondary to reduced body weight. Learning and memory were unaffected up to the highest dose tested. No adverse effects on pup development were seen with tezacaftor in rats at 25 mg/kg/day (estimated relative exposure,  $\sim 1$ ).

### **Pregnancy classification**

The sponsor has proposed Pregnancy Category B3.<sup>13</sup> This is considered appropriate based on the findings with tezacaftor described above and with ivacaftor in previously evaluated studies. Category B3 matches the existing categories for ivacaftor and lumacaftor/ivacaftor.

### **Paediatric use**

Symdeko is proposed for use in children  $\geq 12$  years of age. Ivacaftor is already approved in younger CF patients (alone and in combination with lumacaftor, belonging to the same pharmacological class as tezacaftor).

No juvenile animal study with tezacaftor was submitted. This is acceptable under the relevant TGA adopted guidelines;<sup>7,14</sup> with general toxicity studies, conducted in young adult animals, not identifying developing systems as targets for tezacaftor toxicity. A previously evaluated study in very young rats revealed the development of cataracts with treatment with ivacaftor.

### **Local tolerance, antigenicity and phototoxicity**

A set of adequately conducted studies indicated no dermal irritation potential for tezacaftor (in an *in vitro* assay with human epidermis constructs), showed that the drug did not act as a skin sensitiser (mouse local lymph node assay), and that tezacaftor was not phototoxic (*in vitro* assay in mouse fibroblasts). Mild ocular irritation was observed with tezacaftor *in vivo* in rabbits; the finding is not relevant to patients.

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<sup>12</sup> Another group of pregnant rabbits was initially dosed with M2 at 120 mg/kg/day, but this dose level had to be reduced to 80 mg/kg/day and then abandoned early due to severe injection site reactions. While no adverse effects on embryofetal development were seen in this group, treatment did not continue late enough into gestation for 80 mg/kg/day to be considered a credible no observed adverse effect level (NOAEL).

<sup>13</sup> Pregnancy Category B3 is defined as drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

<sup>14</sup> European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP), Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications, 24 January 2008, EMEA/CHMP/SWP/169215/2005.

## Impurities

The proposed impurity specification for the drug substance is considered to be toxicologically acceptable.

## Comments on the Nonclinical Safety Specification of the Risk Management Plan

Results and conclusions drawn from the nonclinical program for tezacaftor detailed in the sponsor's Risk Management Plan (Part II, Section SII) are in general concordance with those of the nonclinical evaluator.

## Nonclinical summary and conclusions

- 26 CFTR mutant forms are proposed to be identified as tezacaftor/ivacaftor responsive in the PI. For nine of these, evidence for efficacy relies solely on *in vitro* data.
- Treatment involves oral administration of 100 mg tezacaftor and 150 mg ivacaftor in the morning, and 150 mg ivacaftor in the evening, approximately 12 hours apart. The dose of ivacaftor with Symdeko is the same as that approved for Kalydeco (ivacaftor monotherapy) and lower than that approved for Orkambi (lumacaftor/ivacaftor); exposure is not increased compared with that already approved.
- The nonclinical dossier contained studies with tezacaftor and with tezacaftor and ivacaftor in combination, as well as previously evaluated data for ivacaftor as a single agent (not discussed here). The nonclinical dossier was of high quality, with the scope of data consistent with the relevant guideline;<sup>7</sup> and all pivotal safety related studies GLP compliant.
- Tezacaftor was shown to act as CFTR corrector *in vitro* in experiments with primary human bronchial epithelial cells and transfected FRT cells. Treatment with tezacaftor improved processing and trafficking of CFTR, increased its cell surface stability, increased chloride transport and increased airway surface height. Additional increases in chloride transport and airway surface liquid height were obtained with tezacaftor and ivacaftor in combination, and ciliary beat frequency was increased.
- Two of the major human circulating metabolites of tezacaftor have pharmacological activity. One similar (M1), and the other much less (M2), compared with the parent molecule.
- Experiments with FRT cells showed appropriately large increases in chloride transport ( $\geq 10$  percentage points over baseline as a percentage of normal CFTR) with tezacaftor and ivacaftor in combination that were statistically significant compared to baseline and compared to that obtained with ivacaftor alone across a broad set of CFTR mutants. The sponsor proposes use of the maximum *in vitro* effect to define tezacaftor/ivacaftor responsiveness; consideration of the increase specifically obtained at therapeutically relevant concentrations is warranted instead. In this case, a small number of mutants identified by the sponsor as tezacaftor/ivacaftor responsive are no longer seen to be so. This is on the basis that the increase in chloride transport obtained with the combination at therapeutically relevant concentrations, while appropriately large and statistically significant compared with baseline, is not statistically significant compared with that obtained with ivacaftor alone. These mutants are D110E, S977F, F1052V and D1152H. The availability of clinical efficacy data for S977F and D1152H that may supersede this is noted. On the other hand, there are ten additional CFTR mutants for which appropriate *in vitro* responsiveness has

been demonstrated, which the sponsor proposes not to identify in the PI document (in contrast to other jurisdictions).

- Secondary pharmacodynamic studies indicated that tezacaftor is not a general protein corrector, with two closely related misfolded mutant proteins not rescued by the drug. Tezacaftor was seen to be a weak inhibitor of voltage gated sodium channels, but no clinical significance is anticipated. Safety pharmacology studies did not indicate likely acute effects on CNS, cardiovascular, respiratory or GI function in patients.
- The pharmacokinetic profile of tezacaftor in the key laboratory animal species used in the nonclinical program was broadly similar to that in humans except with regard to circulating levels of M2. This compound was a major metabolite in human plasma but only a minor one in animals. This aspect has been addressed by the sponsor through the conduct of additional toxicity studies involving direct administration of M2.
- Plasma protein binding by tezacaftor was very high in humans (~ 99%) and similar in laboratory animal species. Tissue distribution was rapid and wide after oral administration in rats; entry into brain was very low. Metabolism of tezacaftor involved dehydrogenation to form M1 and glucuronidation to form M3. Oxidation of M1 leads to M2, and phosphorylation of M1 leads to formation of M5 (not pharmacologically active). Systemic exposure to M1 and M2 in patients is greater than to tezacaftor itself. Roles for CYP3A4 and 3A5 in the metabolism of tezacaftor were identified in *in vitro* experiments with recombinant human CYP isozymes. Excretion was predominantly via the faecal route in rats and dogs, as in humans; biliary excretion was demonstrated in the two laboratory animal species.
- *In vitro* studies did not indicate likely clinically relevant pharmacokinetic drug interactions perpetrated by tezacaftor, although *in vivo* interactions caused by inhibition of the hepatic uptake transporter OATP1B1 cannot be excluded. Of particular note (and in contrast to lumacaftor), induction of CYP3A4 by tezacaftor was modest up to the very high concentrations tested.
- A low order of acute toxicity by the oral route was evident for tezacaftor in mice, rats and dogs.
- Repeat dose toxicity studies by the oral route were conducted in mice (4 weeks), rats (up to 6 months) and dogs (up to 12 months). Tezacaftor/ivacaftor combination studies were conducted in rats (up to 3 months) and dogs (4 weeks), and the toxicity of M2 was investigated in a 4 week study in dogs. Notable findings with tezacaftor comprised inhibition of body weight gain or body weight loss, mild anaemia and microscopic changes in the small intestine. No clear target organs for toxicity were identified for tezacaftor (or M2), and combination studies did not identify novel or exacerbated toxicity.
- Tezacaftor was not genotoxic in the standard battery of tests, and not carcinogenic in a 6 month study in transgenic mice or in a 2 year study in rats.
- Fertility indices were unaffected by tezacaftor in male and female rats, and tezacaftor was not teratogenic in either the rat or the rabbit. Adverse effects on embryofetal development observed with tezacaftor were limited to decreased fetal weight in rabbits. Reductions in pup birth weight, body weight gain and survival, and developmental delays, were seen with tezacaftor in rats. The adverse effects on development were observed only at maternotoxic doses. Assignment to Pregnancy Category B3;<sup>13</sup> as the sponsor proposes, is supported.
- The impurity specification is considered to be toxicologically acceptable.

There are no nonclinical objections to the registration of Symdeko for the proposed indication on safety grounds, but it is recommended that D110E and F1052V be removed from the list of CFTR mutations identified as tezacaftor/ivacaftor responsive in the PI

document. This is based on nonclinical efficacy data for therapeutically relevant concentrations that predict no significant benefit for Symdeko compared with ivacaftor monotherapy for these mutations (and there being no clinical data). The addition of R117H, G178R, S549N, S549R, G551D, G551S, G1244E, S1251N, S1255P and G1349D is warranted from nonclinical data, however. The proposed PI document should be amended as directed.

## V. Clinical findings

A summary of the clinical findings is presented in this section.

### Introduction

#### Information on the condition being treated

CF is a progressive, systemic and genetic disease that is caused by mutations in the CFTR gene resulting in the reduced function and/or quantity of the functional CFTR protein (responsible for chloride transport) at the cell surface in multiple organs, including the lungs and pancreas. In patients with CF, loss of chloride transport due to defects in CFTR results in the accumulation of thick, sticky mucus in the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption, reproductive dysfunction, and elevated sweat chloride concentration. Lung disease (persistent lung infections and progressive lung damage) is the primary cause of morbidity and mortality in patients with CF.

More than 270 CFTR mutations are known to cause CF. Disease severity and rate of disease progression is dependent on the extent of CFTR mediated chloride transport loss associated with each of the CFTR mutations that make up a patient's genotype. CFTR mutations that result in complete or near complete loss of CFTR mediated chloride transport result in CF characterised by an early onset and relatively rapid disease progression. Examples of mutations that result in minimal CFTR function are mutations that cause a severe defect in the processing and trafficking of CFTR (for example F508del), mutations with a defect in channel gating (for example G551D), and stop codon mutations (for example G542X). Mutations that result in a more modest reduction in CFTR mediated chloride transport, referred to as a 'residual function' (RF) CFTR mutation, may result in CF that is more slowly progressive but that still eventually reaches a severe disease stage and causes premature death. The reported median age of death is 24 years for patients who are homozygous for the F508del CFTR mutation (F/F genotype) and 38 years for patients with an RF mutation.

#### Current treatment options

Currently, there is no cure for CF. The majority of CF therapies targets the symptoms of the disease. Despite these adjunctive treatments with nutritional supplements, antibiotics, and mucolytics, the overall predicted median age of survival of individuals born today with CF is approximately 40 years of age.

CFTR modulators are small molecules that target specific defects caused by mutations in the CFTR gene and thus treat the underlying cause of the disease. CFTR modulators are not intended as a replacement for or an alternative to any of the current non modulator therapies, but rather provide added benefit. The primary goal of CF modulator therapy is to maintain and restore respiratory function, as assessed by forced expiratory volume in 1 second (FEV1).

Current treatment guidelines for CF patients recommend using CFTR modulator and non-modulator medications concomitantly to maintain and improve lung function, reduce the risk of infections and exacerbations, slow disease progression, and improve quality of life. Kalydeco (ivacaftor) and Orkambi (lumacaftor/ivacaftor) are the only currently approved CFTR modulators and are indicated for CF patients with specific mutations (for example Kalydeco is approved for CF patients with G551D mutation or R117H mutation; Orkambi is approved for CF patients who are homozygous for the F508del mutation).

### **Clinical rationale**

According to the sponsor, not all patients are able to tolerate the currently approved modulator therapies. In addition, not all CFTR genotypes are indicated for the approved modulator therapies. Furthermore, people treated with Kalydeco and Orkambi continue to have a progressive decline in lung function, albeit at a slower rate than without these treatments. Therefore, the sponsor is of the opinion that new modulator treatments are needed to fulfil an unmet medical need.

Tezacaftor is a broad acting CFTR corrector that acts directly on CFTR to facilitate the cellular processing and trafficking of normal CFTR, F508del CFTR, and other mutant CFTR forms. This increases the amount of CFTR protein at the cell surface and results in increased chloride transport. The CFTR protein delivered to the cell surface by tezacaftor can be potentiated by ivacaftor to further increase chloride transport. The combination of tezacaftor and ivacaftor therefore increases both the amount and function of CFTR, resulting in greater increases in chloride transport than either tezacaftor or ivacaftor alone. The mechanism of tezacaftor/ivacaftor is the same as the approved CFTR modulator, Orkambi (lumacaftor/ivacaftor).

### **Guidance**

The sponsor has confirmed that issues identified in the pre-submission meeting had been addressed.

### **Contents of the clinical dossier**

The submission contains the following clinical information relevant to the proposed indication:

- 2 pivotal efficacy/safety studies (Studies 106 and 108);
- 3 supporting efficacy/safety studies (Study 110 (interim analysis of ongoing open label extension study), Study 101 and Study 103);
- 9 pharmacology studies.

The submission also contained a clinical overview, summary of clinical efficacy, summary of clinical safety and literature references.

In this evaluation report, Studies 106 and 108 will be evaluated as the pivotal efficacy/safety studies (Study 106 involved CF patients homozygous for the F508del CFTR mutation ('F/F'); Study 108 involved CF patients heterozygous for the F508del CFTR mutation and a second mutation that results in residual CFTR function ('F/RF')). Studies 110, 101 and 103 will be evaluated as supportive efficacy/safety studies. Study 110 is an ongoing open label study providing supportive data on the persistence of treatment effects. Studies 101 and 103 provide additional supportive efficacy data in F/F subjects.

## Paediatric data

This submission includes paediatric data involving adolescents  $\geq 12$  years of age.

## Good clinical practice

The clinical studies reviewed in this evaluation were in compliance with guidelines.<sup>15</sup>

## Pharmacokinetics

### Studies providing pharmacokinetic data

**Table 8: Submitted pharmacokinetic (PK) studies**

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose mass balance	VX13-661-005
	- Multi-dose	
	Bioequivalence† - Single dose	VX13-661-004
	- Multi-dose	VX10-661-001
	Food effect	VX13-661-004
	Food effect	VX10-661-001
PK in special populations	Target population§ - Single dose	
	- Multi-dose	VX11-661-101
	Hepatic impairment	VX15-661-009
	Renal impairment	
	Neonates/infants/children/adolescents	
	Elderly	
	Other special population	
Genetic/gender related PK	Males versus females	
	Other genetic variable	
PK interactions	Ivacaftor and Itraconazole	VX14-661-006
	Midazolam and Digoxin	VX14-661-006

<sup>15</sup> European Medicines Agency (EMA) Committee for Proprietary Medicinal Products (CPMP), July 1996, Note for Guidance on Good Clinical Practice, CPMP/ICH/135/95

PK topic	Subtopic	Study ID
	Oral Contraceptive	VX15-661-008
Population PK analyses	Healthy subjects	N032
	Target population	N019
	Target population	

† Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

No PK studies were excluded from consideration.

### Evaluator's conclusions on pharmacokinetics

The sponsor has provided a reasonably comprehensive set of studies on the PK of tezacaftor in healthy controls and patients with CF. These studies have adequately addressed the main PK issues to inform the clinical use of the medication. Most studies have used an appropriate design and were powered to meet a priori objectives. Systemic exposure of tezacaftor and ivacaftor were comparable when administered as separate tablets and in the FDC formulation used in Phase III studies. When given with fat containing food the exposure (AUC) to ivacaftor was increased, but not tezacaftor. The PK parameters of tezacaftor administered alone or in combination with ivacaftor were comparable. Similarly, there did not appear to be any significant difference in PK between healthy subjects and patients with CF. PK of tezacaftor is approximately dose proportional between 10 and 300 mg. The drug is extensively metabolised mainly by CYP3A4. Strong inducers or inhibitors of CYP3A4 are expected to alter tezacaftor systemic availability accordingly. Tezacaftor does not inhibit or induce CYP3A4. Population PK analysis suggested that body weight was the only significant covariate affecting tezacaftor clearance. In patients with moderate hepatic impairment, tezacaftor steady state AUC was increased ~ 36%. As a consequence it is recommended that tezacaftor/ivacaftor dose is reduced. There were no studies in patients with renal impairment, but given that this is a minor route of elimination it is not anticipated that dose adjustments are needed in mild to moderate impairment. Tezacaftor does not appear to alter the effectiveness of the oral contraceptive pill. Tezacaftor is a weak inhibitor of P-gp.

The PK data in the PI and Consumer Medicine Information (CMI) adequately reflect the findings of the studies presented in the application.

## Pharmacodynamics

### Studies providing pharmacodynamic data

**Table 9: Submitted pharmacodynamic (PD) studies**

PD Topic	Subtopic	Study ID
Primary Pharmacology	Sweat Chloride	VX11-661-101
	ppFEV1	VX11-661-101
Secondary	QTc study	VX15-661-010

PD Topic	Subtopic	Study ID
Pharmacology	Effect on PD parameter D	
PD Interactions	Oral Contraceptive	VX15-661-008
	Drug B	
	Drug C	
Population PD and PK-PD analyses	Target population	N019
	Target population	N021

No PD studies were excluded from consideration.

### Evaluator's conclusions on pharmacodynamics

The sponsor has provided a series of studies related to the safety and putative mechanism of action of tezacaftor in healthy subjects and patients with CF. Studies that were presented were appropriately designed. A thorough QT interval corrected (QTc) study evaluated the effects of tezacaftor taken alone at a therapeutic and suprathreshold dose in healthy volunteers. The drug did not affect the QT interval at a dose three times that proposed for clinical usage. Tezacaftor taken alone and when combined with ivacaftor, reduced sweat chloride levels. Increasing exposure to tezacaftor alone increased the percent predicted FEV1 (ppFEV1) measure but not strictly dose dependently. When combined with ivacaftor there was a dose dependent effect. The combination treatment was more effective than tezacaftor alone. On the basis of these findings and a PK/PD modelling study, the dose of the combined medication for the pivotal Phase III studies was chosen as 100 mg tezacaftor once daily (qd)/150 mg ivacaftor 12 hourly (q12h).

In a crossover study combined administration of tezacaftor/ivacaftor had no effect on follicle stimulating hormone (FSH), luteinizing hormone (LH) and progesterone serum concentrations during oral contraceptive use.

Data presented in the PI and CMI adequately reflect the results of the studies presented.

## Dosage selection for the pivotal studies

### Dose selection rationale

The dose regimen in the pivotal studies was tezacaftor 100 mg qd in the morning and ivacaftor 150 mg q12h (that is, tezacaftor/ivacaftor 100 mg/150 mg in the morning and ivacaftor 150 mg 12 hours later). The dose regimen of ivacaftor 150 mg q12h was selected for the Phase III pivotal studies because it was the approved ivacaftor dose regimen for CF patients aged 12 years and older. The dose regimen of tezacaftor 100 mg qd was selected based on results of the dose ranging Study 101 which evaluated tezacaftor doses of 10, 30, 100, and 150 mg qd, alone or in combination with ivacaftor 150 mg q12h. Results showed that there were statistically significant improvements in ppFEV1 with tezacaftor 100 mg qd/ivacaftor 150 mg q12h over placebo and no further increase in ppFEV1 over placebo with a higher tezacaftor dose (that is, tezacaftor 150 mg qd/ ivacaftor 150 mg q12h) (least squares (LS) mean treatment difference compared to placebo for the absolute changes in ppFEV1 from Baseline through Day 28 was 1.44 (95% CI: -1.43, 4.31; p = 0.3230)

percentage points with tezacaftor 10 mg qd/ivacaftor 150 mg q12h, 3.03 (95% CI: 0.19, 5.88; p = 0.0369) percentage points with tezacaftor 30 mg qd/ivacaftor 150 mg q12h, 3.89 (95% CI: 0.94, 6.83; p = 0.0101) percentage points with tezacaftor 100 mg qd/ivacaftor 150 mg q12h and 3.75 (95% CI: 0.82, 6.68; p = 0.0125) percentage points with tezacaftor 150 mg qd/ivacaftor 150 mg q12h).

These results were consistent with Phase II/III PK/PD analyses showing that exposures observed with the clinical dose of tezacaftor (100 mg qd) were on the flat part of dose response curve. An alternative regimen with the same total daily dose of tezacaftor was also evaluated in Studies 101 and 103 (tezacaftor 50 mg q12h/ivacaftor 150 mg q12h) but resulted in a lower mean change in ppFEV1 versus placebo. Tezacaftor 100 mg qd/ivacaftor 150 mg q12h was therefore selected to be the dosing regimen for the pivotal Phase III studies (Studies 106 and 108).

In terms of study drug comparator, placebo was used as the control treatment for Study 106. The sponsor explained that this was because no CFTR modulators were approved for the F/F genotype study population at the time of study initiation in November 2014.

Study 108 was placebo and active (ivacaftor) controlled. Placebo was deemed ethical and necessary to adequately assess the benefit and safety of tezacaftor/ivacaftor in Study 108 because there were no approved CFTR modulating therapies for treatment of subjects with F/RF genotypes (study population) at the time of study conduct. An active control arm was included in Study 108 because *in vitro* and clinical data (from Study 770-113) supported the potential efficacy of ivacaftor monotherapy in patients with RF mutations. Therefore an ivacaftor control arm was included to assess the contribution of tezacaftor to ivacaftor for efficacy and to compare the safety profiles.

### **Evaluator's conclusions on dose finding for the pivotal studies**

The rationale for the dose selection and dosing regimen for the pivotal Phase III trials is sound. The choice of comparators in the pivotal studies is acceptable.

## **Efficacy**

### **Studies providing efficacy data**

Studies 106 (F/F subjects) and 108 (F/RF subjects) provided pivotal efficacy data. An interim analysis of the ongoing open label extension Study 110 provided supportive data on the persistence of treatment effects. Two Phase II studies, Studies 101 and 103, provided additional supportive efficacy data in F/F subjects.

### **Evaluator's conclusions on efficacy**

Overall, the study design, inclusion and exclusion criteria, and study endpoints of the 2 pivotal Phase III studies (Studies 106 and 108) were appropriate and in line with the recommendations of the TGA adopted guidelines.<sup>16</sup> The primary and secondary efficacy endpoints in the pivotal studies allowed assessment of the effect of Symdeko on ppFEV1, pulmonary exacerbations, respiratory symptoms (as measured by Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score), nutritional status (as measured by changes in BMI), and CFTR function (as measured by sweat chloride

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<sup>16</sup> European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP), Guideline on the clinical development of medicinal products for the treatment of cystic fibrosis, 22 October 2009, EMEA/CHMP/EWP/9147/2008-corr\*

concentration) in adolescent and adult patients (age  $\geq 12$  years) with cystic fibrosis who were homozygous for the F508del CFTR mutation (Study 106; F/F population) or heterozygous for F508del and a mutation that results in RF of the CFTR protein (Study 108; F/RF population). Baseline demographic and disease characteristics were comparable among treatment groups in each study, and were consistent with the target patient population in the respective studies.

Efficacy results were generally supportive of a positive treatment effect of Symdeko (tezacaftor/ivacaftor) in the treatment of patients with cystic fibrosis, in both the F/F and F/RF populations. Treatment with tezacaftor/ivacaftor resulted in statistically significant improvements in ppFEV1 that were sustained across all visits during the 24 week treatment period in F/F subjects in Study 106 and 8 week treatment period in F/RF subjects in Study 108. In Study 106, there was a statistically significant improvement from Baseline in absolute ppFEV1 through Week 24 in the tezacaftor/ivacaftor group compared to the placebo group (LS mean treatment difference of 4.0 percentage points;  $P < 0.0001$ ). In Study 108, there was also a statistically significant improvement in absolute ppFEV1 from Baseline to the average of Week 4 and Week 8 in the tezacaftor/ivacaftor group compared to the placebo group (LS mean treatment difference of 6.8 percentage points;  $P < 0.0001$ ). According to the sponsor, the larger improvement in ppFEV1 for the F/RF population than for the F/F population (6.8 percentage points versus 4.0 percentage points) is consistent with results from *in vitro* studies, which showed that tezacaftor/ivacaftor increased chloride transport more for RF CFTR forms than for F508del CFTR forms. In both studies, improvements in absolute change from Baseline in ppFEV1 with tezacaftor/ivacaftor were rapid in onset and were detected for both populations (F/F in Study 106 and F/RF in Study 108) by Day 15 and were sustained at each subsequent visit.

Tezacaftor/ivacaftor treatment was also associated with a statistically significantly lower event rate per year of pulmonary exacerbations (PEX) (0.64) compared to placebo (0.99) through Week 24 in the F/F population (Study 106; rate ratio versus placebo was 0.65;  $P = 0.0054$ ). In the F/RF population (Study 108), the estimated event rate of PEX through Week 8 was numerically lower for tezacaftor/ivacaftor (0.34 events per year) than for placebo (0.63 events per year), but the lower event rate was not considered statistically significant (rate ratio was 0.54;  $P = 0.1031$ ).

In terms of effect on respiratory symptoms, there was improvement in CFQ-R respiratory domain score from Baseline with tezacaftor/ivacaftor compared to placebo in both the F/F population (LS mean treatment difference versus placebo for the absolute change in CFQ-R respiratory domain score from Baseline through Week 24 of 5.1 points; nominal  $P < 0.0001$ ) and the F/RF population (LS mean treatment difference versus placebo for the absolute change in CFQ-R respiratory domain score from Baseline to the average of Week 4 and Week 8 of 11.1 points;  $P < 0.0001$ ).

In terms of effect on nutritional status, there was a numerically greater increase in BMI from Baseline to Week 24 with tezacaftor/ivacaftor compared to placebo in the F/F population (0.18 kg/m<sup>2</sup> versus 0.12 kg/m<sup>2</sup>), but the difference was not statistically significant (treatment difference of 0.06 kg/m<sup>2</sup>;  $P = 0.4127$ ). BMI was an exploratory endpoint in Study 108 and results showed that in the F/RF population, there was also a numerically greater increase in BMI from Baseline to the average of Week 4 and Week 8 with tezacaftor/ivacaftor compared to placebo (0.34 kg/m<sup>2</sup> versus 0.18 kg/m<sup>2</sup>).

Tezacaftor/ivacaftor was associated with improved CFTR function. Results showed that there was a greater reduction in the absolute sweat chloride concentration from Baseline with tezacaftor/ivacaftor compared to placebo in both the F/F population (LS mean treatment difference in absolute sweat chloride concentration from Baseline to Week 24 of -10.1 mmol/L;  $P < 0.0001$ ) and the F/RF population (LS mean treatment difference in

absolute change in sweat chloride from Baseline to the average of Week 4 and Week 8 of -9.5 mmol/L;  $P < 0.0001$ ).

Efficacy results were also generally supportive of the benefit of tezacaftor/ivacaftor over ivacaftor monotherapy. In the F/RF population in Study 108, there was statistically significantly greater improvement in the absolute change from study baseline in ppFEV1 to the average of Week 4 and Week 8 with tezacaftor/ivacaftor compared to ivacaftor monotherapy (LS mean treatment difference of 2.1 percentage points,  $P < 0.0001$ ). There was also a statistically significantly greater effect on CFTR function with tezacaftor/ivacaftor compared to ivacaftor monotherapy (mean treatment difference in absolute change in sweat chloride concentration from Baseline of -5.1 points,  $P < 0.0001$ ).

Results from the open label rollover Study 110 generally supported the persistence of effects when subjects continued on tezacaftor/ivacaftor. In subjects (F/F population) who had received tezacaftor/ivacaftor in Study 106, improvements in ppFEV1 and in CFQ-R respiratory domain score at Week 24 of Study 106 were sustained through Week 24 in Study 110 when they continued on tezacaftor/ivacaftor. In subjects (F/RF population) who had received tezacaftor/ivacaftor in Period 2 of Study 108, improvements in ppFEV1 and in CFQ-R respiratory domain score at Week 8 of Study 108 were also sustained through Week 16 in Study 110. Subjects who had received tezacaftor/ivacaftor in Study 106 maintained a low event rate per year of PEx (0.72) compared to in Study 106 (0.64), and those who had received tezacaftor/ivacaftor in Study 108 also maintained a low PEx event rate per year in Study 110 (0.20) compared to in Study 108 (0.34).

Efficacy results in the supportive Studies 101 and 103 were generally consistent with results in the pivotal Phase III studies.

Efficacy sections of the proposed PI are evaluated and found to be appropriate. With regards to the treatment of F/RF patients, the proposed indication is:

*For patients who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence.*

According to *in vitro* data, 25 RF mutations were found to be responsive to tezacaftor/ivacaftor; see Table 10.

**Table 10: RF CFTR mutations that were found to be responsive to tezacaftor/ivacaftor *in vitro***

<i>E56K</i>	<i>R117C</i>		<i>S977F</i>	<i>F1074L</i>	
<i>P67L</i>	<i>E193K</i>	<i>D579G</i>	<i>F1052V</i>	<i>D1152H</i>	
<i>R74W</i>	<i>L206W</i>	<i>711+3A→G</i>	<i>K1060T</i>	<i>D1270N</i>	
<i>D110E</i>	<i>R352Q</i>	<i>E831X</i>	<i>A1067T</i>	<i>2789+5G→A</i>	
<i>D110H</i>	<i>A455E</i>	<i>S945L</i>	<i>R1070W</i>	<i>3272-26A→G</i>	<i>3849-10kbC→T</i>

Clinical data demonstrating responsiveness to tezacaftor/ivacaftor are available for 16 of these RF mutations in the proposed indication (Study 108; see Table 11).<sup>17</sup> The remaining 9 mutations are included in the proposed indication based on meeting the criteria for *in vitro* responsiveness to tezacaftor/ivacaftor; see Table 12.

<sup>17</sup> In Study 108, eight subjects had the RF mutation R347H. However, the *in vitro* response of this mutation was not statistically significant for tezacaftor/ivacaftor compared to ivacaftor and it is therefore not included in the indication.

**Table 11: Subjects enrolled by CFTR residual function mutations on the second allele, full analysis set from Study 108**

Genotype	Placebo N = 161 n (%)	IVA N = 156 n (%)	TEZ/IVA N = 161 n (%)
<b>Class V non-canonical splice mutation</b>			
F508del/2789+5G->A	21 (13.0)	28 (17.9)	25 (15.5)
F508del/3272-26A->G	24 (14.9)	23 (14.7)	24 (14.9)
F508del/3849+10kbC->T	49 (30.4)	40 (25.6)	44 (27.3)
F508del/711+3A->G	2 (1.2)	2 (1.3)	2 (1.2)
<b>Class II to IV mutations</b>			
F508del/A455E	15 (9.3)	14 (9.0)	11 (6.8)
F508del/D110H	1 (0.6)	0	1 (0.6)
F508del/D1152H	15 (9.3)	15 (9.6)	21 (13.0)
F508del/D579G	2 (1.2)	2 (1.3)	2 (1.2)
F508del/E831X	1 (0.6)	1 (0.6)	0
F508del/L206W	4 (2.5)	2 (1.3)	4 (2.5)
F508del/P67L	10 (6.2)	12 (7.7)	11 (6.8)
F508del/R1070W	3 (1.9)	1 (0.6)	2 (1.2)
F508del/R117C	0	1 (0.6)	1 (0.6)
F508del/R347H	3 (1.9)	3 (1.9)	2 (1.2)
F508del/R352Q	1 (0.6)	2 (1.3)	2 (1.2)
F508del/S945L	9 (5.6)	9 (5.8)	7 (4.3)
F508del/S977F	1 (0.6)	1 (0.6)	2 (1.2)

**Table 12: Summary of CFTR mutations indicated as responsive to tezacaftor/ivacaftor by both clinical and *in vitro* data, or *in vitro* data only**

Clinical and In Vitro Data Available			In Vitro Data Available <sup>a</sup>	
<i>F508del</i> <sup>b</sup>	<i>S977F</i>	<i>711+3A→G</i>	<i>E56K</i>	<i>K1060T</i>
<i>P67L</i>	<i>R352Q</i>	<i>E831X</i>	<i>R74W</i>	<i>F1074L</i>
<i>D110H</i>	<i>A455E</i>	<i>2789+5G→A</i>	<i>D110E</i>	<i>D1270N</i>
<i>R117C</i>	<i>D579G</i>	<i>3272-26A→G</i>	<i>E193K</i>	
<i>L206W</i>	<i>R1070W</i>	<i>3849+10kbC→T</i>	<i>A1067T</i>	
<i>S945L</i>	<i>D1152H</i>		<i>F1052V</i>	

<sup>a</sup> These mutations were included based on *in vitro* responsiveness to TEZ/IVA. Clinical data are not available.

<sup>b</sup> A patient must have 2 copies of the *F508del* mutation or at least 1 copy of a responsive mutation to be indicated.

The sponsor has provided the rationale for the inclusion of these 9 mutations without clinical data. RF mutations are rare and this would therefore limit the amount of clinical data available. In addition, the sponsor stated that a robust and established *in vitro* model system based on the scientific understanding of the molecular basis of CFTR dysfunction had been used, and provided evidence that the *in vitro* pharmacodynamics responses were reasonably predictive of clinical efficacy responses.<sup>18</sup>

Human bronchial epithelia cells (HBE) cells derived from CF subjects homozygous for F508del (F/F-HBE) were used to demonstrate the positive *in vitro* response of F508del CFTR to tezacaftor/ivacaftor. These *in vitro* results were generally predictive of

<sup>18</sup> The criteria used to establish *in vitro* response were: (1) a statistically significant increase in chloride transport over baseline normal; (2) a ≥ 10 percentage point 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.

the positive clinical study results for the F/F subjects in Study 106. The *in vitro* studies also predicted negative clinical responses. In the FRT *in vitro* model, the F508del CFTR response to tezacaftor/ivacaftor, which represents the response of a single allele, did not reach the threshold of an increase in chloride transport over baseline of  $\geq 10$  percentage points of normal, suggesting that a single allele of F508del in the absence of a tezacaftor/ivacaftor responsive allele would not be sufficient to provide clinical benefit. These *in vitro* results were confirmed by the outcomes of Study 107, in which the population of subjects who were heterozygous for F508del and a second allele that was not predicted to respond to tezacaftor/ivacaftor did not meet the pre specified futility rules for continuing the study.

Overall, the sponsor's rationale for the inclusion of these 9 mutations without clinical data in the proposed indication is considered reasonable. This takes into account the consideration that tezacaftor/ivacaftor has been designated an orphan drug, there is no cure for CF, there is a paucity of treatments available for CF and the generally benign safety profile of tezacaftor/ivacaftor (safety data suggests that tezacaftor/ivacaftor was well tolerated with adverse events largely limited to events expected as manifestations of CF disease and, to mild to moderate symptoms such as headache).

## Safety

### Studies providing safety data

The safety data to support this submission was drawn from 13 completed clinical studies with tezacaftor/ivacaftor; 8 Phase I studies in subjects without cystic fibrosis, 2 Phase II studies (Studies 101 and 103) and 3 Phase III studies (Studies 106, 108 and 107);<sup>19</sup> and from 1 ongoing open label extension (OLE) study in subjects with CF which evaluated long term safety and for which an interim analysis (data cut-off date 6 March 2017) had been performed (Study 110). The sponsor has also provided multiple pooled integrated safety datasets involving different groupings of the safety data of these studies.

In this evaluation report, safety data from the pivotal Phase III studies 106 and 108 will be evaluated as providing pivotal safety data, with supportive data from the OLE Study 110 providing longer term safety data. Safety data from the Phase II Studies 101 and 103 and the pooled integrated safety datasets were evaluated and were found to be consistent with the safety findings in the pivotal studies, and did not raise any additional safety concerns.

### *Pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

### *Pivotal and/or main efficacy studies*

In the pivotal efficacy Studies 106 and 108, the following safety data were collected:

- Adverse events (AE) from the time of informed consent through to the end of study participation. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1;
- Safety laboratory tests (standard haematology and chemistry tests);
- Other safety variables included vital signs and pulse oximetry, 12 lead ECGs, physical examination, and ophthalmologic examinations;

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<sup>19</sup> Study 107 investigated the use of Symdeko in subjects with CF who were heterozygous for the F508del mutation and with a second *CFTR* mutation that is not likely to respond to tezacaftor and/or ivacaftor therapy (F508del/not responsive [NR])

Safety assessments were performed according to the schedule in the report.

### **Other studies**

#### *Other efficacy studies*

Study 110 provided data on AEs, vital signs, pulse oximetry, physical examination, clinical laboratory values, 12 lead ECGs, and ophthalmologic examinations (in subjects < 18 years of age (age on the date of informed consent in the parent study)).

### **Patient exposure**

In Study 106, a total of 509 subjects received at least 1 dose of study drug. The mean treatment duration was 22.9 weeks in the placebo group and 23.0 weeks in the tezacaftor/ivacaftor group. The majority of subjects received > 16 weeks of treatment (245 (95.0%) subjects in the placebo group and 238 (94.8%) subjects in the tezacaftor/ivacaftor group).

In Study 108, a total of 246 subjects received at least 1 dose of study drug. The mean treatment duration was 7.9 weeks in the tezacaftor/ivacaftor group, 8.0 weeks in the ivacaftor group, and 7.9 weeks in the placebo group. All subjects in each treatment group received at least 4 weeks of treatment.

In Study 110, a total of 867 subjects received at least 1 dose of tezacaftor/ivacaftor, with a mean exposure of 33.5 weeks at the interim data cut-off date.

Overall, the study drug exposure is adequate to assess the safety profile of tezacaftor/ivacaftor.

### **Safety issues with the potential for major regulatory impact**

#### ***Liver function and liver toxicity***

##### *Pivotal and/or main efficacy studies*

###### Study 106

The incidence of AEs associated with elevated transaminases was low and similar between tezacaftor/ivacaftor (4.0%) and placebo (5.8%). None of these events were serious or led to death. The majority of events were mild or moderate in severity and did not lead to treatment discontinuation or interruption. The incidence of AEs in the System Organ Class (SOC) of hepatobiliary disorders was low and similar between tezacaftor/ivacaftor (0.8%) and placebo (1.6%). No AEs in the SOC of hepatobiliary disorders occurred in more than 1 subject in any treatment group.

Evaluation of laboratory liver function test (LFT) results did not trigger any safety concerns. The overall incidence of subjects with transaminase elevations > 3 times the upper limit of normal (ULN) was low and similar between tezacaftor/ivacaftor (4.8%) and placebo (5.1%). No subject in the tezacaftor/ivacaftor group had a concurrent elevation of alanine transaminase (ALT) or aspartate transaminase (AST) > 3 times ULN and total bilirubin > 2 times ULN (versus one subject in the placebo group).

###### Study 108

The incidence of AEs associated with elevated transaminases was low and similar across treatment groups (2.5% (4 out of 162) with tezacaftor/ivacaftor versus 3.8% (6 out of 157) with ivacaftor versus 1.2% (2 out of 162) with placebo. None of these events were serious or led to death. The majority of events were mild or moderate in severity and did not lead to treatment discontinuation or interruption. There were no AEs in the SOC of hepatobiliary disorders.

Evaluation of laboratory LFT results did not trigger any safety concerns. The overall incidence of subjects with transaminase elevations > 3 times the ULN was low and similar among groups (0.6% with tezacaftor/ivacaftor versus 1.9% with ivacaftor versus 0.6% with placebo). No subject in the tezacaftor/ivacaftor group or placebo group had a concurrent elevation of ALT or AST > 3 times the ULN and total bilirubin > 2 times the ULN (versus one subject (0.6%) in the ivacaftor group).

#### *Other studies*

Study 110

The incidence of AEs associated with elevated transaminases was low (3.2%). The majority of AEs of elevated transaminases were considered mild in severity (16 subjects (1.8%)). There were no AEs of elevated transaminases that were serious, led to death, or led to treatment discontinuation. The incidence of AEs in the SOC of hepatobiliary disorders was low (0.6%).

Evaluation of laboratory LFT results did not trigger any safety concerns.

#### **Renal function and renal toxicity**

##### *Pivotal and/or main efficacy studies*

Studies 106 and 108

Evaluation of renal function laboratory parameters did not trigger any safety concerns.

##### *Other studies*

Study 110

Evaluation of renal function laboratory parameters did not trigger any safety concerns.

#### **Other clinical chemistry**

##### *Pivotal and/or main efficacy studies*

Studies 106 and 108

Evaluation of other clinical chemistry laboratory parameters did not trigger any safety concerns.

##### *Other studies*

Study 110

Evaluation of other clinical chemistry laboratory parameters did not trigger any safety concerns.

#### **Haematology and haematological toxicity**

##### *Pivotal and/or main efficacy studies*

Studies 106 and 108

Evaluation of haematological laboratory parameters did not trigger any safety concerns.

##### *Other studies*

Study 110

Evaluation of haematological laboratory parameters did not trigger any safety concerns.

#### **Electrocardiograph findings and cardiovascular safety**

##### *Pivotal and/or main efficacy studies*

Studies 106 and 108

Evaluation of electrocardiograph findings did not trigger any safety concerns.

*Other studies*

## Study 110

Evaluation of electrocardiograph findings did not trigger any safety concerns.

***Vital signs and clinical examination findings****Pivotal and/or main efficacy studies*

In Study 106, evaluation of vital signs, pulse oximetry and physical examination findings did not trigger any safety concerns. Ophthalmologic examination findings did not raise any safety concerns. The incidences of treatment emergent cataracts were generally similar between the tezacaftor/ivacaftor and placebo groups (6.9% (14 out of 203) with tezacaftor/ivacaftor versus 5.2% (11 out of 212) with placebo).

In Study 108, evaluation of vital signs, pulse oximetry and physical examination findings did not trigger any safety concerns.

*Other studies*

## Study 110

Evaluation of vital signs, pulse oximetry and physical examination findings did not trigger any safety concerns. Ophthalmologic examination findings did not raise any safety concerns. At the time of interim analysis, there were 2 subjects with AEs of cataract recorded after Day 1 in Study 110. This AE was recorded for 1 subject at Day 336, and reported as unlikely to be related to study drug. Another subject had an AE of cataract recorded at Day 157, which was reported as possibly related to study drug, but who had a normal eye exam without cataract at the Week 16 visit (Day 166).

**Post marketing data**

Not applicable.

**Evaluator's conclusions on safety**

Overall, safety data suggests that tezacaftor/ivacaftor was well tolerated with adverse events consistent with events expected as manifestations of CF disease. Safety results from the pivotal Studies 106 and 108 showed that the incidence of treatment related AE was similar between tezacaftor/ivacaftor and placebo (25.5% versus 25.6% in Study 106; 22.8% versus 23.5% in Study 108). The most commonly reported treatment related AEs with tezacaftor/ivacaftor in Study 106 (F/F population) were headache (3.6% versus 3.1% with placebo) and nausea (2.8% versus 1.2%); the most commonly reported treatment related AE with tezacaftor/ivacaftor in Study 108 (F/RF population) was blood creatine phosphokinase (CPK) increase (3.1% versus 3.1% with placebo).

The incidence of serious adverse events (SAE) was lower with tezacaftor/ivacaftor than with placebo (Study 106: 12.4% versus 18.2%; Study 108: 4.9% versus 8.6%). The most commonly reported SAE with tezacaftor/ivacaftor in both studies was infective pulmonary exacerbation of CF (Study 106: 9.2% versus 12.4% with placebo; Study 108: 2.5% versus 4.9% with placebo). The incidence of treatment related SAE with tezacaftor/ivacaftor was low (Study 106: 2.0% versus 1.2% with placebo; Study 108: 0% versus 1.2% with placebo).

Evaluation of incidence of AEs associated with elevated transaminases, laboratory LFT results and ophthalmologic examination findings in the pivotal studies did not trigger any safety concerns.

Safety results in Study 110 showed that continued treatment with tezacaftor/ivacaftor was generally well tolerated and was not associated with increased safety concerns. The

incidence of treatment related AEs was 19.5% (comparable with the incidence in subjects on tezacaftor/ivacaftor in Study 106 (25.5%) and Study 108 (22.8%)). The most commonly reported treatment related AE was cough (2.4%), sputum increased (2.2%) and infective pulmonary exacerbation of CF (2.2%). Among these, the incidence of treatment related SAEs was low (1.8%; comparable with the incidence in subjects on tezacaftor/ivacaftor in Study 106 (2.0%) and Study 108 (0%)). Evaluation of incidence of AEs associated with elevated transaminases, laboratory LFT results and ophthalmologic examination findings in Study 110 did not trigger any safety concerns.

Safety sections of the proposed PI are evaluated and found to be appropriate.

## First round benefit-risk assessment

### First round assessment of benefits

Table 13 summarises the assessment of benefits of Symdeko for the proposed indication at the first round evaluation.

**Table 13: Summary of first round assessment of benefits**

Indication	
Benefits	Strengths and Uncertainties
<p>Potential benefit is in the treatment of patients with cystic fibrosis who are homozygous (F/F) or heterozygous (F/RF) (with responsive mutation) for the F508del mutation.</p> <p>Currently approved CFTR modulators in Australia are Kalydeco (ivacaftor) and Orkambi (lumacaftor/ivacaftor). Approved indications for both are restricted to specific CFTR mutations. Currently approved indications for Kalydeco are for the treatment of CF in patients aged 2 years and older who have a G551D or other gating (class III) mutation in the CFTR gene, and in patients aged 6 years and older who have an R117H mutation in the CFTR gene. At the time of the first round evaluation, the currently approved indication for Orkambi is for the treatment of cystic fibrosis in patients age 12 years and older who are homozygous for the F508del mutation in the CFTR gene. There is therefore a need for more treatment options in CF patients who are homozygous or heterozygous for the F508del mutation.</p>	<p>Treatment with tezacaftor/ivacaftor resulted in statistically significant improvements in ppFEV1 that were sustained across all visits during the 24 week treatment period in F/F subjects in Study 106 and 8 week treatment period in F/RF subjects in Study 108 (mean treatment difference compared to the placebo of 4.0 percentage points (P &lt; 0.0001) and 6.8 percentage points (P &lt; 0.0001) in the F/F and F/RF populations, respectively).</p> <p>Tezacaftor/ivacaftor treatment was also associated with a statistically significantly lower event rate per year of PEx (0.64) compared to placebo (0.99) through Week 24 in the F/F population (P = 0.0054). However, in the F/RF population, the numerically lower event rate of PEx through Week 8 with tezacaftor/ivacaftor (0.34 events per year) compared to placebo (0.63 events per year) was not considered statistically significant (P = 0.1031).</p> <p>Tezacaftor/ivacaftor treatment was also associated with improved patient symptoms (improvement in CFQ-R respiratory domain score from Baseline) and CFTR function (reduction in sweat chloride from Baseline) in both the F/F and F/RF populations.</p> <p>Tezacaftor/ivacaftor had less AE than Orkambi.</p> <p>No studies on long term efficacy.</p>

## First round assessment of risks

Table 14 summarises the assessment of risks of Symdeko for the proposed indication at the first round evaluation.

**Table 14: Summary of first round assessment of risks**

Risks	Strengths and Uncertainties
<p>Safety data suggests that tezacaftor/ivacaftor was well tolerated. Adverse events were largely limited to events expected as manifestations of CF disease and, to mild to moderate symptoms such as headache.</p>	<p>The most commonly reported treatment related AEs with tezacaftor/ivacaftor in Study 106 (F/F population) were headache (3.6% versus 3.1% with placebo) and nausea (2.8% versus 1.2%). The most commonly reported treatment related AE with tezacaftor/ivacaftor in Study 108 (F/RF population) was blood CPK increased (3.1% versus 3.1% with placebo).</p> <p>Safety results in Study 110 showed that continued treatment with tezacaftor/ivacaftor was generally well tolerated and was not associated with increased safety concerns.</p> <p>Limited long term data.</p> <p>Uncertainty around use in genotypes/phenotypes not tested in clinical trials.</p>

## First round assessment of benefit-risk balance

Overall, the benefit-risk balance for the use of Symdeko in the treatment of patients with cystic fibrosis aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence is positive.

Efficacy results showed that treatment with tezacaftor/ivacaftor resulted in statistically significant improvements in ppFEV1 that were sustained across all visits during the 24 week treatment period in F/F subjects and 8 week treatment period in F/RF subjects. Safety data suggests that tezacaftor/ivacaftor was well tolerated with adverse events largely limited to events expected as manifestations of CF disease and to mild to moderate symptoms such as headache.

## First round recommendation regarding authorisation

It is recommended that the application for the registration of Symdeko in the treatment of patients with CF aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence be approved.

## Clinical questions and second round evaluation

The questions from the first round report are presented in bold italics followed by a summary of the sponsor's response and then the evaluator's assessment of the sponsor's response.

## Pharmacokinetics

### Question 1

**The population PK did not identify gender as a significant covariate influencing the PK of tezacaftor. However there was no post hoc analysis of data from the studies where multi dose PK parameters were evaluated. Does the sponsor have such an analysis?**

#### *Sponsor's response*

The sponsor presented an analysis of tezacaftor AUC<sub>0-24</sub> by gender from five studies (Studies 101, 103, 106, 107 and 108). Steady state AUC values for the tezacaftor 100 mg qd dose were simulated for the subjects in the pivotal studies administered this dose using the population pharmacokinetic (popPK) model. The analysis showed that systemic exposure for males (median of 82.4 µg·hours /mL) was similar to that for females (median of 82.0 µg·hours /mL). This analysis was consistent with popPK modeling. There is no clinically significant effect of gender on tezacaftor exposure.

#### *Evaluation of response*

The sample size included in this supplementary analysis by the sponsor was reasonably large (~ 280 males and ~ 280 females). The minimum and maximum values for AUC are within the same range for both genders and the median values are almost identical. The sponsor has provided a satisfactory response to the issue of gender differences in tezacaftor systemic exposure: there is no statistically significant difference for males and females.

### Question 1 (continued)

**Although tezacaftor is a single isomeric form, does the sponsor have any studies which might suggest or refute *in vivo* racemisation following single or multiple doses?**

#### *Sponsor's response*

The sponsor provided a rationalisation, based on the chemistry of the molecule, which suggests that it is highly unlikely that racemisation can occur *in vivo* or *in vitro*. Furthermore the formation of intermediate ketones in the side chain of the molecule, a necessary step for racemisation to occur, was not observed in metabolic studies.

#### *Evaluation of response*

The sponsor's response satisfactorily refutes any suggestion of racemisation *in vivo*.

## Pharmacodynamics

### Question 2

Does the S isomeric form of tezacaftor have pharmacological activity?

#### *Sponsor's response*

[Information redacted]

#### *Evaluation of response*

The sponsor's response is satisfactory. Since tezacaftor is proposed for administration as a single R isomer and does not undergo racemisation, the activity of the S isomer is a moot point.

### Question 2 (continued)

How does the magnitude of change in sweat chloride correlate with clinically relevant endpoints?

*Sponsor's response*

The sponsor has provided an analysis of the relationship between sweat chloride and the clinically relevant end point of ppFEV1 for all subjects participating in the clinical Studies 106 and 108. There was a general trend in the scatter diagrams for a decrease in sweat chloride to be associated with an increase in ppFEV1. The correlation coefficients are low and probably not statistically significant. As the sponsor notes 'changes in sweat chloride do not appear to fully explain the treatment benefit of CFTR modulators seen at the individual subject level'. Nevertheless the changes observed in sweat chloride would appear to be of some clinical utility indicating an on target effect of the medication.

*Evaluation of response*

The sponsor's response is satisfactory.

**Efficacy****Question 3**

Please explain the changes in BMI in the subgroups of subjects with BMI z score < 0 versus > 0 at Baseline in the 2 pivotal clinical studies.

*Sponsor's response*

The sponsor has responded to this clinical question posed in the first round of evaluation. The sponsor conducted analyses on subgroups of subjects with BMI z score < 0 and  $\geq 0$  and results showed that changes in BMI in these subgroups of subjects were consistent with the changes observed in the overall population in each study. In Study 106, the original analysis of BMI in the Study 106 full analysis set showed similar improvement in BMI in the tezacaftor/ivacaftor and placebo groups at Week 24 (LS mean (SD) of absolute change in BMI from Baseline at Week 24: 0.12 (0.05) kg/m<sup>2</sup> with placebo versus 0.18 (0.05) kg/m<sup>2</sup> with tezacaftor/ivacaftor). Analyses in the subgroups of subjects with BMI z score <0 and  $\geq 0$  also showed similar improvements in BMI in the tezacaftor/ivacaftor and placebo groups at Week 24, both for subjects with a baseline BMI z score < 0 (mean (SD) of absolute change in BMI from Baseline at Week 24: 0.23 (0.74) kg/m<sup>2</sup> with placebo versus 0.16 (0.79) kg/m<sup>2</sup> with tezacaftor/ivacaftor) and with BMI z score  $\geq 0$  (0.31 (0.87) kg/m<sup>2</sup> with placebo versus 0.24 (0.96) kg/m<sup>2</sup> with tezacaftor/ivacaftor).

In Study 108, analyses on the overall population showed that there were numerically greater increases in BMI from study baseline with tezacaftor/ivacaftor compared to placebo at Week 8 (mean absolute change from study baseline in BMI at Week 8 of 0.34 kg/m<sup>2</sup> for tezacaftor/ivacaftor, 0.47 kg/m<sup>2</sup> for ivacaftor and 0.18 kg/m<sup>2</sup> for placebo). Analyses in the subgroups of subjects with BMI z score < 0 and  $\geq 0$  showed similar results (subjects with baseline BMI z scores < 0: mean absolute change from study baseline in BMI at Week 8 of 0.75 kg/m<sup>2</sup> for tezacaftor/ivacaftor, 0.76 kg/m<sup>2</sup> for ivacaftor and 0.06 kg/m<sup>2</sup> for placebo; subjects with baseline BMI z score  $\geq 0$ : mean absolute change from study baseline in BMI at Week 8 of 1.09 kg/m<sup>2</sup> for tezacaftor/ivacaftor, 0.29 kg/m<sup>2</sup> for ivacaftor and 0.28 kg/m<sup>2</sup> for placebo).

*Evaluation of response*

The sponsor's response is satisfactory and does not materially change the benefit assessment of Symdeko.

## Second round benefit-risk assessment

### Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Symdeko in the proposed usage are unchanged from those identified in the first round assessment of benefits.

### Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Symdeko are unchanged from those identified in the first round assessment of risks.

### Second round assessment of benefit-risk balance

The benefit-risk balance of Symdeko, given the proposed usage, is favourable.

### Second round recommendation regarding authorisation

It is recommended that the application for the registration of Symdeko in the treatment of patients with CF aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence be approved.

## VI. Pharmacovigilance findings

### Risk management plan

#### Summary of risk management plan (RMP) evaluation<sup>20</sup>

- The sponsor has submitted EU RMP version 1.0; date 18 July 2017; data lock point (DLP) 6 March 2017 and Australian Specific Annex (ASA) version 1.0; dated 13 December 2017 in support of the application.
- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 15.

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<sup>20</sup> Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

**Table 15: Summary of safety concerns with associated pharmacovigilance and risk minimisation strategies**

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
<b>Important identified risks</b>	None	Ü	-	Ü	-
<b>Important potential risks</b>	Effects on liver function tests	Ü	Ü <sup>1</sup>	Ü	-
	Concomitant use of tezacaftor/ivacaftor with strong CYP3A inhibitors or inducers	Ü	Ü <sup>1</sup>	Ü	-
	Cataract	Ü	Ü <sup>1</sup>	Ü	-
<b>Missing information</b>	Use in pregnant and lactating women	Ü	Ü <sup>2</sup>	Ü	-
	Long term safety	Ü	Ü <sup>1,2</sup>	Ü	-
	Patients with moderate or severe hepatic impairment	Ü	Ü <sup>2</sup>	Ü	-
	Patients with ppFEV1 < 40	Ü	Ü <sup>2</sup>	Ü	-

1) Interventional study; 2) Non interventional study through patient registries.

- Routine pharmacovigilance and additional studies have been proposed by the sponsor. This combined approach is acceptable.
- Routine risk minimisation has been proposed for all the safety concerns. This is acceptable.

### **New and outstanding recommendations from second round evaluation**

All the recommendations made in the first round RMP evaluation report have been satisfactorily addressed.

- This report predates the availability of the second round clinical and nonclinical evaluation reports. Safety concerns that may be raised by the clinical or nonclinical evaluators in the second round reports should be addressed with the relevant evaluation areas. If the relevant recommendations have an impact on the safety profile and relevant pharmacovigilance and/or risk minimisation activities, the sponsor should provide information that is relevant and necessary to address the issues in a revised RMP.

### **Proposed wording for conditions of registration**

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available

version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

The Symdeko EU-Risk Management Plan (RMP) (version 1.0; date 18 July 2017; DLP 6 March 2017), with Australian Specific Annex (version 1.0; date 13 December 2017 included with submission PM-2017-04765-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

The following wording is recommended for the periodic safety update report (PSUR) requirement:

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

As Symdeko contains a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

Symdeko (tezacaftor/ivacaftor) is to be included in the Black Triangle Scheme. The PI and CMI for Symdeko must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

## VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

### Background

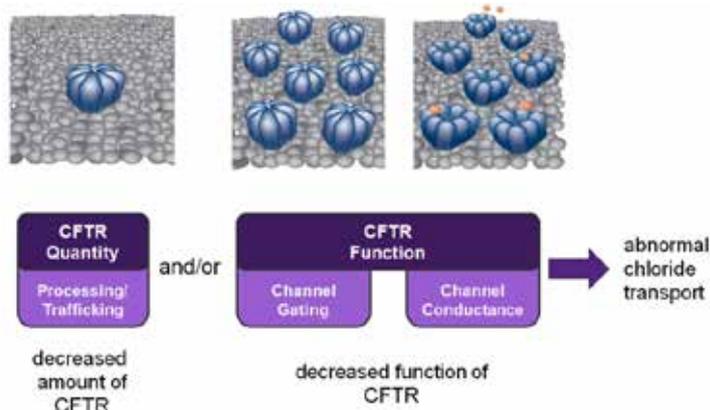
CF is caused by mutations in the gene encoding the CFTR protein. CFTR functions as a regulated chloride channel. The inheritance of CF is autosomal recessive. There are over 1700 mutations in the CFTR gene that cause CF. These are broadly classified as homozygous (with two copies of F508) and heterozygous mutations (when there are two different CF genes; one of which is usually F508del).<sup>21</sup>Homozygous F508del is the most common cystic fibrosis causing mutation. This results in minimal or no functional

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<sup>21</sup>Elborn, J.S. (2016), Cystic fibrosis. *Lancet*, 2016; 388: 2519-2531

expression of CFTR protein and hence leads to the most severe CF disease manifestations. Heterozygous mutations generally lead to some CFTR function and hence are often associated with milder disease. Clinical disease requires disease causing mutations in both copies of the CFTR gene. Each pair of mutations can have a range of effects on the functioning of chloride channel. The functional change of the CFTR protein depends upon the amount of CFTR protein present at cell surface and to the extent to which the mutation has affected CFTR protein's functioning as an effective chloride channel (see Figure 3).<sup>1</sup>

**Figure 3: Pathophysiology of cystic fibrosis**



From a clinical perspective, cystic fibrosis is defined in terms of symptoms or signs of disease in one or more system; and a positive sweat chloride > 60 mmol/L or borderline sweat chloride (30 to 60 mmol/L) and two CF related mutations.<sup>22</sup> Disease severity and rate of disease progression vary depending on the mutation involved. Similarly, responsiveness to CFTR modulators will vary according to the phenotype.

In Australia, patients who are homozygous for the F508del mutation represent 49.3% of patients with cystic fibrosis, followed by gating mutations (G551D) and residual function mutations (R117H) affecting approximately 8% and 3.7% patients respectively.<sup>23 24</sup>

Ivacaftor, a CFTR potentiator, increases the probability of channel opening which works for gating mutations. CFTR correctors tezacaftor and lumacaftor improves intracellular trafficking of normal and mutated CFTR protein to the cell surface; thereby increasing the amount of functional CFTR available at the cell surface for ivacaftor to act on. At the time of this submission tezacaftor was not currently approved in Australia. Ivacaftor is approved by TGA for the treatment of CF patients with heterozygous mutations (see Table 16). These include G551D, along with other gating mutations and R117H, which is one of the residual function mutations. At the time of this submission there was no current application for ivacaftor to extend use for other residual function mutations.

Orkambi (lumacaftor/ivacaftor) is approved for treatment of patients with CF and who are homozygous for F508del mutation. Orkambi has been studied for treatment of CF patients with heterozygous mutations. There was no consistent improvement with lung function, BMI and CFQ-R. However, there was an improvement with CFTR modulation (reduction in sweat chloride).

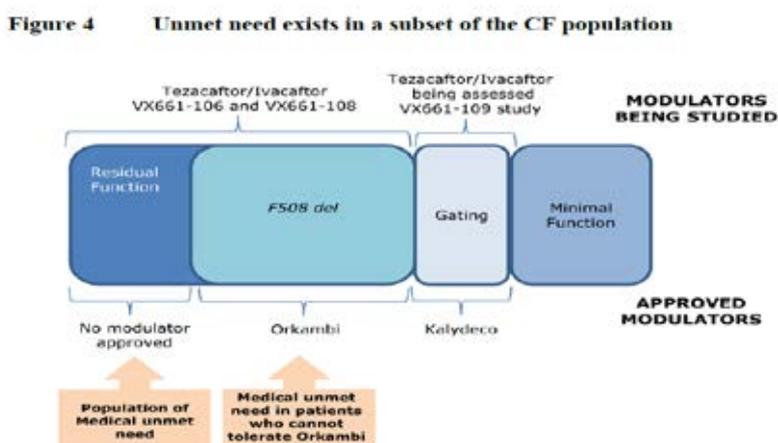
<sup>22</sup>Farrell, P.M. et al. (2017), Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation, *J Pediatr*, 2017; 181S: S4-S15.e1.

<sup>23</sup>Cystic Fibrosis Standards of Care, Australia (2008). Bell, S.C. and Robinson, P.J. (Steering Committee Co-Chairs) Fitzgerald, D.A. (Editor). Accessed from the website of the Thoracic Society of Australia and New Zealand 20 June 2019.

<sup>24</sup> Australian cystic fibrosis data registry annual report (2016). Ruseckaite et al. Accessed from the website of Cystic Fibrosis Australia 20 June 2019

At the time of this submission, there were no TGA approved CFTR modulators for the majority of residual function CF mutations.

**Figure 4: Unmet need exists in a subset of the CF population**



**Table 16: Current TGA approved treatment options for cystic fibrosis at the time of this submission**

Trade name	Active ingredients	Mechanism of action	Indication in approved PI	Remarks
<b>Homozygous</b>				
Orkambi	Lumacaftor/ivacaftor fixed dose combination (FDC)	Combined action of CFTR corrector and potentiator	Orkambi is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who are homozygous for the F508del mutation in the CFTR gene.	Transient decline of forced expiratory volume in 1 second (FEV1) after administration. Increase in liver transaminases, lumacaftor-ivacaftor interactions.
<b>Heterozygous</b>				
Kalydeco	Ivacaftor	CFTR potentiator	Kalydeco is indicated for the treatment of CF in patients aged 2 years and older who have a G551D or other gating (class III) mutation in the CFTR gene. Kalydeco is indicated for the treatment of CF in patients aged 6 years and older who have an R117H mutation in the CFTR gene.	Cataracts in nonclinical and studies in children. GI disturbance and diarrhoea as AEs.

### Overseas regulatory status

FDA approved tezacaftor/ivacaftor on 12 February 2018 for the indication:

*Symdeko is a combination of tezacaftor and ivacaftor, indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis*

*transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence.*

*If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.*

The CHMP gave a positive opinion for tezacaftor/ivacaftor on 26 July 2018. However, at the time the application was under consideration by the TGA, this medicine had not yet been approved by the EMA.<sup>25</sup>

The recommended indication 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.*

Evaluation of this medicine is progressing in Canada.

**Delegate's comment:** It is important to note that the sponsor's proposed indication in this submission to TGA is almost identical to that approved by FDA. The FDA indication also included specific criteria to identify patient's genotype; if previously unknown. The EMA has approved Symdeko for 14 out of 26 mutations that the sponsor proposed to TGA. These are the mutations that had both *in vitro* and clinical data with tezacaftor/ivacaftor. The EMA indication does not include mutations where there are no clinical data to suggest a positive clinical benefit.

## Quality

There are no outstanding issues and the evaluator has recommended approval of this submission from a quality/chemistry perspective. Pivotal studies in this submission utilised the formulation proposed for marketing.

Formulation: tezacaftor/ivacaftor 100 mg/150 mg film coated tablets; co packaged with ivacaftor 150 mg film coated tablets.

## Nonclinical

The evaluator has recommended approval from a safety perspective.

The toxicology evaluator has summarised the following nonclinical findings:

- Tezacaftor was shown to act as CFTR corrector in primary HBE cells and transfected FRT cells. Tezacaftor improved processing and trafficking of CFTR and increased its cell surface stability, chloride transport and airway surface height. Additional increases in these measures, along with ciliary beat frequency were obtained with tezacaftor/ivacaftor.
- *In vitro* model to test PD effects in homozygous F508del mutation consisted of HBE cells from CF patients. Since many heterozygous mutations are rare, compared to

<sup>25</sup> The medicine subsequently received EMA marketing authorisation on 31 October 2018.

homozygous variant, it was not possible to obtain HBE cell lines to express all CFTR mutations. FRT cell model was used to demonstrate PD effects for heterozygous mutations. The same model was used for ivacaftor registration studies. The evaluator accepted this approach.

- The sponsor defined CFTR mutations as tezacaftor/ivacaftor responsive if they met all 3 of the pre-defined *in vitro* criteria:
  - 1) A statistically significant increase in chloride transport from Baseline;
  - 2) A  $\geq 10$  percentage point increase in chloride transport over baseline as percentage of normal CFTR; and
  - 3) A statistically significant increase in chloride transport compared to ivacaftor alone.
  - The sponsor's rationale of choosing  $\geq 10$  percentage point as cut off was: 'because it is predictive or reasonably expected to predict clinical benefit based on extensive natural history studies and previous interventional clinical studies with CFTR modulators shown to provide clinical benefit in people with CF'. Based on this model, those mutations that achieved chloride conductance of greater than 10% of wildtype over baseline when treated with tezacaftor/ivacaftor were identified as 'treatment responsive'. This approach was considered to be acceptable by the toxicology evaluator and is in line with studies submitted to register ivacaftor for the treatment of CF patients with R117H mutation.
- Tezacaftor/ivacaftor responsiveness was defined by the maximum *in vitro* effect. However the toxicology evaluator concluded that the responsiveness obtained at therapeutically relevant concentrations to be more relevant. In the assay system, tezacaftor and ivacaftor were tested at nominal concentrations of up to 10  $\mu\text{M}$  and 3  $\mu\text{M}$ , respectively. However, lower nominal concentrations of tezacaftor and ivacaftor at 3  $\mu\text{M}$  and 1  $\mu\text{M}$  resulted in free drug levels in the assay medium that more closely resembled that in patient plasma. Using this definition, mutations such as D110E, S977F, F1052V and D1152H did not show statistically significant improvement in chloride transport from Baseline with tezacaftor/ivacaftor, when compared to ivacaftor. Hence the toxicology evaluator questioned whether these mutations should be defined as tezacaftor/ivacaftor responsive. These mutations are included in the sponsor's proposed indication. The evaluator has mentioned that availability of clinical data for mutations S977F and D1152H may need to be considered. Clinical correlation was recommended (see later).
- Low order of acute and repeat dose toxicity was noted with tezacaftor/ivacaftor.
- The evaluator has highlighted that in contrast to lumacaftor, CYP3A4 induction by tezacaftor was moderate in an *in vitro* model.
- Tezacaftor was not genotoxic in the standard battery of tests, and not carcinogenic in a 6 month study in transgenic mice or in a 2 year study in rats.
- Fertility indices were unaffected by tezacaftor in male and female rats, and tezacaftor was not teratogenic in either the rat or the rabbit. The adverse effects on development were observed only at toxic levels of doses.
- The evaluator has commented that the proposed pregnancy category as B3 is appropriate.<sup>13</sup>

## Clinical

The clinical evaluator has recommended approval of Symdeko.

## Pharmacokinetics

- Steady state plasma concentrations for tezacaftor and ivacaftor were reached within 8 days and 3 to 5 days; with a comparable accumulation ratio of 1.5 and 2.2 respectively.
- Steady state exposures of tezacaftor and ivacaftor were comparable when administered as separate tablets and as FDC.
- AUC for tezacaftor was approximately 36% higher in patients with moderate hepatic impairment. The Delegate has noted that a dose reduction is recommended for these patients in the PI.
- $T_{max}$  for tezacaftor and ivacaftor were 4 and 6 hours respectively.
- $T_{1/2}$  for tezacaftor and ivacaftor were 15 and 13.7 hours respectively.
- Both tezacaftor and ivacaftor are CYP3A substrates. Tezacaftor neither inhibits nor induces CYP3A; meanwhile, ivacaftor is a weak inhibitor.
- Tezacaftor is extensively metabolised by CYP3A4 and CYP3A5. M1, M2 and M5 are the major metabolites. M1 is pharmacologically active and has similar potency; while M2 and M5 are pharmacologically less active. In healthy adults, steady state AUC of metabolites was approximately 1.5 to 1.6 times greater than that of tezacaftor. M2 was the major circulating metabolite in humans.
- Tezacaftor 100 mg once daily/ivacaftor 150 mg q12h (proposed dose) resulted in comparable PK parameters for tezacaftor, M1, M2, and ivacaftor across healthy subjects and CF patients with homozygous and heterozygous mutations.
- Tezacaftor exposure increased in a dose proportional manner (from 10 mg to 150 mg) when administered alone or in combination with ivacaftor.
- 20% increase in ivacaftor exposure in the presence of tezacaftor. However, as ivacaftor was at the flat part of dose response curve at this exposure, the evaluator did not consider this to be clinically significant.
- The majority of tezacaftor (72%) and ivacaftor (87%) are excreted in faeces.

## Pharmacodynamics

### ***Sweat chloride (PD marker for efficacy)***

Study 101 was conducted in 172 patients who were homozygous for F508del mutation and 18 patients with heterozygous F508del/G551D mutation. These mutations were responsive to tezacaftor/ivacaftor in *in vitro* model. There was no clear dose response with tezacaftor or tezacaftor/ivacaftor for sweat chloride concentration. Sequential dose increases of tezacaftor (10, 30, 100, and 150 mg) alone and in combination with the approved dose of ivacaftor 150 mg q12h and their effect on sweat chloride and ppFEV1 were evaluated. Reduction in sweat chloride was evident by Day 7 and observed through Day 28 for all tezacaftor and tezacaftor/ivacaftor dose groups (range: -2.63 to 20.43 mmol/L) except for the tezacaftor 10 mg once daily group.

### ***Lung function (PD marker for efficacy)***

In Study 101, a dose dependent increase in ppFEV1 was reported with doses of tezacaftor ranging from 10 to 100mg, in combination with ivacaftor 150 mg q12h. There was no further increase with tezacaftor 150 mg.

**QTc (PD marker for safety)**

In healthy volunteers (Study 010), at therapeutic (tezacaftor 100 mg) and suprathreshold (tezacaftor 300 mg) doses, no significant QTc prolongation was reported.

**Pop PK**

- PK data from Studies 101,103, 106, 107 and 108 were pooled and included in the analysis. The study population consisted of 660 CF patients with homozygous and heterozygous F508 del mutation. There were 341 males and 319 females with ages ranging from [information redacted] years and weights ranging from [information redacted] kg. Once daily tezacaftor doses ranged from 10 mg to 150 mg. 22 patients received 50 mg tezacaftor twice daily. Ivacaftor dose was 150 mg q12h (approved dose).
- Tezacaftor clearance rate:
  - 34.3% lower in CF patients weighing 40 kg, compared to their 70 kg counterpart.
  - 20% lower in CF patients with residual function mutations (Study 108), compared to patients with homozygous or gating mutation (Studies 101, 103 and 106).
  - The evaluator did not consider these variations as clinically significant.
- Co administration of ivacaftor did not affect tezacaftor exposure. This is the same finding as in PK study.
- Ivacaftor and tezacaftor had comparable exposures in healthy subjects and CF patients.
- Dose dependent change in sweat chloride and ppFEV1 for tezacaftor/ivacaftor was observed in the pop PK/PD models consisting of homozygous CF patients.

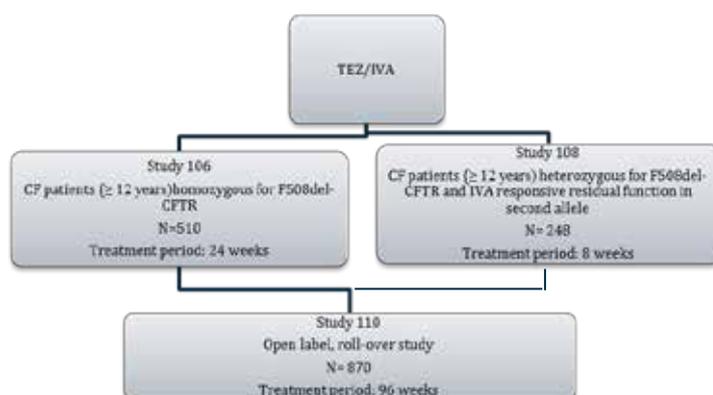
**Dose selection for pivotal studies (Studies 101 and 103)**

- The dose regimen of ivacaftor 150 mg q12h was selected for the Phase III pivotal studies as it was the approved ivacaftor dose regimen for CF patients aged 12 years and older with gating and R117H residual function mutation.
- Dose regimen of tezacaftor 100 mg once daily was selected based on findings from pop PK data and Studies 101 and 103 due to the dose dependent increase in sweat chloride and FEV1.
- The maximal change in sweat chloride and ppFEV1 was at tezacaftor 100 mg once daily/ivacaftor 150 mg q12h. This was at the flat part of dose response curve. Hence chosen as the dose for pivotal studies. The evaluator has agreed with the sponsor's approach.

In Study 101, the sponsor tested an alternative regimen with same total daily dose, that is; tezacaftor 50 mg q12h/ ivacaftor 150 mg q12h, instead of tezacaftor 100 mg once daily/ivacaftor 150 mg q12h. This resulted in a lower mean change in ppFEV1 versus placebo.

**Efficacy**

Figure 5, shown below, provides an overview of the efficacy studies (Studies 106, 108 and 110) included in the clinical dossier.

**Figure 5: Overview of efficacy studies included in the clinical dossier**

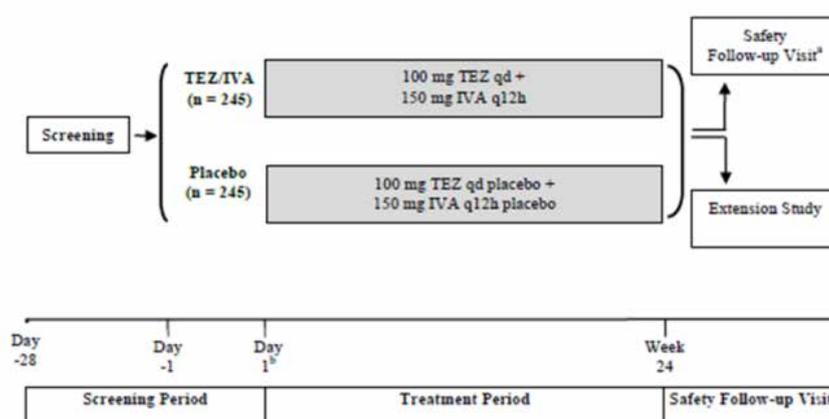
**Delegate's comments:** Studies 106 and 108 were the pivotal studies. Study 107 was included in the dossier. Also, sponsor included a summary of Study 109 findings in the clinical overview. However, a detailed study report was not included in the dossier. The Delegate has summarised these studies in this section of the overview.

### ***Homozygous F508 del mutation***

#### ***Study 106 (Pivotal study)***

##### Study design

Study 106 was a Phase III, randomised clinical trial, multi-centre, parallel group study with a duration of 24 weeks. Figure 6, shown below, is a schematic of the Study 106 design.

**Figure 6: Schematic of Study 106 design**

##### Key inclusion criteria

- Age ≥ 12 years.
- Confirmed diagnosis of CF (defined as a sweat chloride value ≥ 60 mmol/L).
- Homozygous for F508del mutation.
- ppFEV1 of ≥ 40% and ≤ 90%.

##### Baseline demographics

510 patients were randomised, with 93% completing the study. Mean age: 26.3 (10.4) years. A reasonable proportion (23%) of patients were in the 12 to < 18 years age group. The clinical characteristics of the patients were typical of patients with severe disease. Mean BMI: 20 kg/m<sup>2</sup>; BMI z score of -0.48, mean ppFEV1 60%, and 9.3% of patients had

ppFEV<sub>1</sub> < 40%. Mean (standard deviation (SD)) sweat chloride concentration was 100.9 (10.6) mmol/L. Overall, 72% were positive of *P.aeruginosa*. CFQ-R respiratory domain score was 70.

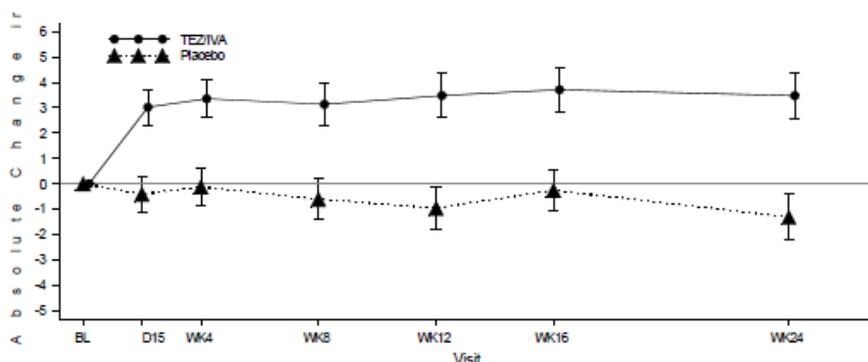
## Results

Primary endpoint: There was a statistically significant improvement in absolute ppFEV<sub>1</sub> from Baseline in tezacaftor/ivacaftor group with a LS mean (SE) of 3.4 percentage points (0.3,  $p < 0.0001$ ) and an improvement of 4.0 percentage points (95% CI: 3.1, 4.8;  $P < 0.0001$ ) compared to placebo (see Table 17). A statistically significant improvement in ppFEV<sub>1</sub> was achieved at Day 15, and persisted up to Week 24 (see Figure 7). The magnitude of improvement in ppFEV<sub>1</sub> for patients with baseline ppFEV<sub>1</sub> < 40% was comparable to those with ppFEV<sub>1</sub> 40 to < 70 and > 70%.

**Table 17: Analysis of absolute change in ppFEV<sub>1</sub> from Baseline (primary endpoint, Study 106)**

Analysis	Statistic	Placebo N = 256	TEZ/IVA N = 248
<b>Primary</b>			
Average absolute change in ppFEV <sub>1</sub> from baseline through Week 24 (percentage points)	n	256	245
	LS mean treatment difference (95% CI)	NA	4.0 (3.1, 4.8)
	P value versus placebo	NA	<0.0001
	LS mean within-group change (SE)	-0.6 (0.3)	3.4 (0.3)
	P value within-treatment	0.0601	<0.0001

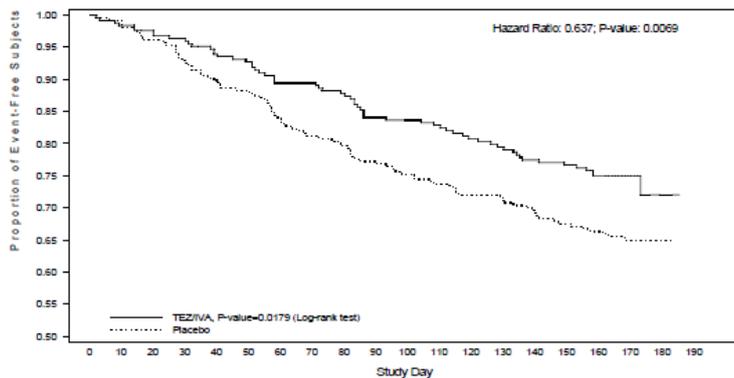
**Figure 7: Absolute change in ppFEV<sub>1</sub> from Baseline (Study 106)**



## Key secondary endpoints

These were as follows:

- A statistically significant 35% reduction in rate of pulmonary exacerbations, when compared to placebo (rate ratio: 0.65,  $p = 0.005$ ). Figure 8, shown below, gives proportion of event free patients on tezacaftor/ivacaftor in Study 106.

**Figure 8: Proportion of event free patients on tezacaftor/ivacaftor (Study 106)**

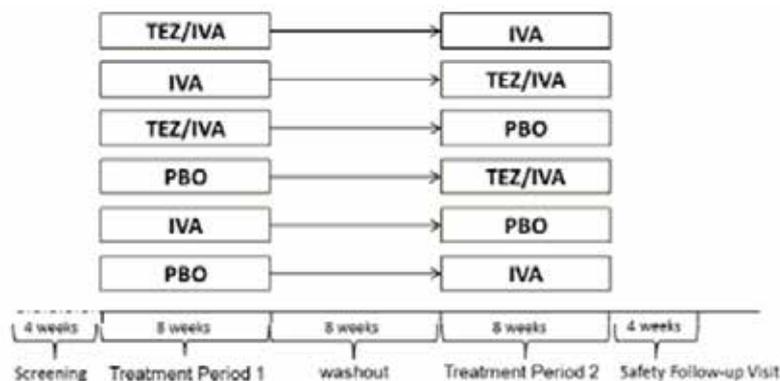
- A 5.1 point increase in CFQ-R respiratory domain score in tezacaftor/ivacaftor group, compared to placebo. Nominal p value was significant (95% CI: 3.2, 7.0, nominal  $p < 0.0001$ ); however, the increase was not considered statistically significant within the testing hierarchy. A greater percentage of patients in tezacaftor/ivacaftor group (51.1%) achieved MCID of 4 points, compared to placebo (35.7%), with an odds ratio of 2.17 (95% CI: 1.469, 3.208;  $P < 0.0001$ ).
- A non-significant treatment difference between tezacaftor/ivacaftor and placebo groups with change in BMI (0.06) from Baseline.
- A statistically significant reduction in sweat chloride from Baseline in tezacaftor/ivacaftor group, compared to placebo (-10.1 mmol/L (95% CI: -11.4, -8.8;  $P < 0.0001$ )).

### ***Heterozygous F508 del mutation***

#### *Study 108*

##### Study design

Study 108 was a Phase III, randomised clinical trial, multi-centre, cross over study. Treatment duration: 8 weeks. N = 248. Figure 9, shown below, is a schematic of the Study 108 design.

**Figure 9: Schematic of Study 108 design**

##### Inclusion criteria

Inclusion criteria were largely similar to Study 106 except for:

- CF diagnosis defined as a sweat chloride value  $\geq 60$  mmol/L; or if the sweat chloride value was  $< 60$  mmol/L, there must have been documented evidence of chronic sino-pulmonary disease

- Heterozygous F508del and a second allele with residual CFTR activity (F/RF) that was identified as responsive to ivacaftor only.

Criteria for including a mutation were both:

- Having residual function based on population level phenotypic data.
- *In vitro* response to ivacaftor alone. This was further defined as an increase in percent normal chloride transport of  $\geq 10$  percentage points in transfected FRT cells expressing the CFTR form produced by the mutation.

Based on *in vitro* findings and previous studies, 26 types of CF mutations were identified as responsive to tezacaftor/ivacaftor in a FRT cell *in vitro* model. All of the patients had heterozygous mutations with around 60% of participants having splice mutations and the rest having missense mutations. Table 18 includes 17 out of 26 CF mutations that had at least one patient included in the study.

**Table 18: List of CFTR residual function mutations included in the study**

Genotype	Placebo N = 161 n (%)	IVA N = 156 n (%)	TEZ/IVA N = 161 n (%)
<b>Class V non-canonical splice mutation</b>			
F508del/2789+5G->A	21 (13.0)	28 (17.9)	25 (15.5)
F508del/3272-26A->G	24 (14.9)	23 (14.7)	24 (14.9)
F508del/3849+10kbC->T	49 (30.4)	40 (25.6)	44 (27.3)
F508del/711+3A->G	2 (1.2)	2 (1.3)	2 (1.2)
<b>Class II to IV mutations</b>			
F508del/A455E	15 (9.3)	14 (9.0)	11 (6.8)
F508del/D110H	1 (0.6)	0	1 (0.6)
F508del/D1152H	15 (9.3)	15 (9.6)	21 (13.0)
F508del/D579G	2 (1.2)	2 (1.3)	2 (1.2)
F508del/E831X	1 (0.6)	1 (0.6)	0
F508del/L206W	4 (2.5)	2 (1.3)	4 (2.5)
F508del/P67L	10 (6.2)	12 (7.7)	11 (6.8)
F508del/R1070W	3 (1.9)	1 (0.6)	2 (1.2)
F508del/R117C	0	1 (0.6)	1 (0.6)
F508del/R347H	3 (1.9)	3 (1.9)	2 (1.2)
F508del/R352Q	1 (0.6)	2 (1.3)	2 (1.2)
F508del/S945L	9 (5.6)	9 (5.8)	7 (4.3)
F508del/S977F	1 (0.6)	1 (0.6)	2 (1.2)

**Delegate's comments:** It is important to note that all of the patients with F508del/E831X mutation were randomised to ivacaftor or placebo groups and not exposed to tezacaftor/ivacaftor. Patients with gating mutations and R117 mutations, for which patients are eligible for treatment with ivacaftor were not included.

Baseline demographics

248 patients were randomised in a 1:1:1:1:1:1 pattern to 1 of 6 treatment sequences (as shown in Figure 9). Mean (SD) sweat chloride was 69.9 (26.1) mmol/L. Around 14% of patients were in the 12 to 18 age group. Mean BMI was around 24 kg/m<sup>2</sup> and ppFEV1 at around 60%. The majority (92.3%) of patients enrolled into the rollover Study 110 upon completion.

Study treatments

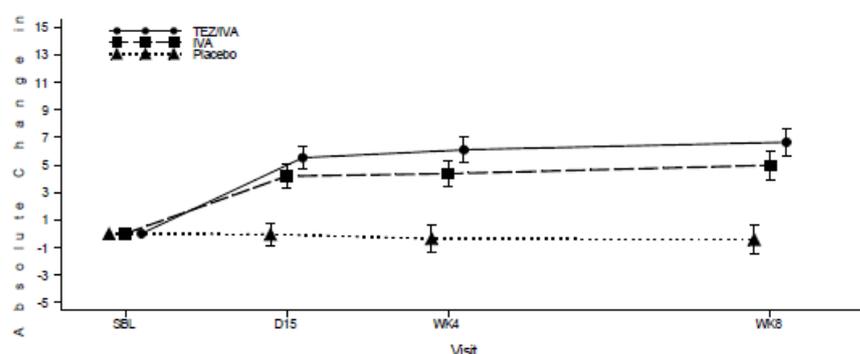
Study drugs were tezacaftor/ivacaftor 100 mg/150 mg FDC tablet, ivacaftor 150 mg tablet, tezacaftor/ivacaftor matching placebo and ivacaftor matching placebo. Study drugs were administered within 30 minutes of consuming a fat containing meal. During each of the two treatment periods, study drug (tezacaftor/ivacaftor, ivacaftor, or placebo) was administered for up to 8 weeks.

Results

Primary endpoint: A statistically significant improvement from Baseline in ppFEV1 for tezacaftor/ivacaftor group compared to placebo (6.8 percentage points (95% CI: 5.7, 7.8;

$P < 0.0001$ ) and ivacaftor (2.1 percentage points (95% CI: 1.2, 2.9;  $P < 0.0001$ ) (see Figure 10, below) Similar to Study 106, a statistically significant improvement in ppFEV1 from Baseline, compared to placebo was achieved at Day 15.

**Figure 10: Absolute change in ppFEV1 from Baseline (Study 108)**



**Table 19: Primary and key secondary efficacy endpoints (Study 108)**

Analysis	Statistic	Placebo N = 161	IVA N = 156	TEZ/IVA N = 161
Absolute change in ppFEV <sub>1</sub> from study baseline to the average of Week 4 and Week 8 (percentage points)	LS mean treatment difference versus placebo (95% CI)	NA	4.7 (3.7, 5.8)	6.8 (5.7, 7.8)
	P value versus placebo	NA	<0.0001	<0.0001
	LS mean treatment difference versus IVA (95% CI)	NA	NA	2.1 (1.2, 2.9)
	P value versus IVA	NA	NA	$P < 0.0001$
	Within-group change (SE)	-0.3 (0.5)	4.4 (0.5)	6.5 (0.4)
	P value within-treatment	0.5035	<0.0001	<0.0001
Absolute change in CFQ-R Respiratory Domain Score from study baseline to the average of Week 4 and Week 8 (points)	LS mean treatment difference versus placebo (95% CI)	NA	9.7 (7.2, 12.2)	11.1 (8.7, 13.6)
	P value versus placebo	NA	<0.0001	<0.0001
	LS mean treatment difference versus IVA (95% CI)	NA	NA	1.4 (-1.0, 3.9)
	P value versus IVA	NA	NA	0.2578
	Within-group change (SE)	-1.0 (1.0)	8.7 (1.0)	10.1 (1.0)
	P value within-treatment	0.3265	<0.0001	<0.0001

### Secondary and other endpoints

- Statistically significant reduction in sweat chloride concentration with tezacaftor/ivacaftor from Baseline to the average of Week 4 and Week 8 with -9.5 mmol/L (95% CI: -11.7, -7.3;  $P < 0.0001$ ), compared to placebo and compared to ivacaftor (-5.1 points (95% CI: -7.0, -3.1;  $P < 0.0001$ )).
- Improvement in CFQ-R was comparable between tezacaftor/ivacaftor (11.1) and ivacaftor (9.7). The difference was statistically significant for tezacaftor/ivacaftor when compared to placebo, but not against ivacaftor.
- Statistically significant gain in mean (SD) BMI from Baseline (0.34 (0.96),  $p < 0.0001$ ) for tezacaftor/ivacaftor. However, it was less than that of ivacaftor (0.47 (0.4)).
- No statistically significant reduction in exacerbations for tezacaftor/ivacaftor, when compared to placebo and ivacaftor.
- For patients in the ivacaftor group:
  - Statistically significant improvement in ppFEV1 and CFQ-R from Baseline, when compared to placebo (see Table 19).
  - Statistically significant reduction in absolute sweat chloride concentration from Baseline, when compared to placebo (-4.5 mmol/L (95% CI: -6.7, -2.3;  $P < 0.0001$ )).

## Study 110

### Study design

Study 110 was a Phase III, non-randomised, open label, rollover safety study. This study is currently ongoing at the time of this evaluation and data included in this summary is based on a pre specified interim analysis. The Delegate has noted that this was performed when patients from Study 106 completed 24 weeks of treatment period, thus having 48 weeks of data. The patients rolled over from Study 108 completed 16 weeks at the time of analysis and thus only have 24 weeks of safety data. Eligible patients from Studies 106 and 108 were offered enrolment in to treatment or observational cohort. No patients chose to enrol into observational cohort. There was no comparator arm in this study.

### Treatment groups

870 patients were enrolled in treatment cohort.

- Homozygous F508del (Study Set 106 and 110)
  - Tezacaftor/ivacaftor: patients who received tezacaftor/ivacaftor in Study 106 and 108 and continued to receive tezacaftor/ivacaftor in Study 110.
- Heterozygous F508del (Study Set 108 and 110)
  - Ivacaftor to tezacaftor/ivacaftor: patients who received ivacaftor in Study 108 and received tezacaftor/ivacaftor in Study 110
- Placebo to tezacaftor/ivacaftor: patients who received placebo in both Studies 106 and 108 and received tezacaftor/ivacaftor in Study 110.

## Results

Primary endpoint: Primary endpoint in this study was related to safety outcome and hence discussed in the safety section.

### Secondary endpoints:

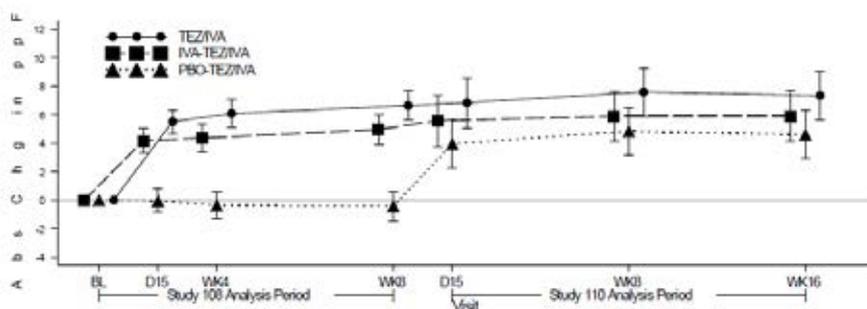
- Homozygous F508del (treatment outcomes at Week 48)
  - Improvement in ppFEV1 remained statistically significant, compared to baseline (3.1 percentage points (95% CI: 1.9, 4.3; P < 0.0001).
  - Slightly higher event rate for pulmonary exacerbations at 0.72, compared to that in Study 106 (0.64).
  - Gain in CFQ-R (3.1) and BMI (0.26) were sustained.
- Heterozygous F508del (treatment outcomes at Week 24)
  - Tezacaftor/ivacaftor group
    - § Improvement in ppFEV1 in Study 108 (6.6) compared to placebo at Week 8 remained statistically significant at 7.4.
    - § Pulmonary exacerbation event rate in Study 108 (0.34) was sustained at (0.2).
    - § Change in CFQ-R at 9.9 was comparable to 9.7 in Study 108.
    - § Increase in absolute change in BMI from 0.36 in Study 108 to 0.74.
  - Ivacaftor to tezacaftor/ivacaftor group
    - § Absolute change in ppFEV1 from Baseline was statistically significant with tezacaftor/ivacaftor at 5.9% (95% CI: 4.1, 7.7; P < 0.0001).
    - § Exacerbation event rate for tezacaftor/ivacaftor was 0.39.
    - § Increase in BMI with tezacaftor/ivacaftor was (0.6) from Baseline.

### § Improvement in CFQ-R of 11 points.

- Placebo to tezacaftor/ivacaftor: The gain in clinical endpoints when switched over from placebo to tezacaftor/ivacaftor in Study 110 was comparable to tezacaftor/ivacaftor groups in Studies 106 and 108.

Figure 11, shown below, gives the absolute change from Baseline in ppFEV1 in Study 110).

**Figure 11: Absolute change from Baseline in ppFEV1 (Study 110)**



### Study 107

#### Study design

This was a Phase III, random clinical trial, in CF patients who are heterozygous for the F508del CFTR mutation and with a second CFTR mutation that is not likely to respond to tezacaftor and/or ivacaftor therapy (F508del/NR). It is not stated in the clinical study report (CSR) whether these mutations were of gating or residual type. The sponsor used the following factors to determine mutations that are not likely to respond:

- Biological plausibility for the mutation to respond (class of mutation, based on *in vitro* data).
- Evidence of clinical severity on a population basis based on the patient registry.
- *In vitro* testing (mutations that responded with chloride transport < 10% of wild type CFTR were considered minimal function and nonresponsive).

#### Baseline demographics

168 patients were randomised into tezacaftor/ivacaftor and placebo groups. Overall, baseline demographic characteristics were similar to pivotal studies.

#### Results

There was a numerical improvement in ppFEV1, with a treatment difference of 1.2 percentage points; however it did not achieve statistical significance. Secondary endpoints such as sweat chloride concentration change in BMI and number of pulmonary exacerbations did not achieve statistical significance with treatment difference for tezacaftor/ivacaftor group, when compared to placebo.

### Study 109

The sponsor conducted this study in CF patients with the heterozygous for F508del and a second allele with a gating mutation that is clinically demonstrated to be ivacaftor responsive. Study 109 compared clinical efficacy of tezacaftor/ivacaftor with ivacaftor. 151 CF patients with this mutation were randomised 1:1 to receive tezacaftor 100 mg once daily/ivacaftor 150 mg twice daily or ivacaftor monotherapy at 150 mg twice daily after a 4-week run-in period of ivacaftor monotherapy. This study did not achieve its primary endpoint of absolute change in ppFEV1 from Baseline through Week 8 with tezacaftor/ivacaftor compared to ivacaftor and hence was terminated.

**Delegate's comments:** It is important to note that in *in vitro* model using FRT cells, G551D was 'treatment responsive' to ivacaftor and had statistically significant improvement in chloride transport with tezacaftor/ivacaftor, compared to ivacaftor. However, in clinical study, there was no corresponding improvement in ppFEV1 (primary endpoint). This gating mutation is not included in the proposed indication.

## **Safety**

Safety assessment was largely based on data from the two pivotal Phase III studies (Studies 106 and 108) and one ongoing open label extension study (Study 110).

### ***Patient exposure***

Overall, 758 patients received treatment with tezacaftor/ivacaftor across Studies 106 and 108. The mean treatment periods were 23 weeks and 7.9 weeks in Studies 106 and 108 respectively. In Study 110, 867 patients received treatment with tezacaftor/ivacaftor, with a mean treatment duration of 33.5 weeks until the interim data cut-off date.

### ***AEs***

In Studies 106 and 108, incidence of AEs was comparable across tezacaftor/ivacaftor, ivacaftor and placebo groups. Infective exacerbation of CF, cough and headache were frequently reported. These are common manifestations of CF. Most of the AEs were mild to moderate in severity.

### ***Treatment emergent adverse events***

TEAEs were largely mild and comparable across treatment groups in Studies 106 and 108. In Study 108, increase in CPK was reported as a TEAE. The incidence of this event in tezacaftor/ivacaftor group was slightly higher than ivacaftor group (3.1% versus 2.5%), but similar to placebo group (3.1%).

### ***Deaths and SAEs***

#### ***Deaths***

No deaths were reported in Studies 106, 108 and 110 in the case study report submitted to the TGA. However, the clinical review by FDA has commented about an event of death in Study 110. The sponsor needs to clarify as part of their pre ACM response.

#### ***Haemoptysis***

Overall, across Studies 106 and 108, the incidence of SAE was lower in tezacaftor/ivacaftor group, compared to ivacaftor and placebo groups. Infective pulmonary exacerbation of CF and haemoptysis were the common TEAEs. In Study 106, 2 events of haemoptysis were reported in patients on tezacaftor/ivacaftor. One of the events resolved without change of treatment. The other event resolved after medical intervention. This event of haemoptysis was reported as life threatening and related to study drug. The incidence of haemoptysis is less than previous studies with ivacaftor (8.3%) and lumacaftor/ivacaftor (13.8%).

TEAEs that led to treatment discontinuation were low in tezacaftor/ivacaftor group (2.8%, nil events and 0.8% in Studies 106, 108 and 110, respectively).

#### ***Elevated transaminases***

Across both pivotal studies and the follow up study, incidence of elevated transaminases was lower in tezacaftor/ivacaftor group than comparator groups, including ivacaftor (Study 106: 4% for tezacaftor/ivacaftor versus 5.8% for placebo; Study 108: 2.5% for tezacaftor/ivacaftor versus 3.8% for ivacaftor versus 1.2% for placebo). In

tezacaftor/ivacaftor, majority of events were mild and did not lead to treatment discontinuation.

#### *Cataract*

In Study 106, at Baseline, a higher incidence of cataract was noted in tezacaftor/ivacaftor group (6% versus 4.3%). During study period, an increased number of patients in tezacaftor/ivacaftor group developed cataract compared to placebo group (6.9% versus 5.2%). Incidence in patients in the age group 12 to < 18 years was lower than their adult counterparts (3.9% versus 7.9%). Cataracts are known potential AE of ivacaftor. Precautionary statements related to development of cataract are inserted in the PI.

#### *Distal intestinal obstruction syndrome (DIOS)*

In long term safety Study 110, in patients 12 to 18 years of age, there was an increased incidence of distal intestinal obstruction syndrome in tezacaftor/ivacaftor group (n = 5, 5.5%), compared to placebo (n = 1, 1.2%). In patients > 18 years of age, there were no such events in tezacaftor/ivacaftor, compared to 4 events in placebo (0 versus 4(1.3%)). The Delegate has proposed to include this information in PI and as an important potential risk in RMP.

## Risk management plan

The RMP and ASA included the following safety concerns, as shown in Table 20.

### Summary of safety concerns

**Table 20: Summary of safety concerns regarding Symdeko**

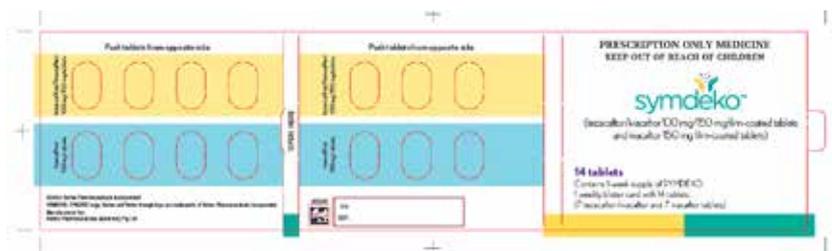
Important identified risks	<ul style="list-style-type: none"> <li>• None</li> </ul>
Important potential risks	<ul style="list-style-type: none"> <li>• Effects on liver function tests</li> <li>• Concomitant use of TEZ/IVA with strong CYP3A inhibitors or inducers</li> <li>• Cataract</li> </ul>
Missing information	<ul style="list-style-type: none"> <li>• Use in pregnant and lactating women</li> <li>• Long-term safety</li> <li>• Patients with moderate or severe hepatic impairment</li> <li>• Patients with ppFEV<sub>1</sub> &lt;40</li> </ul>

There were no outstanding issues from the RMP evaluation.

The RMP evaluator has commented that the dosing regimen that involves taking tablets containing different ingredients in the morning and evening could be a source of confusion that could lead to medication error. The RMP team has not suggested alternative packaging or risk mitigation activities. The pharmaceutical chemistry evaluator was satisfied with the labelling. The sponsor has stated that there were no events of medication errors in clinical studies.

### Packaging of symdeko tablets

Figure 12, shown below, illustrates the packaging of the Symdeko in tezacaftor/ivacaftor drug product.

**Figure 12: Image of symdeko package**

The RMP evaluator has stated that the routine pharmacovigilance plan proposed by the sponsor is acceptable for all safety concerns. The sponsor has proposed to submit safety data from the ongoing Study 110 and a planned Study 117 as additional pharmacovigilance activities. The evaluator has concluded that the additional pharmacovigilance activities proposed are consistent with the approach adopted for other ivacaftor containing products and hence acceptable. The Delegate agrees with evaluator's conclusions related to pharmacovigilance plan.

**Delegate's comments:** The sponsor needs to add 'Distal Intestinal Obstruction Syndrome' as an important potential risk to the summary of safety concerns.

## Risk-benefit analysis

### Delegate's considerations

The Delegate's overarching consideration was to determine whether there is sufficient evidence to suggest whether tezacaftor/ivacaftor:

- Has significant treatment benefit in homozygous F508del CFTR mutation;
- Has significant treatment benefit in heterozygous mutations that correlates with *in vitro* study findings; and
- Has additional treatment benefits compared to ivacaftor;<sup>26</sup> or other CFTR modulators available.

### *Efficacy*

#### *Homozygous F508del CFTR (severe disease phenotype)*

The clinical data supports the efficacy of tezacaftor/ivacaftor in CF patients with homozygous F508 mutation. However the magnitude of change was small. A statistically significant and clinically relevant improvement was observed with ppFEV1 (primary endpoint); along with a significant reduction in rate of exacerbations and sweat chloride concentration from Baseline, compared to placebo. The improvement in FEV1 and reduction in exacerbations were also reflected in quality of life measures with the treatment difference of CFQ-R compared to placebo that exceeded minimal clinically important difference (MCID) of 4 units.<sup>27</sup> The change in CFQ-R was not statistically significant, when compared to placebo, within the hypothesis testing hierarchy used to control Type I error. It is noted that, at Baseline, patients had relatively high score for CF related quality of life (mean CFQ-R: 70).

<sup>26</sup>European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP), 23 March 2017, Guideline on clinical development of fixed combination medicinal products, EMA/CHMP/158268/2017

<sup>27</sup> European Medicines Agency (EMA), Human Medicines Development and Evaluation, Report of the workshop on endpoints for cystic fibrosis clinical trials, London, 27-28 September 2012. 29 November 2012 EMA/769571/2012.

Orkambi (lumacaftor/ivacaftor) is currently registered for the treatment of CF patients with homozygous F508del mutation. There was no head to head comparison study.

Comparison of key clinical endpoints between Symdeko and Orkambi in homozygous F508del is demonstrated in Table 21.

**Table 21: Comparison of key clinical endpoints between Symdeko and Orkambi in homozygous F508del**

Clinical endpoint (Treatment difference against placebo at 24 weeks)	Orkambi (lumacaftor/ivacaftor) N = 182	Symdeko (tezacaftor/ivacaftor) N = 248
ppFEV1	3.0	4.8
CFQ-R	1.5 (not significant)	5.0 (not significant)
Sweat chloride (change from Baseline)	No data in patients > 12 years.	-10.1 (significant)
BMI (mean absolute change)	0.13 (significant)	0.06 (not significant)
Exacerbations (rate ratio)	0.66 (significant)	0.65 (significant)

Overall, the improvements in primary and secondary endpoints at Week 24 in Study 106 were sustained for a further 24 weeks during Study 110. These data suggest a marginal benefit in efficacy for tezacaftor/ivacaftor, compared to lumacaftor/ivacaftor.

*Heterozygous F508delCFTR (moderate disease phenotype)*

In the pathophysiology of cystic fibrosis, the relationship between genotype, phenotype and clinical characteristics is complex. Genotype is defined by the allelic configuration of CF genes. This further determines the extent of chloride channel dysfunction and hence the phenotypical expression.

The *in vitro* model adopted by the sponsor examines the change in CFTR function by the degree of improvement in chloride transport. However, the Delegate considers that evidence to suggest that *in vitro* test alone (that is based on 10% increase in chloride transport over baseline) to be inadequate to identify treatment responsive mutations. The Delegate agrees with the nonclinical evaluator's recommendation to consider tezacaftor/ivacaftor responsiveness at therapeutic concentration rather than at maximal concentration of tezacaftor and ivacaftor. The rationale is to have a better correlation with clinical findings.

From a clinical perspective, the ability of the *in vitro* model to be able to predict whether patients with these mutations will have a significant clinical benefit with tezacaftor/ivacaftor is critical.<sup>16</sup> CF patients with mutations that showed *in vitro* responsiveness were included in Study 108. In this study, at Week 8, treatment with tezacaftor/ivacaftor achieved a significant improvement in lung function and CFTR function, compared to placebo and ivacaftor. The magnitude of improvement was in line with previous studies with ivacaftor and lumacaftor/ivacaftor. The duration of the study (8 weeks) was not adequate to assess treatment effects on CFQ-R and rate of exacerbations. Study 110 was primarily a safety follow up study and hence not designed and powered to assess efficacy. However, overall, treatment effects for tezacaftor/ivacaftor group appear to be sustained at Week 16 of Study 110. 17 out of 26 mutations had both *in vitro* and clinical data. Most of these mutations that had treatment responsiveness in *in vitro* test also had a clinical benefit in Study 108 (see below). Overall,

this is suggestive of a similar direction of response between *in vitro* and clinical studies. However, there was high variability between the magnitude of *in vitro* and clinical responses. There was no good correlation between the magnitude of improvement in chloride transport in *in vitro* model and lung function (ppFEV1) in clinical studies.

After randomisation in Study 108, all patients with the E831X mutation were randomised to ivacaftor and placebo, with none of them in tezacaftor/ivacaftor group. Hence, there is no data on the treatment response for this mutation. Also, there were no patients included in Study 108 with these CFTR mutations: E56K, R74W, D110E, E193K, F1052V, K1060T, A1067T, F1074L and D1270N. Mutation D110H had a statistically significant improvement in chloride transport with tezacaftor/ivacaftor compared to ivacaftor in the *in vitro* model. However, there was no improvement in ppFEV1 for patients in tezacaftor/ivacaftor arm in Study 108. Hence, from an efficacy perspective, the Delegate considers that there is insufficient evidence to support inclusion of these mutations in the proposed indication.

*In vitro* clinical correlation: In spite of the 'treatment responsiveness' demonstrated *in vitro* with G551D mutation, treatment with tezacaftor/ivacaftor in Study 109 did not achieve a significant change in lung function. This highlights the discordance that could happen between *in vitro* findings and treatment outcome. 9 out of 26 CF mutations proposed by the sponsor are based on *in vitro* data only. It is uncertain whether individual patients with these specific mutations who achieved significant *in vitro* findings also will achieve significant treatment outcomes.

### **Safety**

In clinical studies, SAEs and AEs leading to premature treatment discontinuation occurred more frequently in placebo patients compared to tezacaftor/ivacaftor patients. Most of the events were manifestations of CF and mild to moderate in severity. In contrast to the clinical studies with lumacaftor/ivacaftor, where a decline in lung function immediately after lumacaftor/ivacaftor administration was reported, respiratory symptom related treatment emergent adverse events (TEAEs) did not appear to be a drug related side effect of tezacaftor/ivacaftor. Slightly lower proportion (3.1%) of patients discontinued due to AE in Study 106, compared to studies with Orkambi (3.4%). Incidence of elevated transaminases with tezacaftor/ivacaftor (2.5%) was also lower than that reported with Orkambi (10%). No age-related trends for AEs or SAEs were noted. These findings suggest a better safety profile for tezacaftor/ivacaftor, compared to lumacaftor/ivacaftor.

Cataracts are known potential risk associated with CF and with ivacaftor monotherapy. More patients in tezacaftor/ivacaftor group in Study 108 were found to have treatment emergent cataracts than patients in placebo group. Cataracts remain as a potential safety risk in patients treated with tezacaftor/ivacaftor and are listed as a precaution in PI.

In Study 110, in the sub group of patients aged 12 to 18 years, there was an increased incidence of distal intestine obstruction syndrome in tezacaftor/ivacaftor group, compared to placebo (5.5% versus 1.2%). This is a known CF manifestation. The Delegate has recommended to add this information in PI and RMP.

### **Conclusion**

Taking these aspects into consideration, the Delegate's overall impression is that, for the treatment of CF in patients with F508del homozygous mutation, tezacaftor/ivacaftor is expected to have added benefit over placebo. The benefits of tezacaftor/ivacaftor over lumacaftor/ivacaftor (Orkambi) are marginal in relation to efficacy and significant in relation to safety profile.

For the treatment of CF in patients with heterozygous mutation, there is sufficient evidence to support registration for those mutations where clinical studies have been performed.

However, the Delegate considers there is insufficient evidence in support of use of tezacaftor/ivacaftor in those heterozygous mutations with lack of clinical data due to:

- Uncertainty around *in vitro* model to predict magnitude of clinical outcome.
- Uncertainty around correlation of CF genotype with its corresponding phenotypical expression and clinical outcomes to justify extrapolation of *in vitro* findings in the absence of clinical data.

The Delegate indicates that the recommended PI and RMP changes are required prior to registration.

#### **Delegate questions for sponsor**

1. Please comment on the reliability (specificity and sensitivity) of *in vitro* model (FRT cell) used to identify treatment responsive heterozygous mutations.
2. In Study 106, at Baseline, the median value for sweat chloride was 101.5 with min of 38.5 and max of 140.0. Please explain how those with sweat chloride < 60 were defined as having CF.
3. In Study 108, at Baseline, median sweat chloride was 74.3 with min of 11.0 and max of 135.0. Please describe how patients with sweat chloride < 60 were included in the study.
4. In the FDA clinical review of tezacaftor/ivacaftor, an event of death was reported in Study 110. This event does not seem to be reported in the CSR submitted to TGA. Please clarify.
5. In the Study 110 CSR, sponsor has mentioned that patients with specific genotypes with inadequate response to clinical efficacy in Studies 106, 107, 108 and 109 were recommended to discontinue treatment in Study 110. Please clarify whether there were any patients who were not allocated in to treatment cohort in Study 110 and if so, which genotypes did they have?
6. In Study 108, patients with R347H mutation that was ivacaftor responsive but not identified as tezacaftor/ivacaftor responsive at maximal concentration in *in vitro* study were recruited. There were 8 patients included in the study, with 2 of them in tezacaftor/ivacaftor arm. This mutation is not included in the proposed indication. However, data from these patients have been used in the analysis. Please explain why there was a disparity in defining treatment responsiveness between *in vitro* and clinical studies. Also, its potential implications.

#### **Proposed action**

The Delegate has no reason to say, at this time, that the application for Symdeko should not be approved for F508 homozygous mutations or heterozygous mutations that have been assessed in the clinical study and found to have a clinical benefit.

The Delegate is not in a position to approve the registration of Symdeko for F508 heterozygous mutations that have not been assessed in the clinical study or not found to have clinical benefit.

#### **Request for Advisory Committee on Medicines (ACM) advice**

1. Please comment on correlation between genotype/phenotype/clinical characteristics of cystic fibrosis
2. Does sweat chloride concentration correlate with CFTR function and disease severity?

3. Does improvement in sweat chloride concentration correlate with an improvement in disease manifestations?
4. Does the method by which patients with cystic fibrosis in Australia have their genotype tested need further clarification in Symdeko PI?
5. Please comment whether the packaging of Symdeko tablets is acceptable.

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

### Response from sponsor

The sponsor notes the Delegate's pre ACM assessment for the positive recommendation of approval for Symdeko for patients homozygous for F508del or heterozygous for F508del and a CFTR mutation resulting in RF that has been assessed in the clinical study and found to have a clinical benefit. The sponsor proposes to retain the full indicated list of 25 RF mutations, and provides the company's position and rationale within the pre ACM response below.

The sponsor firstly provides a position statement with respect to advice sought by the Delegate, as follows:

Disease severity and rate of disease progression is determined by the extent of CFTR mediated chloride transport loss associated with each of the CFTR mutations that make up a patient's genotype. Sweat chloride concentrations generally correlate with CFTR function and disease severity. CFTR mutations that result in complete or near complete loss of CFTR mediated chloride transport (for example, F508del) result in CF characterized by an early onset and relatively rapid disease progression.<sup>28</sup> Patients homozygous for the F508del mutation (F/F) have high sweat chloride levels (generally > 90 mmol/L) and a severe phenotype characterized by early onset of symptoms, progressive lung function decline, and early childhood pancreatic insufficiency.<sup>28</sup> Mutations that result in a more modest reduction in CFTR mediated chloride transport, referred to as RF CFTR mutations, may result in CF that is more slowly progressive but that still reaches a severe disease stage and causes premature death.<sup>28,29</sup> Compared to F/F patients, patients with CFTR mutations having RF generally have lower sweat chloride levels (< 86 mmol/L), progressive lung function decline that begins later, and pancreatic insufficiency that is lower in frequency.<sup>29,30</sup> The median age of death is 24 years;<sup>30</sup> for patients with the F/F genotype and 38 years for patients with an RF mutation.<sup>31</sup>

Among subjects with the same genotype, there is some variability in phenotype, including sweat chloride values, lung function, and pancreatic disease. The variability is likely due to a combination of physiologic, environmental, and genetic modifiers that influence CF disease severity.<sup>32</sup> In a published analysis of aggregate data from 8 clinical studies of Kalydeco (ivacaftor monotherapy) in patients with CF, there was a statistically significant correlation between sweat chloride levels and ppFEV1 changes at the population level

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28 McCloskey, M. et al. (2000), Clinical Features Associated with a Delayed Diagnosis of Cystic Fibrosis, *Respiration*, 2000; 67: 402-407.

29 Moskowitz, S.M. et al. (2008), Clinical practice and genetic counseling for cystic fibrosis and CFTR-related disorders, *Genet Med*, 2008; 10: 851-868.

30 McKone, E.F. et al. (2003), Effect of genotype on phenotype and mortality in cystic fibrosis: a retrospective cohort study, *Lancet*, 2003; 361: 1671-1676.

31 McKone, E.F. et al. (2006), CFTR Genotype as a Predictor of Prognosis in Cystic Fibrosis\*, *Chest*, 2006; 130: 1441-1447.

32 O'Neal, W.K. et al. (2018), Cystic Fibrosis Disease Modifiers: Complex Genetics Defines the Phenotypic Diversity in a Monogenic Disease, *Annu Rev Genomics Hum Genet*, 2018; 19: 201-222.

( $P < 0.0001$ ); there was a lack of correlation for individual patients,<sup>33</sup> likely due to many factors that impact lung function, including the degree of permanent lung tissue damage, pulmonary exacerbation rates, and environmental factors. Unlike the lung, CFTR dysfunction in the sweat gland does not lead to tissue damage, and sweat chloride levels remain relatively constant, despite inherent intra subject variability.<sup>34</sup>

Study 108 was designed and powered based on the anticipated change in ppFEV<sub>1</sub> for the overall eligible population. The sponsor considered the inherent intra individual variability of ppFEV<sub>1</sub>;<sup>28</sup> (varying from 5 to 12 percentage points within a day or week, respectively, in healthy volunteers);<sup>35</sup> and sweat chloride (in CF patients the 95% limits of repeatability was between 13.2 to 13.5 mmol/L).<sup>36</sup> The sponsor grouped 25 mutations with scientifically and clinically related characteristics into a well powered study with over 200 subjects, thereby providing confidence in the clinical response of this group of mutations and allowing the evaluation of a broad population of CF patients with the potential to respond to tezacaftor/ivacaftor. The positive result in Study 108 across multiple clinical endpoints confirmed that the mutations prospectively selected for enrolment based on *in vitro* responses were responsive in the clinic. Given the rarity of these mutations, well powered clinical studies that evaluate each individual CFTR genotype will not be possible for the sponsor or other sponsors. The positive benefit: risk profile of tezacaftor/ivacaftor supports the availability of this treatment for all CF patients with the proposed mutations who otherwise do not have a CFTR treatment available that targets the underlying cause of their disease. Due to the within subject variability observed in spirometry and sweat chloride assessments, there is limited value in assessing response data by individual mutation because the small sample sizes do not allow interpretation of results of these endpoints with any confidence. Given the information above, the sponsor considers it is appropriate not to include a table with clinical response data for individual mutations in the PI.

Symdeko is comprised of a fixed-dose combination tablet of tezacaftor/ivacaftor 100 mg/150 mg in the morning and an ivacaftor 150 mg tablet in the evening. This was the regimen studied in the pivotal Phase III studies. The co packaging of tezacaftor/ivacaftor and ivacaftor tablets in a single pack was designed to aid patient compliance and to reduce the potential for medication errors compared to individual packaging of the morning and evening doses. There have been no reports related to medication errors in subjects who received Symdeko combination therapy in the Phase III clinical studies, and no safety findings that could be related to medication errors have been identified. The safety experience with Symdeko suggests that the potential for medication error is low, and any potential medication errors are unlikely to lead to serious adverse events. On the contrary, having the tablets in 2 separate packs adds complexity and has the potential to lead to confusion for the patient. In conclusion, given the favourable safety profile of Symdeko, the lack of safety findings related to medication errors in the Phase III clinical studies, the clear product packaging, and the clear guidance and instructions provided in the PI and CMI, the sponsor believes that the potential for medication errors is low, is not expected to impact the overall benefit: risk profile of Symdeko, or to affect the public health of the CF population.

The sponsor addresses the specific Delegate's questions to sponsor:

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33 Fidler, M.C. et al. (2017), Correlation of sweat chloride and percent predicted FEV<sub>1</sub> in cystic fibrosis patients treated with ivacaftor, *J Cyst Fibros*, 2017; 16: 41-44.

34 Kirk, J.M. et al. (1992), Variation of Sweat Sodium and Chloride with Age in Cystic Fibrosis and Normal Populations: Further Investigations in Equivocal Cases, *Ann Clin Biochem*, 1992; 29: 145-152.

35 Pellegrino, R. et al. (2005), Interpretative strategies for lung function tests, *Eur Respir J*, 2005; 26: 948-968.

36 Vermeulen, F. et al. (2017), Variability of sweat chloride concentration in subjects with cystic fibrosis and G551D mutations, *J Cys Fibros*, 2017; 16: 36-40).

**1. Please comment on the reliability (specificity and sensitivity) of *in vitro* model (FRT cells) used to identify treatment responsive heterozygous mutations.**

The FRT assay is reproducible and has been clinically validated in multiple clinical studies of ivacaftor monotherapy, lumacaftor/ivacaftor, and tezacaftor/ivacaftor as FRT cells do not express endogenous CFTR, their use as model allows for the isolation of treatment effects of CFTR modulators on the protein produced by single CFTR form. Results from *in vitro* experiments using the FRT cell system are robust and reproducible over time as a result of controlled, standardized procedures and experimental methodology. CFTR mediated chloride transport was normalized to the mean values obtained from independently created FRT cell lines expressing normal CFTR, thus providing consistency in result interpretation against a pre-specified threshold for determining responsiveness to tezacaftor/ivacaftor (that is, change from Baseline that was statistically significant and  $\geq 10$  percentage points, as a percentage of normal CFTR). To calculate sensitivity and specificity of the FRT assay for clinical outcomes, clinical studies would need to provide the clinical responses for subjects predicted by the FRT assay to be non-responsive to a CFTR modulator (CFTRm). As all the sponsor CFTR modulator studies, including Study 108, have prospectively enrolled only mutations predicted by *in vitro* data to be responsive, the specificity and sensitivity and of the assay cannot be calculated. In the development programs for tezacaftor/ivacaftor and other CFTRm, the sponsor has leveraged the well-established mechanisms of action of CFTRm and the extensive understanding of CFTR biology. Experience with Kalydeco and Orkambi demonstrated that the *in vitro* response of CFTR mutations in established model systems predicts the clinical response of the mutations to CFTRm, thus demonstrating *in vitro* to *in vivo* translation of response to CFTRm. The *in vitro* model systems that the sponsor developed and optimized in the development of Kalydeco and Orkambi were used in the development of tezacaftor/ivacaftor.

Based on historical data from other approved CFTR modulators of the sponsor and the positive outcome of Study 108, the sponsor believes the FRT assay reliably predicts clinical response to tezacaftor/ivacaftor. Mutations were selected for inclusion in Study 108 based on the similar clinical phenotype of populations with each RF mutation, as well as the *in vitro* response in the FRT assay. The positive Study 108 results demonstrate that combining the comprehensive understanding of CFTR mutation biology, the known mechanism of action of tezacaftor and ivacaftor, and the *in vitro* assay results successfully predicted the clinical response. Therefore, the sponsor has confidence that all mutations in the proposed Symdeko indication are clinically responsive to tezacaftor/ivacaftor.

- 2. In Study 106, at Baseline, the median value for sweat chloride was 101.5 with minimum of 38.5 and maximum of 140.0. Please describe how patients with sweat chloride < 60 were included in the study; [and]**
- 3. In Study 108, at Baseline, median sweat chloride was 74.3 with minimum of 11.0 and maximum of 135.0. Please describe how patients with sweat chloride < 60 were included in the study.**

Sweat chloride concentrations at the Screening Visit or documented in the medical record were used to determine eligibility; however, given the lower sweat chloride concentrations in CF patients with RF mutations compared to F508del homozygous patients, the criteria differed between Studies 106 and 108. All subjects in Studies 106 and 108 met the eligibility criteria for sweat chloride.

Subjects in Study 106 were required to have a sweat chloride concentration  $\geq 60$  mmol/L at the Screening Visit or documented in the medical record. As noted in the Delegates' question, the minimum value for baseline (Day 1) sweat chloride in Study 106 was < 60

mmol/L. Two subjects had sweat chloride values < 60 mmol/L on Day 1. Subject [information redacted] (tezacaftor/ivacaftor group) had a mean sweat chloride value on Day 1 of 38.5 mmol/L; this subject was eligible for the study based on a screening value of 104 mmol/L. Subject [information redacted] (placebo group) had a sweat chloride value on Day 1 of 42 mmol/L; this subject was eligible for the study based on having a sweat chloride result of 138 mmol/L at the time of diagnosis, as documented in their medical record.

Given the lower sweat chloride concentrations of CF patients with residual function mutations, subjects in Study 108 were not required to have sweat chloride > 60 mmol/L. Subjects with sweat chloride values < 60 mmol/L were eligible if they had documentation of an eligible CFTR genotype and evidence of chronic sinopulmonary disease manifested by (but not limited to) at least one of the following: (1) persistent colonisation/infection with typical CF pathogens, including *Staphylococcus aureus*, *Haemophilus influenzae*, and mucoid and non-mucoid *Pseudomonas aeruginosa*; (2) chronic cough and sputum production; (3) persistent chest radiograph abnormalities (for example, bronchiectasis, atelectasis, infiltrates, hyperinflation); or (4) nasal polyps, chronic sinusitis; radiographic or computed tomographic abnormalities of the paranasal sinuses. All subjects in Study 108 who had a sweat chloride value < 60 mmol/L had documented evidence of chronic sinopulmonary disease.

**4. In the FDA clinical review of tezacaftor/ivacaftor, an event of death was reported in Study 110. This event does not seem to be reported in the CSR submitted to the TGA. Please clarify.**

The death reported in Study 110 occurred after the data lock point for the interim analysis for Study 110 (6 March 2017) and therefore was not part of the CSR submitted in the TGA submission. Information about the death was provided to the FDA as part of the Day 90 post-submission safety update report that is required to be submitted during the New Drug Application (NDA) review. The event involved a subject with multiple significant CF comorbidities who died due to respiratory failure approximately 2 months after having discontinued study drugs. The death was considered unrelated to study drug treatment by the investigator and sponsor.

**5. In the Study 110 CSR, sponsor has mentioned that patients with specific genotypes with inadequate response to clinical efficacy in Studies 106, 107, 108 and 109 were recommended to discontinue treatment in Study 110. Please clarify whether there were any patients who were not allocated in to treatment cohort in Study 110 and if so, which genotypes did they have?**

All subjects who participated in Study 110 were enrolled in the Treatment Cohort. No subjects elected to enrol in the Observational Cohort. Based on the results of Studies 107 and 109 not meeting their primary endpoint, all subjects from these studies who had enrolled in the Treatment Cohort of Study 110 were discontinued, and the eligible genotypes from these studies were not included in the proposed indication. No subject with F/F or F/RF mutations who completed Studies 106 or 108 were discontinued from Study 110 based upon genotype.

**6. In Study 108, patients with R347H mutation that was ivacaftor responsive but not identified as tezacaftor/ivacaftor responsive at maximal concentration in in vitro study were recruited. There were 8 patients included in the study, with 2 of them in tezacaftor/ivacaftor arm. This mutation is not included in the proposed indication. However, data from these patients have been used in the analysis. Please explain why there was a disparity in defining treatment responsiveness between in vitro and clinical studies. Also, its potential implications.**

The criteria for defining response were different for the clinical study and the indication. Mutations were selected for the clinical study based on response to ivacaftor, and

mutations were selected for the indication based on response to tezacaftor/ivacaftor. More detailed rationale for this is provided below. *In vitro* and clinical results for R347H were consistent and showed that this mutation is responsive to ivacaftor monotherapy and that additional benefit was not provided by the tezacaftor/ivacaftor combination. The *in vitro* criteria for inclusion in the indication were mutations that when expressed in FRT cells had (1) increases in chloride transport at least 10 percentage points over baseline with tezacaftor/ivacaftor, and (2) a significantly greater increase in chloride transport with tezacaftor/ivacaftor than with ivacaftor alone. Tezacaftor/ivacaftor did not result in a statistically significant increase in chloride transport compared to ivacaftor when tested on FRT cells expressing R347H.

Study 108 enrolled subjects with CFTR mutations that were pre-selected based on a clinical phenotype (characteristic of residual function) and an *in vitro* response in FRT cells to ivacaftor. The rationale for testing responsiveness to ivacaftor *in vitro* was that ivacaftor can only act on CFTR proteins present at the cell surface. Thus, an *in vitro* response to ivacaftor of FRT cells expressing a given mutation confirmed the presence of CFTR protein on the cell surface (characteristic of mutations that result in a RF phenotype). For this reason ivacaftor (rather than tezacaftor/ivacaftor) responsiveness was used to select mutations for Study 108.

The sponsor would like to clarify that there were 4 subjects with R347H enrolled in Study 108, not 8 subjects as indicated in the question. Study 108 was a cross-over design and each subject was randomised to one of 6 treatment sequences in which they received 2 different treatments for 8 weeks each. As a result, data are available for R347H subjects for placebo (n = 3), ivacaftor (n = 3), and tezacaftor/ivacaftor (n = 2) across the 6 treatment sequences. No additional benefit in ppFEV<sub>1</sub> or sweat chloride was observed when R347H subjects received tezacaftor/ivacaftor compared to ivacaftor (which is consistent with the finding that tezacaftor/ivacaftor did not increase chloride transport over ivacaftor in R347H-expressing FRT cells *in vitro*).

R347H was included in the pre-defined analysis set for the primary endpoint, which included all eligible mutations, and the predefined grouping minimises bias in the overall analysis. Based on the consistency between the *in vitro* and clinical results, R347H did not meet criteria for inclusion in the proposed indication. Considering the small sample size for R347H (4 subjects), inclusion of R347H in the analysis does not have implications for the overall response observed in Study 108.

#### ***Remaining sponsor comment on evaluations***

Points in bold italic are extracted from Delegates overview or nonclinical evaluation report

*From the delegate's overview*

#### ***Proposed PI change: Mechanism of action***

The sponsor believes the data from Studies 106 and 108 demonstrated substantial, sustained, and consistent treatment effects across multiple endpoints including ppFEV<sub>1</sub>, CFQ-R respiratory domain score, PEx and BMI for subjects with F/F and F/RF CFTR mutations. These results were confirmed and extended through the Study 110 interim analysis. The sponsor accepts the deletion of 'modifies the course of the disease' but proposes retain part of the statement in relation to Symdeko targeting the underlying cause of CF. It is well established in the scientific community that CF is caused by a reduced quantity and/or function of the CFTR protein of the epithelial surface of the lung, pancreas, and other organ systems. Tezacaftor and ivacaftor directly treat underlying defects in the CFTR protein. Tezacaftor increases the processing and trafficking of CFTR to the cell surface, where ivacaftor can act to increase the channel open probability. The combined effect of tezacaftor/ivacaftor is an improvement in CFTR function (that is,

chloride ion transport). Clinical outcomes demonstrate that tezacaftor/ivacaftor provides multisystem benefits, consistent with CFTR modulation.

***'tezacaftor/ivacaftor responsiveness was defined by the maximum in vitro effect. However the toxicology evaluator concluded that the responsiveness obtained at therapeutically relevant concentrations to be more relevant.'***

The sponsor believes that the best way to account for the pharmacological effect of the major metabolite M1 - tezacaftor is to use a concentration of tezacaftor in the assay that accounts for both the observed *in vivo* concentration and similar biological activity of M1 - tezacaftor and tezacaftor. Therefore, 10 µM tezacaftor was used instead of 3 µM tezacaftor in the assay because the efficacy of 10 µM tezacaftor is equal to the pharmacological effect associated with the combination of the individually clinically relevant concentrations of tezacaftor and M1 - tezacaftor. Using 3 µM tezacaftor would under-estimate the pharmacological contribution of M1 - tezacaftor and significantly underestimate the effect of tezacaftor for those mutations. Based on this, the sponsor proposes to retain D110E and F1052V in the proposed list of RF mutations.

***In vitro-clinical correlation: 'In spite of the 'treatment responsiveness' demonstrated in vitro with G551D mutation, treatment with tezacaftor/ivacaftor in Study 109 did not achieve a significant change in lung function. This highlights the discordance that could happen between in vitro findings and treatment outcome. 9 out of 26 CF mutations proposed by the sponsor are based on in vitro data only. It is uncertain whether individual patients with these specific mutations who achieved significant in vitro findings also will achieve significant treatment outcomes.'***

Results from Study 109 were consistent with predictions from the *in vitro* data, as subjects with gating mutations responded to treatment with tezacaftor/ivacaftor, as assessed by sweat chloride. The sponsor acknowledges that while the *in vitro* FRT data predicts whether an individual mutation will benefit from CFTR modulators, it may not predict the magnitude of the response for clinical endpoints. For this reason, clinical studies in subjects with groups of mutations are done to confirm responsiveness and evaluate benefits across multiple clinical endpoints. In the case of Study 109 the sweat chloride treatment effect (an *in vivo* measure of CFTR function) was greater in patients treated with tezacaftor/ivacaftor than those treated with ivacaftor; these results were consistent with the *in vitro* data. However, the magnitude of change for ppFEV<sub>1</sub> was similar between ivacaftor and tezacaftor/ivacaftor, thus the study did not meet its primary endpoint and these mutations are not included in the proposed indication. Given the improvement in ppFEV<sub>1</sub> observed with ivacaftor monotherapy in patients with mutations that are demonstrated to be highly responsive to ivacaftor monotherapy *in vitro* and in clinical studies, it may be difficult to observe additional acute benefits this endpoint in subjects with these mutations after treatment with tezacaftor/ivacaftor. Unlike ppFEV<sub>1</sub>, sweat chloride levels are a direct measurement of CFTR function, and Study 109 results demonstrated that tezacaftor/ivacaftor reduces sweat chloride more than ivacaftor alone as predicted by the *in vitro* data.

The results of all 4 Phase III studies of tezacaftor/ivacaftor were consistent with the FRT assay results. As described above, Study 109 results were consistent with *in vitro* data. Study 107 was also consistent with the result of the FRT assay showing that 1 copy of the F508del allele is not sufficient to provide benefit. Studies 106 (F/F) and 108 (RF) met their primary endpoint, and support inclusion of all proposed mutations in the label. For the 9 RF mutations that were too rare to be enrolled in Study 108 in sufficient numbers, the predictability of the *in vitro* results for the clinical outcomes support their inclusion in the indication. Note that future studies will not be able to study populations with these mutations in a more robust manner and these patients will likely remain without a treatment option that targets the underlying cause of disease if they are omitted from the Symdeko indication.

### ***Safety – Distal Intestinal Obstruction Syndrome (DIOS)***

***The Delegate has recommended to add this information in PI and RMP. Delegate's comments: 'The sponsor needs to add 'Distal Intestinal Obstruction Syndrome' as an important potential risk to the summary of safety concerns.'***

The totality of clinical evidence does not presently support an association between DIOS and tezacaftor/ivacaftor, and consequently DIOS should not be included in the RMP as an important potential risk or in the PI. The background rate of DIOS in CF patients, including those 12 to 18 years of age, is high. In the pooled Phase III studies, 13.3% of subjects had a prior history of DIOS, and the incidence was higher in subjects homozygous for the F508del mutation (16.7%) than in subjects with F508del/RF genotypes. These data are consistent with the published literature, including Houwen et al<sup>37</sup> who reported a rate of DIOS between 16 to 22% in 12 to 18 year olds. The incidence observed in the tezacaftor/ivacaftor clinical studies, including 12 to < 18 years olds, was well within these background rates.

In the pooled placebo-controlled Phase III studies, the overall incidence of DIOS was balanced (4 subjects [0.8%] on placebo versus 5 subjects [1.0%] on tezacaftor/ivacaftor).

Subjects who completed the Phase III studies were eligible to enrolled in the open label extension Study 110, in which subjects who took active study drug in their parent study continued taking it in Study 110 (Active - tezacaftor/ivacaftor) and subjects who took placebo in their parent study began taking tezacaftor/ ivacaftor in Study 110 (Placebo - tezacaftor/ivacaftor). In this study, no increase in the exposure-adjusted rate of DIOS was evident in either the Placebo - tezacaftor/ivacaftor or Active - tezacaftor/ivacaftor groups with longer-term treatment (approximately 2 fold that of subjects in the PC-SS).

While all 5 reported events of DIOS in Study 110 IA1 were reported in the sub-group of 12 to < 18 year olds who had received tezacaftor/ivacaftor in the parent studies, the clinical details do not suggest an association with tezacaftor/ivacaftor. In 2 subjects, the events were self-limited and resolved without interruption of tezacaftor/ivacaftor and were considered not related to treatment. In the third subject the event of DIOS occurred approximately 3 weeks after tezacaftor/ivacaftor had been interrupted for an unrelated issue and the event of DIOS was considered not related to tezacaftor/ivacaftor. The remaining 2 subjects each had a prior history of DIOS. In 1 subject the event of DIOS resolved after a brief interruption of tezacaftor/ivacaftor treatment and was considered not related. The other subject with a history of DIOS [information redacted] approximately 3 months after interrupting treatment with tezacaftor/ivacaftor.

Overall, the totality of the data does not suggest an association between tezacaftor/ivacaftor and DIOS. The majority of the DIOS events were considered not related to tezacaftor/ivacaftor and the subjects had either a prior history of DIOS or the events were consistent with clinical manifestations of the underlying CF disease. Therefore, the sponsor does not consider 'Distal intestinal obstruction syndrome' as an important potential risk to be included in the Symdeko RMP or included in the PI. The sponsor will continue to evaluate all relevant data as available, for any change in assessment, including at the conclusion of Study 110.

#### ***Nonclinical report***

***Delegates question on non-clinical cataract finding: 'The sponsor notes that the sentence is included in the PIs for Kalydeco and Orkambi. Its inclusion in the PIs for those products predated the addition of text relating to clinical findings of cataracts from post-market data. With analogous findings in patients having been observed, the***

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<sup>37</sup> Houwen, R.H., et al. (2010), Defining DIOS and constipation in cystic fibrosis with a multicentre study on the incidence, characteristics, and treatment of DIOS, *Pediatr Gastroenterol Nutr.* 2010; 50: 38-42.

***animal findings are now considered to be relevant to humans. The final sentence should therefore be removed: 'This finding has not been observed in older animals. The potential relevance of these findings in humans is unknown'. This change is also warranted for Kalydeco and Orkambi in future updates to those products' PIs.***

The sponsor proposes to retain the statement, 'The potential relevance of these [non-clinical] findings in humans is unknown.' as the sentence remains true. The overall ocular safety data for tezacaftor/ivacaftor, Kalydeco, and Orkambi from clinical trials and post-marketing experience do not support an association between drug treatment and cataracts, although a contributing role may not be fully excluded. While cases of cataracts have been reported with ivacaftor monotherapy and combination therapy, these most likely represent background findings not attributable to treatment, as most have been subtle findings, varied in locations (unlike the non-clinical finding, which were nuclear cataracts), and without impact on vision. Confounding factors such as corticosteroid use, exposure to radiation, et cetera, are also present in many cases. A 2 year post-marketing ocular safety study with ivacaftor did not suggest an association between ivacaftor and cataracts, nor was there evidence of progression of cataracts that were present at Baseline, based on the sensitive and highly objective Lens Opacity Classification Score III grading. When coupled with the high background prevalence of lens opacities in CF patients, in the context of the collective clinical trial and post-marketing experience in humans, the reports of cataracts in patients are believed to represent background findings rather than associated with ivacaftor and do not represent a translation of the non-clinical findings from the juvenile rat study in patients. The concluding sentence of the non-clinical text therefore remains true, and the sponsor recommends it remain in the Australian PI.

### **Advisory Committee Considerations<sup>38</sup>**

The ACM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACM taking into account the submitted evidence of efficacy, safety and quality, considered Symdeko, tablets containing 100 mg of tezacaftor and 150 mg ivacaftor, to have an overall positive benefit-risk profile for the indication:

*Symdeko is indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence.*

In providing this advice the ACM noted the following:

- Study 106 was a Phase III, randomised, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of tezacaftor/ ivacaftor in subjects aged 12 years and older with CF, homozygous for the F508del-CFTR mutation. There was a modest, but statistically significant improvement (4.0 percentage points) in the primary outcome, absolute change from Baseline in ppFEV1 through Week 24. There

<sup>38</sup> The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

was a statistically significant reduction (35%) in the rate of pulmonary exacerbations (a secondary outcome) when compared to placebo.

- Study 108 was a Phase III, randomised, double-blind, placebo-controlled, crossover study evaluating the efficacy and safety of tezacaftor/ivacaftor and ivacaftor monotherapy in subjects aged 12 years and older with cystic fibrosis, heterozygous for the F508del-CFTR mutation, and a second allele with a CFTR mutation predicted to have residual function. There was a statistically significant improvement from Baseline in ppFEV1 for tezacaftor/ivacaftor group compared to placebo (6.8 percentage points (95% CI: 5.7, 7.8;  $P < 0.0001$ )) and ivacaftor (2.1 percentage points (95% CI: 1.2, 2.9;  $P < 0.0001$ )). There was a statistically significant improvement in CFQ-R respiratory domain score from Baseline with tezacaftor/ivacaftor compared to placebo.
- Study 107 was a Phase III randomised controlled trial in CF patients who are heterozygous for the F508del-CFTR mutation and with a second CFTR mutation that is not likely to respond to tezacaftor and/or ivacaftor therapy (F508del/NR). There was a numerical improvement in ppFEV1, with a treatment difference of 1.2 percentage points; however it did not achieve statistical significance. Secondary endpoints such as sweat chloride concentration change in BMI and number of pulmonary exacerbations did not achieve statistical significance with treatment difference for tezacaftor/ivacaftor group, when compared to placebo.
- Overall, the incidence of serious adverse events across Study 106 and 108 was lower in the tezacaftor/ivacaftor group compared to the ivacaftor and placebo groups.
- More than 270 disease causing variants of CF have been described. The ACM considered it acceptable to include *in vitro* responding variants as part of the indication in the absence of clinical trial data in those patients with a heterozygous variant that was shown to have *in vitro* evidence of a response (see later). The ACM was of the opinion that the rarity of these mutations would make these very difficult to study, and that not including them in the indication reduces access to treatment for patients with these rare variants.
- Symdeko is approved in the US with an indication similar to that proposed in this application.

### ***Proposed conditions of registration***

The ACM agreed with the Delegate on the proposed conditions of registration.

### ***Proposed PI/ CMI amendments***

The ACM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- A statement in the 'Posology and method of administration' section of the PI to specify that genotype testing should be performed in a National Association of Testing Authorities accredited laboratory.

### ***Specific Advice***

The ACM advised the following in response to the Delegate's specific questions on the submission:

#### ***1. Please comment on correlation between genotype/phenotype/clinical characteristics of cystic fibrosis.***

The ACM advised that there was only a very general correlation between genotype/phenotype and the clinical characteristics of CF, and it was likely that genetic modifiers in other genes have an effect on the pathology. F508del mutation is recognised as the most severe CF causing variant, with pulmonary and pancreatic disease

manifestations, and has high sweat chloride concentrations. However some patients with equivocal sweat chloride tests also have clear evidence of CF.

**2. Does sweat chloride concentration correlate with CFTR function and disease severity?**

The ACM advised that sweat chloride concentration may correlate with CFTR function. Sweat chloride concentration was not necessarily correlated with disease severity. The committee noted that in general, patients with the F508del mutation have higher sweat chloride levels, but in patients with other disease-causing variants, sweat chloride concentration may not be as high and sometimes equivocal.

**3. Does improvement in sweat chloride concentration correlate with an improvement in disease manifestations?**

The ACM considered that the strength of a correlation between improvement in sweat chloride concentration and an improvement in disease manifestation was uncertain at this stage. In the ivacaftor trial 'Study of ivacaftor in cystic fibrosis subjects aged 12 years and older with the G551D mutation (STRIVE)', ivacaftor demonstrated a mean reduction in measured sweat chloride levels of 48.1 mmol/L ( $p < 0.001$ ) compared to placebo and was also associated with significant improvement in lung function and quality of life. The magnitude of the reduction in sweat chloride concentration in the pivotal studies for this application however was not as great.

The ACM also noted that in patients with lower baseline sweat chloride concentrations, while there may not necessarily be an improvement in these levels with treatment, there may be other observed clinical improvements.

The ACM was of the view that factors such as age, disease severity, bacterial colonisation, nutritional status at start of treatment would also be expected to influence the effect of treatment on disease manifestations.

**4. Does the method by which patients with cystic fibrosis in Australia have their genotype tested need further clarification in Symdeko PI?**

The ACM advised that the PI needs to specify that testing should be performed in a National Association of Testing Authorities accredited laboratory.

**5. Please comment whether the packaging of Symdeko tablets is acceptable.**

The ACM considered the packaging of Symdeko to be acceptable.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

## Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Symdeko tezacaftor 100 mg/ivacaftor 150 mg film-coated tablet and ivacaftor 150 mg film-coated tablet composite pack for indicated for:

*Symdeko is indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence. Refer to Table 1 for a list of responsive mutations.*

### **Specific conditions of registration applying to these goods**

- Symdeko (tezacaftor/ivacaftor) is to be included in the Black Triangle Scheme. The PI and CMI for Symdeko must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- EU-Risk Management Plan (EU-RMP), version 1.0, dated 18 July 2017 (DLP 6 March 2017), with Australian Specific Annex, version 1.0, dated 13 December 2017 included with submission PM-2017-04765-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- Submit the results of the 5-year planned Post Authorisation Safety Study (PASS), Study 661-117 when available to TGA.

### **Attachment 1. Product Information**

The PI for Symdeko approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

## **Therapeutic Goods Administration**

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