Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ivacaftor

Proprietary Product Name: Kalydeco

Sponsor: Vertex Pharmaceuticals Australia Pty Ltd

November 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- 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, in that it will provide 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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I. Introduction to product submission

Submission details

Type of submission:	New Chemical Entity
Decision:	Approved
Date of decision:	1 July 2013
Active ingredient:	Ivacaftor
Product name:	Kalydeco
Sponsor's name and address:	Vertex Pharmaceuticals Australia Pty Ltd Level 32 / 101 Miller Street North Sydney NSW 2060
Dose form:	Tablet
Strength:	150 mg
Containers:	Blister pack and bottle
Pack size:	56
Approved therapeutic use:	Kalydeco is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the CFTR gene.
Route of administration:	Oral
Dosage (abbreviated):	The recommended dose for adults and paediatric patients is 150 mg taken orally every 12 h (300 mg total daily dose).
ARTG numbers:	198654 and 198655

Product background

Cystic fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality. Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that result in absent or deficient function of the CFTR protein at the cell surface. Gating mutations result in a CFTR protein with a primary defect of low channel open probability compared to normal CFTR. The *G551D* mutation is the most common gating mutation worldwide and, when paired

with another mutation associated with minimal CFTR function, will most often result in a severe CF clinical phenotype.

Ivacaftor is a CFTR modulator that provides a new therapeutic approach to the treatment of CF by restoring the function of the CFTR protein. Ivacaftor potentiates normal and mutant CFTR forms with a variety of protein defects and increases the CFTR channel opening probability to enhance chloride transport. Currently, in Australia, there are no marketed drugs in this pharmacological class and no approved drugs targeting the dysfunctional CFTR channel.

This AusPAR describes the application by Vertex Pharmaceuticals Australia Pty Ltd (the sponsor) to register 150 mg ivacaftor tablets (Kalydeco) for

> *"the treatment of cystic fibrosis in patients age 6 years and older who have a G551D mutation in the CFTR gene".*

The TGA designated ivacaftor (Kalydeco 150 mg film coated tablet) as an orphan drug on 14 March 2012 for *the treatment of cystic fibrosis (CF) in patients who have a gating or an R117H mutation in the CFTR gene*.

The *G551D* mutation of the CFTR gene is classified as a gating mutation. Therefore, the proposed indication falls within the scope of the Orphan Drug Designation granted by TGA.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 9 July 2013.

At the time this application was considered by the TGA tablets containing ivacaftor were approved in the USA (January 2012), the European Union (EU, July 2012) and Canada (November 2012).

Product Information

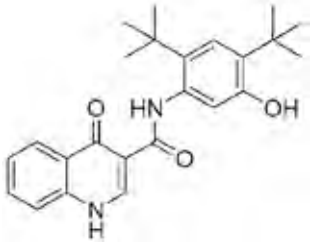
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

The drug substance (structure shown below) is a white to off-white crystalline solid that is manufactured by chemical synthesis. It is practically insoluble in aqueous media and is only slightly soluble in most organic solvents.

Figure 1. Structure of ivacaftor



The drug substance specification includes appropriate tests and limits for appearance, identification, assay and impurities.

Drug product

The product is an unscored, immediate release 150 mg ivacaftor-containing tablet for oral administration that is formulated using conventional excipients.

Separate specifications control the dispersion and tablets. In each case appearance, identification, assay and degradation products are adequately controlled. The tablets specification includes tests to control uniformity of dosage, dissolution, physical form of the drug substance and microbial quality. The dissolution method has been appropriately developed.

Stability data have been generated under accelerated and long-term conditions to justify the proposed shelf life (for tablets stored in HDPE bottles and PVC/Aclar/Al blisters) of 30 months at or below 30°C.

Biopharmaceutics

Most of the clinical trials were conducted using the proposed commercial formulation.

The following biopharmaceutic studies were provided with this submission.

- VX05-770-001: single doses of the drug substance were administered over doses of 25–800 mg in the fasted state (to healthy volunteers and subjects with CF). Doses of 275 mg were administered following high fat and standard breakfasts. Multiple doses were administered over a 14 day period, with 125 mg and 250 mg of the drug substance administered every 12 h following a standard breakfast.
- VX06-770-002: the bioavailability of a 50 mg prototype tablet formulation was determined relative to the reference formulation administered in study VX05-770-001 under fasted and fed conditions.
- VX08-770-007: the bioavailability of the two 150 mg tablets formulations was determined relative to the 50 mg tablet formulation used in study VX06-770-002.
- VX10-770-012: the food effect of the proposed 150 mg formulation was examined.

The studies showed:

- The exposure of ivacaftor increased approximately 2-4 fold when given with food containing fat.
- After oral administration of a single 150 mg dose to healthy volunteers under fed conditions, the means (± standard deviation (SD)) for are under the concentration-time curve (AUC) and maximum concentration (C_{max}) were 10,600 (5260) ng.hr/mL and 768 (233) ng/mL, respectively. The median (range) time to achieve C_{max} (t_{max}) is approximately 4.0 h (3.0-6.0 h) in the fed state.
- After repeated 12 h dosing, steady-state plasma concentrations of ivacaftor were reached by days 3 to 5 with an accumulation ratio ranging from 2.2 to 2.9.
- Following multiple oral dose administrations of ivacaftor, the exposure generally increased with a dose from 25 mg every 12 h to 450 mg every 12 h.
- The pharmacokinetics (PK) of ivacaftor are similar between males and females as well as between healthy volunteers and patients with cystic fibrosis.

No absolute bioavailability study was performed and this was justified on the basis of the poor aqueous solubility of the drug substance and the inclusion of a study comparing tablets to an oral solution.

Advisory committee considerations

The submission was considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) at the 149th (January 2013) meeting.

The PSC endorsed all of the questions raised by the TGA in relation to the pharmaceutic and biopharmaceutic aspects of the submission.

The committee recommended that the TGA request further information from the sponsor on the bioavailability of other formulations.

The PSC advised that the attention of the clinical Delegate and the ACPM should be drawn to the requirement that the optimal absorption of the product requires ingesting with a high fat diet and this may not be clinically appropriate in the setting of people with cystic fibrosis.

Quality summary and conclusions

The company has satisfactorily responded to requests for further information on the chemistry, quality and biopharmaceutical aspects of this application. There are no issues requiring resolution before registration from a pharmaceutical chemistry and biopharmaceutical perspective.

There are no further issues requiring resolution. Approval is recommended from a chemistry and quality control perspective.

III. Nonclinical findings

Introduction

The general quality of the submitted nonclinical data was high. All pivotal safety-related studies were conducted under good laboratory practice (GLP) conditions.

Pharmacology

Primary pharmacology

Ivacaftor was shown to increase the CFTR-mediated chloride channel current at nanomolar concentrations in electrophysiological experiments conducted with transfected mammalian cells or epithelial cells obtained from CF patients. The drug was established to act as a potentiator of the channel (that is, it increases the fraction of time the channel is open). The increase in chloride flux by ivacaftor required the presence of a cyclic adenosine monophosphate (cAMP) agonist, indicating that the drug does not itself activate the channel. It was also demonstrated that the mechanism of action does not involve stimulation of the cAMP/protein kinase A signalling pathway. Single-channel patch-clamp studies on patches of excised cell membranes supported a direct action of the drug on the channel.

Ivacaftor was active at the *G551D* mutant form of the CFTR protein as well as at all other *CFTR* gating mutants tested, wild type *CFTR* and numerous other *CFTR* mutants (including *F508del* (CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein), those with conductance mutations, mild processing mutations and various uncharacterised mutations). Ivacaftor increased chloride flux in human bronchial epithelial cells obtained from a *G551D/F508del* heterozygous subject from a baseline of 5% that of wild type *CFTR* to up to 48% of wild type activity. Similarly, in transfected Fischer rat thyroid epithelial cells, ivacaftor increased *G551D-CFTR*-mediated chloride flux from 1% that of wild type *CFTR* to up to 55%.

Ivacaftor's major metabolites, M1 (hydroxymethyl ivacaftor) and M6 (ivacaftor carboxylate), were approximately 6- and >50-fold less potent than ivacaftor at potentiating cAMP-stimulated chloride ion transport in human bronchial epithelial cells derived from a *G551D/F508del* heterozygous patient. Based on potency and exposure data, metabolite M1 (but not M6) is considered to contribute to pharmacological activity in patients.

No *in vivo* pharmacodynamic (PD) studies were conducted with ivacaftor in animals due to a lack of an adequate animal disease model.

Secondary pharmacodynamics and safety pharmacology

Screening of ivacaftor against a panel of ion channels, receptors and transporters revealed some affinity for the monoamine transporter and the serotonin (5-HT) 2C (5-HT_{2C}) receptor (ligand binding inhibited with respective 50% inhibitory concentration (IC_{50}) values of 0.85 and 0.88 μM). The clinical significance of binding to these targets is considered to be low given the demonstration of very limited penetration of the blood-brain barrier by ivacaftor in rats. Ivacaftor was found to inhibit calcium ion channels ($Ca_V1.2$) and potassium ion channels ($K_V1.5$) with micromolar potency in electrophysiological studies (respective IC_{50} values, 1.3 and 3.4 μM). Secondary PD studies were not conducted with M1 or M6.

Specialised safety pharmacology studies covered the central nervous system (CNS), cardiovascular, respiratory and gastrointestinal systems. Single oral administration of ivacaftor did not impair motor coordination (≤200 mg/kg), affect CNS function (≤1000 mg/kg/day), affect systolic or diastolic blood pressure, heart rate or core body temperature (≤100 mg/kg), or alter respiratory rate or tidal volume (≤1000 mg/kg) in rats. Ivacaftor produced concentration-dependent inhibition of the Human ether-a-go-go gene related (hERG) potassium (K^+) channel in transfected mammalian cells, but only weakly (14–35% inhibition at 0.8–8 μM; tested up to the maximum soluble concentration).

Electrocardiogram (ECG) and heart rate were unaffected by ivacaftor in dogs (≤60 mg/kg single oral dose), while a small transient increase in mean arterial blood pressure was seen 1 h post-dose at 30 and 60 mg/kg orally (119–122 compared with 104 mm Hg in controls; unaffected at 15 mg/kg PO). Ivacaftor delayed stomach emptying (≥250 mg/kg oral dose) and decreased intestinal motility (≥500 mg/kg) in rats fed a charcoal meal. While the mechanism for this is unknown, it is noted that CFTR is believed to be involved in the regulation of faecal water content in the GI tract (Strong *et al.*, 1994[1]; Ameen *et al.*, 2000[2]). Adverse gastrointestinal (GI) effects were observed in animals in the repeat-dose toxicity studies (see *Toxicology* below).

[1] Strong T.V., Boehm K. and Collins F.S. Localization of cystic fibrosis transmembrane conductance regulator mRNA in the human gastrointestinal tract by in situ hybridization. *J. Clin. Invest*. 1994:93: 347–354.
[2] Ameen N., Alexis J. and Salas P. Cellular localization of the cystic fibrosis transmembrane conductance regulator in mouse intestinal tract. *Histochem. Cell Biol*. 2000:114: 69–75.

Pharmacokinetics

Peak plasma concentrations of ivacaftor following oral administration (of the amorphous form of the drug) were reached within 2–8 h in mice, 2–24 h in rats, 8.5–36 h in rabbits, 2.5–12 h in dogs and 2–4 h in humans. Time to achieve the maximum concentration (T_{max}) generally increased with dose in the laboratory animal species (signifying delayed absorption). Approximate oral bioavailability was 20–30% in mice, typically 50–60% in rats and 50% in dogs, dependent on the dosing formulation used. Plasma half lives for ivacaftor were similar in rats, rabbits, dogs and humans (10–14 h) and shorter in mice (3-5 h). C_{max} and AUC were frequently seen to be less than dose-proportional in the laboratory animal species. Greater exposure was apparent in female mice and rats compared with males; no sex difference was evident in dogs. There was plasma accumulation with repeat dosing.

Tissue distribution of radioactivity occurred rapidly following oral administration of radiolabelled (^{14}C) ivacaftor to rats (detectable amounts noted in all tissues at 1 h post-dose, the first time point investigated). Outside of the GI tract, highest levels of radioactivity were observed in the liver, adrenal glands, kidneys and pancreas. Distribution of ivacaftor to the lung (target organ) was shown, with peak concentrations of the drug approximately 5 times higher than the plasma C_{max} (lung:plasma C_{max} for total radioactivity, 3.5). Ivacaftor was detected in the epithelial lining fluid at a concentration 8.1 times higher than in plasma (assessed at 4 h post-dose). Only low levels of radioactivity were found in the brain (the peak level being 36-times less than the plasma C_{max}).

Plasma protein binding by ivacaftor was high (≥99.3%) in all species studied (mouse, rat, dog, monkey and human); metabolites M1 and M6 were also highly protein bound (≥98.5%). The degree of plasma protein binding was independent of drug concentration. Ivacaftor was highly bound to human serum albumin (≥99.7% across a range of human serum albumin (HAS) concentrations [25–65 mg/mL]), α_1-acid glycoprotein (≥99.4%) and human gamma globulin (≥97.4%). No partitioning of ^{14}C-ivacaftor-derived radioactivity into red blood cells was evident in rats.

Metabolism of ivacaftor primarily involved oxidation to form M1 (oxidation of the t-butyl group) and M6 (sequential methyl oxidation to acid). As well as oxidation, metabolism also involved glucuronic conjugation, sulfate conjugation, dehydration/ring closure, decarboxylation and reduction. M1 and M6 were the major circulating metabolites in all species studied (rats, dogs, monkeys and humans), although they were more readily formed in humans compared with animals. All metabolites identified in humans were also detected in rats and/or dogs except for two that were found in human excreta only (M8-glucuronide in urine; M405, a ring closure metabolite derived from M6, found in urine and faeces). Cytochrome P450 (CYP) 3A4 (CYP3A4) was identified as the P450 isoform chiefly responsible for the metabolism of ivacaftor, with some contribution from CYP3A5 also. While the metabolic pathways for ivacaftor in humans and animals are qualitatively similar, plasma levels of M1 and M6 relative to ivacaftor differ markedly: unchanged ivacaftor is the dominant circulating species in laboratory animals while M1 and M6 are dominant in humans and exceed levels of the parent drug (plasma $AUC_{0-24\,h}$ values for M1 and M6 in patients being 4.4- and 3.1-times higher than for ivacaftor itself [based on data in clinical Study G198]). Excretion was predominantly via the faeces in both rats and humans, with minimal renal excretion.

Comparisons of the PK profiles of ivacaftor 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 acceptable models for the assessment of ivacaftor toxicity in humans. Lower relative exposure to metabolites M1 and M6 does limit their predictive value, though.

Pharmacokinetic drug interactions

Ivacaftor showed some inhibitory activity against CYPs 2C8, 2C9 and 3A (and inconsistently against 2C19, 2D6 and 2E1); M1 against CYP2C8, 2C9 and 3A (and to a lesser extent 2A6); and M6 very weak activity against CYP2C8, 2C9 and 3A *in vitro*.
In experiments with human liver microsomes, CYP2C8 was the isoform most sensitive to inhibition (inhibitory constant K_i for ivacaftor, 3.4 μM). Ivacaftor and M1 were also shown to inhibit P-glycoprotein (IC_{50} values for inhibition of digoxin transport in Caco-2 cells, 0.17 and 8.17 μM, respectively). Ivacaftor was found not to be a P-glycoprotein substrate. Ivacaftor, M1 and M6 (up to 30 or 100 μM) did not induce CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19 or 3A4/5 in cultured human hepatocytes, nor did treatment with ivacaftor induce CYP1A, 2B, 2E, 3A or 4A activities in rats *in vivo* (≤200 mg/kg/day PO). Ivacaftor, M1 and M6 did not affect plasma protein binding by warfarin.

Toxicology

Acute toxicity

Ivacaftor displayed a low order of acute toxicity by the oral route in rodents, with no deaths or clinical signs observed up to the highest doses tested (2000 mg/kg in mice and 1000 mg/kg in rats; yielding plasma AUC for ivacaftor 10–17 and 14–21 times higher in the respective species than in patients at the maximum recommended human dose). Microscopic examination revealed gastric changes in both species (epithelial hyperplasia of the forestomach in mice; oedema, inflammation and/or ulceration of the stomach [predominantly forestomach] in rats) and myocardial inflammation and degeneration in rats.

Repeat-dose toxicity

Studies of up to 3 months duration were conducted in mice, 6 months in rats, 7 days in rabbits and 12 months in dogs. All involved oral administration (the intended clinical route). Dosing in animals was once per day, which is less frequent than that proposed clinically (twice per day) but this is not considered to impact on the validity of the studies and does allow for higher peak drug concentrations to be examined. The duration of the pivotal studies, the species used (rats and dogs), group sizes and the use of both sexes were consistent with relevant ICH guidelines.

Relative exposure

Exposure ratios (ERs) have been calculated in table below based on animal:human plasma $AUC_{0\text{-}24\,h}$ values for ivacaftor (ER_{ivac}), and also for the summed AUCs of ivacaftor, M1 and M6 (ER_{sum}). High multiples of the anticipated clinical systemic exposures to ivacaftor were obtained in the animal studies. Exposure ratios are considerably lower, though, for the sum of the drug and its major metabolites. This reflects plasma AUC values for M1 and M6 in animals that were lower than for the parent drug, in contrast to the situation in humans. Systemic exposure to M1 and M6 was almost always at subclinical levels in treated animals. For M1, relative exposure was at most 0.6 in mice (in high-dose females in the 3-month and 2-year [carcinogenicity] study), up to 1.3 and 0.7 in male and female rats in the pivotal 6-month study, and 2.0 and 1.5 in the two sexes in the rat carcinogenicity study, and 0.4 in the pivotal 12-month study in dogs. For M6, exposure met the clinical level in male rats in the pivotal 6-month study but was otherwise very low (exposure multiples of up to 0.2 in mice, 0.2 in the rat carcinogenicity study and 0.1 in the pivotal dog study). Animal studies involving direct administration of the metabolites were reported not to be feasible due to significant difficulties in synthesising the quantities that would be needed. While not ideal, considering the relative similarity of the structures of M1 and M6

compared with ivacaftor, that the metabolites are more polar than the parent drug (so that less partitioning into cell membranes and entry into cells will be expected), and less potent than ivacaftor at the primary pharmacological target (by 6- and >50-times), the safety of the major human metabolites is considered to be able to be adequately addressed by the set of studies submitted.

Table 1. Relative exposure in repeat-dose toxicity and carcinogenicity studies

Species	Study duration [study no.]	Dose (mg/kg /day)	$AUC_{0\text{-}24\,h}$ (µg·h/mL)						Exposure ratio#			
			Ivacaftor		M1		M6		Ivacaftor		Ivacaftor + M1 + M6	
			M	F	M	F	M	F	M	F	M	F
Mouse (CD-1)	3 months [VX-770-TX-012]	100	61.8	81.9	3.19	8.51	1.14	1.15	2.3	3.0	0.3	0.4
		300	159	198	15.5	35.8	4.42	8.05	6	7	0.8	1.0
		600	208	188	22.4	40.2	5.57	10.1	8	7	1.0	1.0
		1000	301	299	31.4	71.1	4.46	19.3	11	11	1.5	1.7
	2 years (carcinogenicity) [VX-770-TX-013]	25	16.1	21.5	11.1	14.6	2.00	0.79	0.6	0.8	0.13	0.16
		75	116	80.2	11.1	36.6	0.60	1.57	4.3	2.9	0.6	0.5
		200	112	203	26.3	76.1	2.73	4.85	4.1	7	0.6	1.2
Rat (SD)	4 weeks (juvenile) [VX-770-TX-025]	10	17.6	30.5	2.30	1.31	0.21	0.06	0.6	1.1	0.09	0.14
		25	62.2	98.1	8.85	3.71	0.64	0.15	2.3	3.6	0.3	0.4
		50	114	162	21.4	12.6	2.20	0.69	4.2	6	0.6	0.8
	3 months [VX-770-TX-001]	50	98.1	180	NA	NA	NA	NA	3.6	7	>0.4	>0.8
		100	271	299	NA	NA	NA	NA	10	11	>1.2	>1.3
		200	565	678	NA	NA	NA	NA	21	25	>2.5	>2.9
		400	406	824	NA	NA	NA	NA	15	30	>1.8	>3.6
	6 months (pivotal) [VX-770-TX-010]	50	445	561	131	75.2	38.9	14.7	16	21	2.7	2.8
		100	339	666	97.8	70.8	47.4	18.3	12	24	2.1	3.3
		150	476	734	160	87.3	85.0	25.6	18	27	3.1	3.7
	2 years (carcinogenicity) [VX-770-TX-014]	5	53.4	71.0	20.7	21.1	0.75	0.36	2.0	2.6	0.3	0.4
		15	213	249	76.6	61.2	2.87	1.22	8	9	1.3	1.4
		50	467	853	234	180	17.0	7.76	17	31	3.1	4.5
Dog (Beagle)	12 months (pivotal) [VX-770-TX-011]	15	222		47.5		6.4		8		1.2	
		30	252		47.5		5.9		9		1.3	
		60	303		44.9		6.4		11		1.5	
Human (CF patients; ≥6 years old) Steady state [G198]		[150 mg; twice daily]	27.2		119.8		83.4		–		–	

= animal:human plasma $AUC_{0\text{-}24\,h}$. Metabolites were not quantified in the 3-month rat study. M = male, F = female

Major toxicities

The major targets for ivacaftor toxicity were the liver, GI tract, heart and kidney, with some effects also observed in the male mammary glands and bone marrow. In addition, ivacaftor was found to cause cataracts in very young rats (see *Paediatric use* below).

Hepatocellular necrosis (central lobular) and/or inflammation were observed in 3-month studies in mice at doses ≥600 mg/kg/day (ER_{ivac}, ≥7; ER_{sum}, 1.0) and in rats at ≥200 mg/kg/day (ER_{ivac}, ≥15; ER_{sum}, ≥1.8). The histopathological findings were accompanied by changes in serum chemistry indicative of liver damage: increases in alanine transaminase (ALT) and/or alkaline phosphatatse (ALP) in mice, and increases in ALT and gamma-glutamyltransferase (GGT) in rats. Rats also showed prolongation of activated partial thromboplastin time (APTT) and prothrombin time (PT), increases in blood urea nitrogen (BUN), and a dose-dependent increase in liver weight. Hepatotoxicity was not observed in the pivotal 6-month rat study (≤150 mg/kg/day; ER_{ivac}, ≤27; ER_{sum}, ≤3.7), although bodyweight-relative liver weight was increased at all doses (≥50 mg/kg/day) and there was a slight elevation of ALT at ≥100 mg/kg/day. Hepatotoxicity was also not observed in the rodent carcinogenicity studies, or in the studies in dogs (≤60 mg/kg/day for up to 12 months; ER_{ivac}, ≤11; ER_{sum}, ≤1.5). An association with hepatic drug accumulation is seen: following treatment for 3 months, the terminal liver concentration of ivacaftor in rats dosed at 200 mg/kg/day (the lowest observed level (LOEL) for hepatotoxicity) was 24-times higher than in dogs dosed at 60 mg/kg/day (the no observed effect level (NOEL)

for hepatotoxicity in the species), while plasma exposure was only 3.5-times higher in rats compared with dogs.

Rats treated with ivacaftor at doses ≥200 mg/kg/day for 3 months showed vacuolation and cystic/ dilated lymphatics in the duodenum, jejunum and ileum. Unformed/watery stools were observed among animals at 400 mg/kg/day; chronic enteropathy (affecting all segments of the small and large intestines) was identified as the cause of death of a female rat treated at this dose level. Gastrointestinal toxicity was not encountered in the pivotal 6-month rat study (≤150 mg/kg/day; ER_{ivac}, ≤27; ER_{sum}, ≤3.7). In the pivotal 12-month study in dogs, treatment with ivacaftor was associated with stool abnormalities (unformed, watery, containing mucus) at all dose levels tested (≥15 mg/kg/day) and with vomiting at ≥30 mg/kg/day. Vomiting (as well as abnormal stools) occurred at 15 mg/kg/day in shorter studies in dogs (2 weeks and 3 months duration). Ivacaftor did not cause GI tract lesions in dogs though.

Instances of atrioventricular block were observed in single dogs per group treated at 60 mg/kg/day in the 3-month study and at each dose level (15, 30 and 60 mg/kg/day) in the 12-month study. This is recognised to be a spontaneous finding in the Beagle dog, although the finding was not reported in any of the concurrent control animals here. The relationship to treatment is unclear but is potentially related to ivacaftor's ability to block the $Ca_V1.2$ channel (IC_{50}, 1.3 μM). The incidence of supraventricular premature complex was slightly increased in dogs treated at ≥30 mg/kg/day in the pivotal 12-month study (relative exposure based on animal:human C_{max} for ivacaftor, >5). This was suggested to be related to an exaggeration of the respiratory sinus arrhythmia and canine-specific control of heart rates; the effect does not translate to morbidity or mortality. The sponsor's clinical overview states that "treatment with ivacaftor was not associated with an increased incidence of clinically significant cardiac arrhythmias, including supraventricular ectopy".

The incidence and severity of cardiomyopathy and coronary artery medial degeneration were increased in rats at ≥100 mg/kg/day in the 6-month study (ER_{ivac}, ≥12; ER_{sum}, ≥2.1), representing an exacerbation of spontaneous, age-related changes in the species. Ivacaftor did not cause cardiac lesions in dogs (≤60 mg/kg/day for up to 12 months; ER_{ivac}, ≤11; ER_{sum}, ≤1.5).

Treatment at ≥100 mg/kg/day was associated with convoluted basophilic tubular epithelia in the kidneys of male rats in the 3-month study (ER_{ivac}, ≥10; ER_{sum}, ≥1.2). In the pivotal 6-month rat study, an increased incidence/severity of chronic progressive nephropathy with tubular basophilia was observed in females at ≥50 mg/kg/day (ER_{ivac}, ≥21; ER_{sum}, 2.8) and males at ≥100 mg/kg/day (ER_{ivac}, ≥12; ER_{sum}, ≥2.1). Again, this is consistent with an exacerbation of common spontaneous changes recognised in ageing rats. No treatment-related renal lesions were observed in ivacaftor-treated dogs (≤60 mg/kg/day for up to 12 months; ER_{ivac}, ≤11; ER_{sum}, ≤1.5).

Additional histopathological changes were observed in the 3-month rat study. The incidence of female-type and mixed-type mammary tissue in male rats was increased with treatment at ≥200 mg/kg/day, and bone marrow hypocellularity was observed in both sexes at 400 mg/kg/day (ER_{ivac}, ≥15; ER_{sum}, ≥1.8). These dose levels were beyond the maximum tolerated dose (MTD). There were no similar findings in dogs or in the pivotal rat study.

Genotoxicity

The potential genotoxicity of ivacaftor was investigated in the standard battery of tests, including an *in vitro* bacterial reverse mutation assay, an *in vitro* Chinese hamster ovary cell chromosomal aberration assay and an *in vivo* mouse bone marrow micronucleus assay. The conduct of the studies was in accordance with relevant ICH guidelines. Concentrations and doses were appropriate (up to maximum recommended levels or

limited by cytotoxicity). A suitable set of *Salmonella typhimurium* and *Escherichia coli* strains was used in the bacterial gene mutation assay. All definitive assays were appropriately validated and returned negative results for ivacaftor.

Carcinogenicity

The carcinogenic potential of ivacaftor by the oral route was investigated in 2-year studies in mice and rats. Group sizes were appropriate. Suitable dose levels were selected for the mouse study, but dose selection in the rat study was not entirely appropriate. The high-dose level selected in rats (50 mg/kg/day) exceeded the MTD, requiring dosing to be stopped earlier than scheduled (in week 89 compared with week 104) due to excessive mortality. This should have been evident from the results of the already completed 6-month rat study where inhibition of body weight gain in males treated at this dose level exceeded 10%. Nevertheless, the study is considered adequate given the number of surviving animals at the late stages of the study. No treatment-related increase in tumour incidence was observed in either mice (≤200 mg/kg/day; ER_{ivac}, ≤4–7; ER_{sum}, ≤0.6–1.2) or rats (≤50 mg/kg/day; ER_{ivac}, ≤17–31; ER_{sum}, ≤3–4.5).

Reproductive toxicity

Reproductive toxicity studies submitted by the sponsor covered all stages (fertility, early embryonic development, embryofetal development, and pre- and post-natal development). Numbers of animals and the timing and duration of treatment were appropriate. All studies were conducted by the oral route.

Relative exposure

Only ivacaftor was quantified in plasma in the reproductive toxicity studies. Toxicokinetic data from rats in the 6-month repeat-dose toxicity study has been used below to allow calculation of relative exposure with respect to the summed AUC for ivacaftor, M1 and M6.

Table 2. Relative exposure in reproductive toxicity studies

Species	Study	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg·h/mL)		Exposure ratio#	
			Ivacaftor	Ivacaftor + M1 + M6	Ivacaftor	Ivacaftor + M1 + M6
Rat (SD)	Male fertility	50	337*	470*	12	2.0
		100	445*	663*	16	2.8
		200	800*	1225*	29	5.3
	Female fertility; Embryofetal development; Pre-/postnatal development	50	205	492*	7.5	2.5
		100	332	680*	12	3.0
		200	528	1518*	19	6.6
Rabbit	Embryofetal	25	41.9	≥41.9	1.5	0.2

Species	Study	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg·h/mL)		Exposure ratio#	
			Ivacaftor	Ivacaftor + M1 + M6	Ivacaftor	Ivacaftor + M1 + M6
(NZW)	development	50	114	≥114	4.2	0.5
		100	338	≥338	12	1.5
Human (CF patients) Steady state [G198]		[150 mg; twice daily]	27.2	230.4	–	–

= animal:human plasma $AUC_{0-24\,h}$; * = based on data obtained on day 90 in Study VX-770-TX-010

Low (but variable) placental transfer was seen for ivacaftor and/or its metabolites in rats and rabbits, while transfer of ^{14}C-ivacaftor-derived radioactivity in the milk of lactating rats was found to be high.

Fertility was impaired in rats treated with ivacaftor at 200 mg/kg/day (ER_{ivac}, 19–29; ER_{sum}, 5–7), with disruption of oestrus cycling and reduced corpora lutea, as well as increased pre-implantation loss, seen. This occurred in conjunction with significant toxicity (mortality and excessive inhibition of body weight gain). While no effects on sperm parameters were observed, the design of the study (involving pairing of treated males with treated females) does not allow for a definitive conclusion that the reduction in fertility observed did not involve effects in males. No effect on fertility was observed in rats at ≤100 mg/kg/day (ER_{ivac}, ≤12–16; ER_{sum}, 3).

Ivacaftor was not teratogenic in either rats or rabbits. Embryofetal development was found to be unaffected in rabbits at doses ≤100 mg/kg/day (ER_{ivac}, ≤12; ER_{sum}, ≤1.5). In rats, treatment at 200 mg/kg/day (ER_{ivac}, 19; ER_{sum}, 6.6), a maternotoxic dose, reduced fetal body weight and increased the incidence of rib and sternal skeletal variations. The NOEL for embryofetal development in the rat was 100 mg/kg/day (ER_{ivac}, 12; ER_{sum}, 3.0).

Ivacaftor did not affect postnatal development (including assessment of sexual maturation, learning and memory, and reproductive function) in the offspring of rats treated with ivacaftor at ≤100 mg/kg/day during gestation and lactation (ER_{ivac}, ≤12; ER_{sum}, ≤3.0). A dose of 200 mg/kg/day was associated with reduced pup birth weight, reduced postnatal body weight gain, and decreased perinatal survival and survival to weaning; this dose level was maternotoxic.

Pregnancy classification

The sponsor proposes Pregnancy Category B1.[3] This category applies where "studies in animals have not shown evidence of an increased occurrence of fetal damage". Given findings of reduced fetal weight and increased skeletal variations in rats (as well as decreased body weight and survival in the pre-/postnatal development study), the drug should instead be placed in Pregnancy Category B3.[4]

[3] Use in Pregnancy Category B1 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 not shown evidence of an increased occurrence of fetal damage.
[4] Use in 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

Local tolerance

Local tolerance tests were adequately conducted and revealed no dermal irritation (in rabbits), no significant ocular irritation (*in vitro* bovine cornea assay) and no skin sensitisation potential (mouse local lymph node assay) for ivacaftor.

Paediatric use

Cataracts were observed in very young rats (7 days old at the start of dosing) treated with ivacaftor for 4 weeks. This was evident at all dose levels tested (≥10 mg/kg/day PO; ER_{ivac}, ≥1.1; ER_{sum}, ≥0.14). This finding has not been observed in older rats (treated beginning at 7 weeks of age) or in the pre-/postnatal development study in the species, or in dogs (≥3.75 months old at the start of dosing in the 12-month study). The cataracts were located in the lens nucleus, the oldest portion of the lens (new fibres are added to the peripheral area as the lens develops). Given the very early state of ocular development in the animals in the study (rats are born with their eyes closed; eye opening typically takes place on postnatal day 14 or 15), together with the absence of ophthalmological changes in the other studies, this finding is considered of little relevance to the proposed use in children 6 years and older.

Impurities

Three residual solvents required toxicological qualification. The proposed limits were qualified after deriving permitted daily exposure (PDE) values based on published toxicity data and using the formula given in ICH Q3C(R3).[5]

The proposed specifications for impurities in Kalydeco are acceptable from a nonclinical perspective.

Comments on the safety specification of the risk management plan

Results and conclusions drawn from the nonclinical program for ivacaftor detailed in the sponsor's draft Risk Management Plan (RMP) are in general concordance with those of the nonclinical evaluator. The draft RMP should be updated to reflect the finalisation of the juvenile rat toxicity study (including the outstanding histopathological assessment [VX-770-TX-025]) in which cataracts were observed in treated animals. There is no alteration to the preliminary conclusion though (that is, that relevance to humans 6 years of age and older is unlikely).

Nonclinical summary and conclusions

- The nonclinical data comprised an adequate set of studies to characterise the pharmacology, PK and toxicity of ivacaftor according to applicable guidelines. All pivotal safety-related studies were conducted according to GLP.
- Ivacaftor was shown to potentiate the activity of the CFTR-mediated chloride channel *in vitro*, increasing channel current at nanomolar concentrations. The drug was active at *G551D-CFTR* and numerous other *CFTR* forms. No *in vivo* nonclinical efficacy studies were conducted due to a lack of relevant animal models.
- The major metabolites of ivacaftor, M1 (hydroxymethyl ivacaftor) and M6 (ivacaftor carboxylate), are 6- and >50-times less potent than the parent drug. Based on potency

which is considered uncertain in humans.

[5] ICH Topic Q 3 C (R3) Impurities: Residual Solvents. Note for guidance on impurities: residual solvents. (CPMP/ICH/283/95). March 1998.

and exposure data, M1 (but not M6) is considered to contribute to pharmacological activity in patients.

- Secondary PD studies identified activity for ivacaftor at the monoamine transporter and 5-HT_{2C} transporter, and some inhibitory activity against $Ca_V1.2$ and $K_V1.5$ ion channels.
- Safety pharmacology studies covered the CNS, cardiovascular, respiratory and gastrointestinal systems. The hERG K^+ channel was inhibited by ivacaftor, but only weakly. Gastric emptying and GI motility were reduced by ivacaftor in rats. No effects on CNS or respiratory function were observed.
- Moderate oral bioavailability was demonstrated in laboratory animal species. Tissue distribution of radioactivity following oral administration of ^{14}C-ivacaftor was rapid and wide; CNS penetration was minimal. Plasma protein binding was high. Metabolism of ivacaftor was shown to be mainly through CYP3A4, with some contribution from CYP3A5. Inhibition of CYP2C8, CYP2C9, CYP3A and P-glycoprotein was observed *in vitro* with ivacaftor and/or M1. Excretion was predominantly via the faecal route, with minimal renal excretion.
- Ivacaftor displayed a low order of acute oral toxicity in laboratory animal species.
- Pivotal repeat-dose toxicity studies were conducted by the oral route in rats (6 months) and dogs (12 months). The liver (hepatocellular necrosis; inflammation), gastrointestinal tract (enteropathy; vomiting and stool abnormalities), heart (atrioventricular block; supraventricular premature complex; cardiomyopathy and coronary artery medial degeneration) and kidney (convoluted basophilic tubular epithelia; chronic progressive nephropathy) were identified as the major targets for toxicity. Cataracts were seen to develop in very young rats treated with ivacaftor.
- Ivacaftor was not genotoxic in the standard battery of tests, and not carcinogenic in 2-year oral studies conducted in mice and rats.
- Impairment of (male or female) fertility was noted in rats. Treatment with ivacaftor during gestation was associated with a decrease in fetal weight and an increased incidence of minor fetal skeletal variations in rats. The drug was not teratogenic in either rats or rabbits. Pup birth weight, survival and postnatal body weight gain were decreased in rats in a pre-/postnatal development study. The observed effects all occurred in conjunction with general toxicity.
- Local tolerance tests revealed no dermal or ocular irritation or skin sensitisation for ivacaftor.

Conclusions and recommendation

- The nonclinical dossier contained no major deficiencies.
- Primary pharmacology studies, showing increased CFTR-mediated chloride flux *in vitro*, support the drug's use for the proposed indication.
- Activity at the monoamine transporter and the 5-HT_{2C} receptor, revealed for ivacaftor in secondary pharmacology studies, is not considered to be of clinical significance given the drug's expected limited entry into the CNS. The relevance of ivacaftor's ability to block $Ca_V1.5$ and the ECG abnormalities observed in treated dogs is likely to be low, but the findings do warrant particular attention to the ECG assessments in the clinical studies.
- The findings in repeat-dose toxicity studies in rodents are not considered to be of particular relevance to patients based on consideration of relative exposure and species specificity. Hepatotoxicity was seen to involve rodent-specific hepatic drug

accumulation; cardiac and renal lesions reflect an exacerbation of common age-related findings in rats. Ivacaftor was well tolerated in the studies in dogs, with no treatment-related histological changes evident. The relevance of GI disturbances (emesis and stool abnormalities) in dogs is readily addressed by clinical data.

- The finding of cataracts in very young rats is considered to be of little relevance to the proposed patient population (≥6 years of age) given that treatment evidently requires drug exposure at a very early stage of lens development.
- Ivacaftor is not genotoxic and is not considered to pose a carcinogenic hazard.
- Adverse effects seen in developmental studies in rats are considered most likely to have occurred secondary to maternal toxicity, but warrant placement of the drug in Pregnancy Category B3 (rather than B1 as the sponsor proposes).
- There are no nonclinical objections to the registration of Kalydeco for the proposed indication.
- The RMP should be updated in line with recommendations under *Comments on the Safety Specification of the Risk Management Plan* above.

Recommendations regarding revisions to nonclinical statements in the proposed PI are beyond the scope of the AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Ivacaftor is a selective potentiator of the CFTR protein which targets the underlying defect of CF. Ivacaftor acts by increasing the CFTR channel opening probability to enhance chloride transport. Currently, in Australia, there are no marketed drugs in this pharmacological class and no approved drugs targeting the dysfunctional CFTR channel.

In 2006, Vertex Pharmaceuticals Incorporated (Vertex) began the clinical development of ivacaftor in the US and subsequently expanded the development to include the EU, Canada, and Australia.

Scope of the clinical dossier

The submission contained the following clinical information:

Module 5[6]:

- Clinical pharmacology studies, including 15 that provided PK data and 2 that provided PD data.
- Population PK analyses.
- Two pivotal Phase III efficacy and safety studies (102 and 103).
- Two Phase II studies (101 and 104).

[6] The full numerical titles of studies mentioned in this section are: VX08-770-102, VX08-770-103, VX06-770-101, VX08-770-104 and VX08-770-105, respectively.

- One open, uncontrolled long term study (105).
- Other information included pooled analyses, meta-analyses, Integrated Summary of Efficacy, Integrated Summary of Safety.

Module 2

- Clinical overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Paediatric data

The submission included PK, PD, efficacy and safety data in children aged 6 years and over.

Good clinical practice

All clinical studies were performed in compliance with Good Clinical Practices (GCP).

Guidance

The studies were developed in general accordance with the European Medicines Agency (EMA) *Guideline on the Clinical Development of Medicinal Products for the Treatment of Cystic Fibrosis, the Guidance for Industry for Chronic Obstructive Pulmonary Disease*[7]*, the ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population* (CPMP/ICH/2711/99, January 2011) and precedent from other drugs approved for CF.

Pharmacokinetics

Studies providing pharmacokinetic data

These are shown in Table 3.

Table 3. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose	VX06-770-002 VX08-770-007 VX10-770-012 VX05-770-001
	Multi-dose	VX05-770-001
	Mass balance study	VX06-770-003
	Food effect	VX-06-770-002 VX08-770-007 VX10-770-012
PK in special	Target population	

[7] see for example, *Guideline on the clinical development of medicinal products for the treatment of cystic fibrosis (EMEA/CHMP/EWP/9147/2008-corr*). 2009. Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease* (COPD) (Draft 3) (CPMP/EWP/562/98 Rev. 1). 2010.

PK topic	Subtopic	Study ID
populations	Multi-dose	
	Hepatic impairment	VX10-770-013
	Renal impairment	No studies
	Neonates/infants/children/ adolescents	VX08-770-103
	Elderly	No studies
Genetic/ gender-related PK	Males vs. Females	VX05-770-001 VX09-770-008 X08-809-005 VX06-770-101 VX08-770-102 VX08-770-103 VX08-770-104
PK interactions	Oral contraceptives	VX08-770-005
	ketoconazole	VX08-770-006
	Rifampicin	VX09-770-009
	Midazolam, rosiglitazone, fluconazole	VX09-770-010
	Desipramine	VX10-770-011
	VX08-809	VX08-809-005
Population PK analyses	Target population	Report G198

The effect of ivacaftor on the ECG QT interval[8] was also studied (Study VX09-770-008).

None of the PK studies had deficiencies that excluded their results from consideration.

Summary of pharmacokinetics

Ivacaftor is orally available and food increases the bioavailability of ivacaftor tablet formulations approximately 2- to 4-fold. The mean apparent volume of distribution (Vz/F) of ivacaftor after a single dose was similar for healthy subjects and subjects with CF (Vz/F was 220 L in healthy subjects and 203L in subjects with CF). Ivacaftor is extensively

[8] QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A lengthened QT interval is a biomarker for ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death. QTc is QT interval corrected for heart rate.

metabolised and the major metabolites (M1 and M6) were detected in plasma, urine, and faeces. In urine and faeces, M1 and M6 metabolites accounted for approximately 65% of total administered radioactivity. There was negligible urinary excretion of ivacaftor as unchanged parent drug. Following a single oral dose in the fed state, the apparent terminal half-life was approximately 12 h. The mean (SD) apparent clearance (CL/F) of ivacaftor was 12.1 L/h in healthy subjects and 12.4 L/h in subjects with CF. When administered as a solution formulation in the fasted state, over a single dose range of 25 to 800 mg in healthy male subjects, the AUC of ivacaftor increased proportionally to the dose. Ivacaftor 150 mg every 12 h (q12h) in healthy subjects reached steady-state by Day 5 with a median accumulation ratio of 2.2 to 2.9 across studies.

Ivacaftor PK was similar in healthy controls and patients with CF. Population PK analyses also predict steady-state ivacaftor exposure (AUC and minimum observed concentration [C_{min}]) in adult subjects with CF that are similar to those obtained in healthy adult subjects. Children (6-11 years) with CF had approximately 52% and 8% higher mean and median C_{min} of ivacaftor, and approximately 2-fold higher mean and median AUC of ivacaftor than adults. Ivacaftor PK were generally similar between males and females.

Moderate hepatic impairment (Child-Pugh Class B[9]) had an approximately 2-fold increase in ivacaftor $AUC_{0-\infty}$ compared with healthy subjects matched for demographics. Renal impairment has not been studied since renal excretion is not a major route of elimination. Ivacaftor is a sensitive CYP3A substrate. Ivacaftor is a weak CYP3A inhibitor and is not a CYP2C8 or CYP2D6 inhibitor. *In vitro* studies suggested that ivacaftor is not a P-glycoprotein substrate but is a P-glycoprotein inhibitor.

The proposed PI adequately reflects the findings of the studies presented and issues appropriate precautions based on the experimental findings.

Evaluator's overall conclusions on pharmacokinetics

The sponsor has provided an extensive range of PK studies evaluating single and multiple doses of ivacaftor in healthy subjects and in patients with the target condition, cystic fibrosis. Generally, the majority of studies have been performed to a high standard and *a priori* power analysis has been undertaken to justify sample sizes. There were some studies where power was inadequate and these have been acknowledged by the sponsor. Principally these were in studies of the PK in children, where relatively small numbers participated and sampling times were probably inadequate to reliably assess the parameters (particularly terminal elimination half-life).

Drug-drug interaction studies have primarily focused on the medications with effects on CYP3A, as ivacaftor is primarily metabolised by this cytochrome subgroup. Special population PK studies have been conducted but there were no studies in renal impairment. This was justified by the sponsor on the basis that ivacaftor is only minimally excreted in the urine. On the other hand, a study in severe renal failure or end stage renal disease might be useful. It seems unlikely that there would be any major changes in PK that could affect clinical outcome but there are no data. Given that the treatment of CF is likely to involve the concomitant use of multiple medications (at times) the drug-drug interaction studies presented did not appear to focus specifically on such poly-pharmacy situations and the assessment of either the PK (or PD) effects on ivacaftor.

The proposed PI reflects adequately the PK studies that have been performed and provides suitable warnings about the potential for drug-drug interactions based on the studies that have been performed as well as theoretical possibilities given the known

[9] The Child-Pugh score is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement. The total point score is then used to determine the patient's Child-Pugh class (A, B or C).

metabolic pathways for ivacaftor. However, lack of evaluation in patients with mild hepatic impairment needs to be stated more clearly in the PI.

Pharmacodynamics

Table 4 below shows the studies relating to each PD topic.

Table 4. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on FEV1 and sweat chloride ion levels	VX06-770-101
Secondary Pharmacology	Effect on QTc interval	VX09-770-008
Gender other genetic and Age-Related Differences in PD Response	No studies	
PD Interactions	No studies	
Population PD and PK PD analyses	Target Population§	Report G198

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

Adult subjects with CF who had at least 1 *G551D-CFTR* allele treated with ivacaftor had increased forced expiratory volume in 1 second (FEV1; clinical endpoint) and responses of biomarkers of CFTR function (decreases in both sweat chloride levels and nasal potential difference (NPD)). Ivacaftor did not affect the QTcF of the ECG at either therapeutic or supra-therapeutic doses. A PK/PD model was developed to describe the minimum concentration of ivacaftor required to produce clinically significant alterations in FEV1 and sweat chloride levels. Based on the modelling a dose of 150 mg every 12 h would achieve the C_{min} of approximately 423 ng/ml needed to achieve an EC_{90} (the concentration at which the effect is 90% maximum) for FEV1 in adults and children.

Mechanism of action

The cystic fibrosis transmembrane conductance regulator protein is an epithelial chloride channel responsible for aiding in the regulation of salt and water absorption and secretion in various tissues. Although CF affects multiple organs, the leading cause of mortality is the progressive loss of lung function. Forced expiratory volume in 1 second is a validated clinical endpoint to assess the effect of therapies in CF lung disease. As ivacaftor affects the CFTR protein and increases channel activity it should result in increased chloride transport. As the CFTR protein is expressed in sweat glands and in nasal epithelium, ivacaftor is expected to potentiate CFTR function in both these tissues. A decrease in either NPD or sweat chloride concentration is indicative of increased CFTR function.

In a Phase II study treatment with ivacaftor from 75 to 250 mg q12h of adult subjects with CF and the *G551D-CFTR* mutation in at least 1 allele resulted in decreased sweat chloride and NPD values and increased FEV1 that was apparent by Day 3 for sweat chloride and FEV1 and by Day 14 for NPD [not measured earlier] and persisted through Day 14 in Part 1 and Day 28 in Part 2 (Study VX06-770-101). Results for all 3 PD endpoints showed a

statistically significant linear trend of increasing response with increasing dose. Significant mean changes from baseline in FEV1 (absolute volume, percent predicted, and relative change in percent predicted) were observed in the 75, 150 and 250 mg ivacaftor groups at Day ≥3, Day 14, and Day ≥14, but not in the 25 mg ivacaftor group. The treatment differences between the 150 mg group were statistically significant in the Day 14 and Day ≥14 analyses compared to placebo. A significant mean change from baseline in the zero chloride plus isoproterenol (isoprenaline) response phase of the NPD measurement (greater negative ion current reflecting the flow of chloride across the cell membrane mediated by CFTR) was observed in the 75, 150 and 250 mg ivacaftor groups in the Day 14 and Day ≥14 analyses, but not in the 25 mg ivacaftor group. The treatment differences between the 150 mg and 250 mg ivacaftor groups versus the placebo group were significant in the Day 14 and Day ≥14 analyses. A statistically significant decrease from baseline in maximum sweat chloride was observed in all ivacaftor groups (25, 75, 150 and 250 mg) in the Day ≥3, Day 14, and Day ≥14 analyses which were significantly different from placebo in the Day ≥3, Day 14, and Day ≥14 analyses.

Evaluator's overall conclusions on pharmacodynamics

A small number of PD studies, which were generally well conducted and mostly adequately powered, were presented by the sponsor. Study 101, a dose ranging trial, also examined the relationship between ivacaftor concentrations and biological end points (FEV1, sweat chloride levels). The numbers in the study were modest but a direct E_{max} (maximum effect) model with baseline effect described the relationship between ivacaftor plasma concentration and FEV1 or sweat chloride. This was confirmed by PK/PD modelling study which included data from about 400 CF adults and children with CF.

The cardiovascular safety of ivacaftor was assessed in healthy volunteers. Assay sensitivity was established by using moxafloxacin as a control condition. There was no significant effect on QTcF[10] at doses which exceeded those recommended in clinical practise. There are no PD interaction studies with alcohol or sedative agents examining impairment of cognitive or psychomotor function which might be relevant in adults or adolescents.

Dosage selection for the pivotal studies

Study VX06-770-101 (Study 101) was a 2-part[11], double-blind, placebo-controlled, cross-over, multiple-dose, multicentered, randomised study of up to 28 days of dosing in 39 subjects (male and female) with CF and the *G551D* mutation on at least 1 *CFTR* allele and FEV1 ≥40% of predicted normal for age, sex, and height.

Ivacaftor was administered at a dosage of 25 mg, 75 mg, 150 mg or 250 mg every 12 h (q12h), 30 minutes after the start of a meal or snack. Ivacaftor or placebo was taken for 28 days in the study (Part 1: 2 periods of 14 days; Part 2: 1 period of 28 days).

Results from Study 101 suggested that ivacaftor was well tolerated, with all subjects completing dosing and study visits without discontinuations or interruptions.

[10] QT interval corrected for heart rate using Fridericia's formula

[11] The study was conducted in 2 parts: Part 1 consisted of Group A and Group B. Subjects in Group A were randomised to receive either 25 mg ivacaftor q12h, 75 mg ivacaftor q12h, or placebo for 14 days. Subjects in Group B were randomized to receive either 75 mg ivacaftor q12h, 150 mg ivacaftor q12h, or placebo for 14 days. Following a 7- to 28-day washout period, subjects receiving ivacaftor crossed over to the alternate dose strength of ivacaftor for an additional 14 days. Placebo subjects continued to receive placebo for an additional 14 days. Part 2 consisted of Group C, whose subjects did not participate in Part 1. Subjects were randomised to receive 150 mg ivacaftor q12h, 250 mg ivacaftor q12h, or placebo for 28 days.

The secondary endpoints of the study included efficacy assessments of NPD[12], sweat chloride levels, and FEV1 (Part 1 and Part 2) and Cystic Fibrosis Questionnaire-Revised (CFQ-R) (Part 2 only). Results from Part 1 showed statistically significant changes from baseline in FEV1, sweat chloride levels and NPD for the ivacaftor 75 mg and 150 mg groups compared with placebo following every 12 hours (q12h) dosing for 14 days. Results from Part 2 showed statistically significant greater improvements with ivacaftor 150 and 250 mg dosing (for 28 days) compared with placebo in FEV1, sweat chloride levels and NPD. Subjects receiving ivacaftor 150 and 250 mg dosing also reported improvements greater than the minimal clinically important difference (MCID) of 4 points in the respiratory domain of the CFQ-R. Furthermore, the number and proportion of subjects considered responders (based on the criteria of >10% relative increase in FEV1, ≥ -5 mV increase in zero chloride plus isoproterenol (isoprenaline) response in NPD, ≥20 mmol/L decrease in sweat chloride from the baseline measurement after 14 days of dosing (Part 1, Part 2, and Part 1 and Part 2 combined) and after 28 days of dosing (Part 2)) were consistently greater in groups receiving 150 and 250 mg ivacaftor compared with placebo.

Phase IIa of Study 101 established proof-of-concept for ivacaftor treatment and provided dose selection information for subjects with CF. Based on results of this study and modelling and simulations using data from a Phase I study (Study 007), a dose of 150 mg q12h was selected for Phase III Study 102 and a dose of 100 mg was selected for Part A, a lead-in PK evaluation, of Phase III Study 103. Subsequent modelling and simulations additionally using data from Part A of Study 103 resulted in selecting the 150 mg q12h dose for subjects age 6 to 11 years in Part B of the Phase III Study 103.

Efficacy

Studies providing efficacy data

The ivacaftor development program includes 2 pivotal Phase III placebo-controlled studies of subjects with CF who have a *G551D* mutation in the *CFTR* gene (Studies 102 and 103) and 1 uncontrolled Phase III, open-label rollover study (Study 105) of long-term treatment of subjects who completed 48 weeks of treatment in Study 102 or 103. Treatment with ivacaftor (all studies) or placebo (Studies 102 and 103) was administered in addition to each subject's prescribed CF therapy. The use of inhaled hypertonic saline was not permitted in Studies 102 and 103 but was allowed in Study 105. All 3 studies were conducted using the commercial formulation of ivacaftor. A summary of the pivotal Studies 102 and 103 and the extension Study 105 is shown in Table 5.

[12] NPD is a direct measure of transepithelial ion transport. Electrodes are place on the nasal mucosa and the forearm to measure the transepithelial potential difference. The nasal mucosa is then bathed in a series of solutions: Ringer's solution, amiloride, zero chloride solution, isoproterenol (isoprenaline), and ATP. The transepithelial NPD under conditions of zero chloride perfusion solution in the presence of isoproterenol (isoprenaline) is the NPD measurement most indicative of CFTR activity. The transepithelial NPD under conditions of zero chloride concentration perfusion solution in the presence of isoproterenol (isoprenaline) was of primary interest, and was the primary PD assessment for this procedure.

Table 5. Summary of efficacy studies.

Study Identifier	Study Design and Type of Control	Study Centers	Key Inclusion Criteria	Treatment	Number of Subjects Assessed for Efficacy/ Completed 24 Weeks/ Completed 48 weeks	Duration of Treatment	Efficacy Endpoints[a]
Phase 3 Controlled Studies							
VX08-770-102	Randomized, placebo-controlled, double-blind, parallel-group, multiple-dose	65 sites in North America, Europe, and Australia	Confirmed diagnosis of CF, *G551D* mutation, 12 years of age and older	Ivacaftor 150 mg q12h Placebo (Randomized 1:1)	83/80/77 78/71/68	48 weeks	**Primary** • Absolute change from baseline in percent predicted FEV_1 through Week 24 **Secondary** • Change from baseline in CFQ-R through Weeks 24[b,c] and 48 • Change from baseline in sweat chloride through Weeks 24[b] and 48 • Time to first pulmonary exacerbation through Weeks 24 and 48[b] • Change from baseline in weight at Weeks 24 and 48[b] • Absolute change from baseline in percent predicted FEV_1 through Week 48 **Tertiary** • Pulmonary exacerbations through Week 24 and 48 • Rate of decline in FEV_1 through Weeks 24 and 48 • Change from baseline in oxygen saturation through Weeks 24 and 48 • Change from baseline in EQ-5D through Weeks 24 and 48 • Hospitalizations through Weeks 24 and 48 • Outpatient sick visits to the clinic or hospital for CF-related complications through Weeks 24 and 48 • Antibiotic therapy for sinopulmonary signs/symptoms through Weeks 24 and 48
VX08-770-103	Randomized, placebo-controlled, double-blind, parallel-group, multiple dose	24 sites in North America, Europe, and Australia	Confirmed diagnosis of CF, *G551D* mutation, 6 to 11 years of age	Ivacaftor 150 mg q12h Placebo (Randomized 1:1)	26/26/26 26/23/22	48 weeks	**Primary** • Absolute change from baseline in percent predicted FEV_1 through Week 24 **Secondary** • Change from baseline in weight at Weeks 24[b]and 48 • Change from baseline in sweat chloride through Weeks 24[b] and 48 • Change from baseline in CFQ-R through Weeks 24[b,c] and 48 • Absolute change from baseline in percent predicted FEV_1 through Week 48 **Tertiary** • Pulmonary exacerbations through Weeks 24 and 48 • Rate of decline in FEV_1 through Weeks 24 and 48 • Change from baseline in oxygen saturation through Weeks 24 and 48 • Hospitalizations through Weeks 24 and 48 • Outpatient sick visits to the clinic or hospital for CF-related complications through Weeks 24 and 48 • Antibiotic therapy for sinopulmonary signs/symptoms through Weeks 24 and 48
Phase 3 Uncontrolled Study							
VX08-770-105	Non-randomized, open-label, multiple-dose	67 sites in North America, Europe, and Australia enrolled subjects from Studies 102 and 103	Completed Study 102 or 103	Ivacaftor 150 mg q12h	144 from Study 102/ not applicable 48 from Study 103/ not applicable This study is ongoing.	96 weeks	**Primary** No primary efficacy endpoint **Secondary** • Rate of decline in percent predicted FEV_1 • Absolute change from baseline (Day 1) of Study 105 in FEV_1 • Absolute change from baseline (Day 1) of previous ivacaftor study in FEV_1 • Change from baseline (Day 1) of Study 105 in CFQ-R • Change from baseline (Day 1) of previous ivacaftor study in CFQ-R • Pulmonary exacerbations • Rate of change in weight **Tertiary** • Change from baseline (Day 1) of Study 105 in EuroQol Questionnaire (EQ-5D) • Change from baseline (Day 1) of previous ivacaftor study in EQ-5D • Hospitalizations • Outpatient sick visits to the clinic or hospital for CF-related complications • Antibiotic therapy for sinopulmonary signs/symptoms

a Additional efficacy assessments included relative change from baseline in percent predicted FEV1 absolute and relative change from baseline in FEV1, absolute and relative change from baseline in FVC, percent predicted FVC, FEF25-75%, percent predicted FEF25-75%, FEV1/FVC, CFQ-R non-respiratory domains, measures of nutritional status, and levels of inflammatory mediators (Study 102).
b Key secondary endpoint. To control the overall Type I error rate, the primary endpoint and key secondary endpoints were tested in sequence as described in Section 2.1.1 (Study 102) and Section 2.1.2 (Study 103).
c The key efficacy endpoint was the change in the CFQ-R respiratory domain only. In Study 102, pooled adults/adolescents and 12 to 13 year old CFQ-R versions were used for this analysis, while the child version was used in Study 103.

Other efficacy studies

Two Phase II studies were conducted to assess the effect of ivacaftor in subjects with CF. Study 101 was conducted in subjects who have a *G551D* mutation in the *CFTR* gene, and Study 104 was conducted in subjects homozygous for the *F508del* mutation in the *CFTR* gene.

Study 101 was a dose-ranging study designed to explore the PK and PD after 14 and 28 days of treatment with ivacaftor in subjects with CF who have a *G551D* mutation in the *CFTR* gene. Treatment with ivacaftor with doses ranging from 75 mg to 250 mg q12h resulted in improved CFTR activity as measured by decreased sweat chloride and NPD values as well as improved lung function as measured by increased FEV1.

Study 104 was a randomised, double-blind, placebo-controlled, parallel-group, 16-week study (Part A) with a 96-week, open-label extension (Part B) in subjects homozygous for the *F508del* mutation in the *CFTR* gene. No clinical benefit was observed in Part A or over the first 24 weeks of open-label treatment in Part B; therefore, Part B of the study was terminated early.

Evaluator's conclusions on clinical efficacy

Two Phase II studies (101 and 104) were conducted to assess the effect of ivacaftor in subjects with CF. In the dose-ranging Study 101, treatment with ivacaftor with doses ranging from 75 mg to 250 mg q12h resulted in improved CFTR activity as measured by decreased sweat chloride levels and NPD values as well as improved lung function as measured by increased FEV1.

The randomised, double-blind, placebo-controlled, parallel-group, 16-week Study 104 (Part A) with a 96-week, open-label extension (Part B) in subjects homozygous for the *F508del* mutation in the *CFTR* gene showed no apparent clinical benefit during Part A of the study or over the first 24 weeks of open-label treatment in Part B; therefore, Part B of the study was terminated early.

The recommended dosing regimen for ivacaftor is 150 mg q12h. Chronic administration of ivacaftor is required to maintain improvement in CFTR and thus clinical benefit. For Phase IIb and Phase III studies, plasma ivacaftor C_{min} at steady state ($C_{min,ss}$) was chosen as the target exposure parameter to maintain CFTR activity throughout a dose interval. The ivacaftor dose was selected to provide a median $C_{min,ss}$ of at least the predicted EC_{90} for FEV1. Dosing recommendations were based on a combination of factors, including safety, tolerability, PK/PD modelling, simulations and efficacy.

Based on safety, tolerability, PK/PD modelling, and simulations using data from Studies 101 and 007, the ivacaftor dose selected for Study 102 (subjects 12 years of age and older) was 150 mg q12h, and the ivacaftor dose selected for Study 103 Part A (lead-in PK, subjects 6 to 11 years of age) was 100 mg. Based on subsequent modelling and simulations using data from Studies 007 and 103 Part A, the ivacaftor dose selected for the placebo-controlled treatment period in Study 103 Part B (subjects 6 to 11 years of age) was 150 mg q12h. Population PK/PD exposure-response analyses indicate that 150 mg ivacaftor q12h resulted in a median $C_{min,ss}$ of at least the EC_{90} for FEV1 across age groups ranging from 6 years of age to adults.

Two placebo-controlled Phase III studies were designed to assess the efficacy and safety of 24 weeks of treatment with ivacaftor 150 mg q12h in subjects aged 12 years and older (Study 102) and 6 to 11 years (Study 103). Placebo-controlled treatment was continued through 48 weeks to further assess safety and to confirm the durability of response. Subjects who completed 48 weeks of treatment were eligible to enrol in a long-term open-label study (Study 105).

Since ivacaftor is a systemic therapy that targets the underlying defect in CF, Studies 102 and 103 were designed to evaluate both pulmonary effects (FEV1, respiratory symptoms, and pulmonary exacerbations) and important extrapulmonary measures associated with CF (such as weight, body mass index (BMI), sweat chloride levels, and inflammatory mediators).

The same primary endpoint: the absolute change from baseline in percent predicted FEV1 through Week 24, was selected for the placebo-controlled Phase III studies. This is the recommended primary clinical endpoint in efficacy studies for CF and chronic obstructive pulmonary disease. The efficacy assessments used in the pivotal Phase III studies were widely accepted and generally recognised as reliable, accurate, and relevant to the study of subjects with CF.

The duration of evaluation in Studies 102 and 103 was consistent with recent registration studies for other therapies approved for CF and with guideline recommendations establishing durability of efficacy in chronic progressive lung diseases, including CF and chronic obstructive pulmonary disease.

Based on agreement with regulatory authorities and in consideration of the small size of the population of patients who have the *G551D* mutation in the *CFTR* gene, both the studies were adequately powered to detect clinically relevant differences between ivacaftor and placebo. Study 102 was designed to enrol a minimum of 80 subjects to provide at least 80% power to detect a treatment effect of 4.5 percentage points in absolute change in percent predicted FEV1. Study 103 was designed to enrol a minimum of 30 subjects (based on feasibility due to the size of the available population) and although it was not designed to achieve statistical significance, it was anticipated to be supportive, demonstrating a treatment effect of similar magnitude as in Study 102.

In the placebo-controlled Phase III studies, the intended commercial formulation of ivacaftor was administered orally q12h for 48 weeks to subjects with CF age 6 years and older who have a *G551D* gating mutation in the *CFTR* gene. Subject demographics and baseline characteristics were, in general, representative of the population of patients with CF for whom ivacaftor is intended. Subjects also continued on their prescribed CF therapies during the studies (with the exception of hypertonic saline). Thus, the treatment effect of ivacaftor occurred in addition to any benefit the subjects incurred while on their already-prescribed medications. Within each study, the baseline demographics of subjects (including age, weight, sex, baseline FEV1, and use of concomitant medications) were generally comparable in the ivacaftor and placebo groups.

Analysis of the primary endpoint in the placebo-controlled Phase III studies (absolute change in percent predicted FEV1 through Week 24) showed a substantial and durable treatment effect (10.6 to 12.5 percentage points) that was highly significant (P <0.0001). The improvements in FEV1 were rapid in onset and durable through the 48-week treatment period. In all subgroups evaluated (including disease severity, age, sex, and geographic region), a treatment effect in percent predicted FEV1 favouring ivacaftor was observed.

According to EMA and FDA regulatory guidance, FEV1 is the recommended primary clinical endpoint in efficacy studies for CF and chronic obstructive pulmonary disease. Improvement in FEV1 has served as the primary clinical efficacy measure in definitive CF clinical studies supporting the registration of 2 chronic CF pulmonary therapies. In the pivotal clinical studies of inhaled dornase alfa and tobramycin, 24 weeks of treatment in subjects with mild to severe CF lung disease resulted in 6% (dornase alfa) and 8% (tobramycin) relative improvement in percent predicted FEV1. FEV1 was also a secondary endpoint in the pivotal studies of inhaled aztreonam, where a relative improvement in percent predicted FEV1 of 10.2% was seen after 28 days.

Analysis of other pulmonary outcomes showed clinically meaningful improvements in respiratory symptom scores (CFQ-R) in both Studies 102 and 103 and significant reduction in the risk of pulmonary exacerbations as well as substantially decreased frequency and duration of pulmonary exacerbations. Treatment with ivacaftor resulted in statistically significant improvements in measures of nutritional status, as measured by weight and BMI. The BMI-for-age z-score of subjects aged 6 to 20 years who were treated

with ivacaftor in the placebo-controlled Phase III studies also improved compared with the score for subjects treated with placebo. At Week 48 in both Studies 102 and 103, subjects treated with ivacaftor had BMI-for-age z-scores above the 50th percentile, whereas subjects treated with placebo had scores below 50th percentile.

In addition to clinically meaningful improvements in CF lung disease and nutritional measures, ivacaftor is the first treatment to demonstrate an effect on CFTR function, as measured by sweat chloride levels. The decrease in sweat chloride levels with ivacaftor treatment is consistent with the *in vitro* effect of ivacaftor on *G551D-CFTR*. Analyses of the relationship between the change in sweat chloride levels and clinical outcomes demonstrate that the overall improvement in CFTR activity during treatment with ivacaftor, as represented by a sweat chloride reduction of at least 20 mmol/L, was associated with significantly improved pulmonary and nutritional measures. These analyses are limited by the minimal number (2 out of 101) of any subjects treated with ivacaftor who did not have a reduction of sweat chloride that was less than 20 mmol/L and by the variability in FEV1. Thus, it remains to be determined whether a smaller magnitude of improvement in CFTR activity might also be associated with clinical benefit.

Improvements in FEV1 were similar through Week 24 and Week 48 of treatment. The treatment difference for ivacaftor versus placebo through Week 48 was 10.5 percentage points in Study 102 and 10.0 percentage points in Study 103; these differences were statistically significant (P<0.0001 for Study 102 and P = 0.0006 for Study 103). Similarly, reductions in sweat chloride concentration were durable through Week 48, consistent with a sustained improvement in CFTR function. The magnitude of observed treatment effect was similar through Week 24 and Week 48 of treatment. The treatment difference for ivacaftor versus placebo through Week 48 was -48.1 mmol/L in Study 102 and -53.5 mmol/L in Study 103;these differences were statistically significant (P<0.0001 in both studies). Substantial, durable, and consistent improvements were also observed in other clinical endpoints, including the risk of experiencing a pulmonary exacerbation, respiratory symptoms as measured by CFQ-R, weight gain, and frequency and duration of pulmonary exacerbations.

In study 105, treatment with ivacaftor was durable for up to 96 weeks. For subjects previously treated with ivacaftor for 48 weeks in Studies 102 and 103, the improvements in FEV1, respiratory symptoms, and weight gain in the previous study were generally sustained with an additional 48 and 24 weeks of treatment with ivacaftor in the current study. Ivacaftor–treated subjects continued to experience pulmonary exacerbations, consistent with the pathophysiology of the disease. However, ivacaftor treatment delayed the onset of pulmonary exacerbations, and the reduction in the number of pulmonary exacerbations per subject observed with ivacaftor treatment in Study 102 was sustained in Study 105, for a total treatment duration of 96 weeks. For subjects previously treated with placebo for 48 weeks in Study 102 and Study 103, the improvements in FEV1, respiratory symptoms, weight gain, and pulmonary exacerbations observed after ivacaftor treatment were comparable to the improvements observed with ivacaftor treatment in Study 102 and Study 103.

Ivacaftor is the first therapy to demonstrate an effect on both pulmonary and extrapulmonary manifestations of CF in registration studies. Ivacaftor is unique in demonstrating broad effects in both pulmonary outcomes and nutritional status after 24 and 48 weeks of treatment; and the magnitude of the improvements in all of these measures is large and clinically meaningful.

Overall, results from the Phase III studies of ivacaftor showed that systemic treatment with ivacaftor was highly effective in the treatment of CF, as evidenced by improvement in CFTR function and substantial, durable improvements in important clinical outcomes, including FEV1, pulmonary exacerbations, respiratory symptoms, and nutritional status. The design of the Phase III studies adequately demonstrated the effects of ivacaftor,

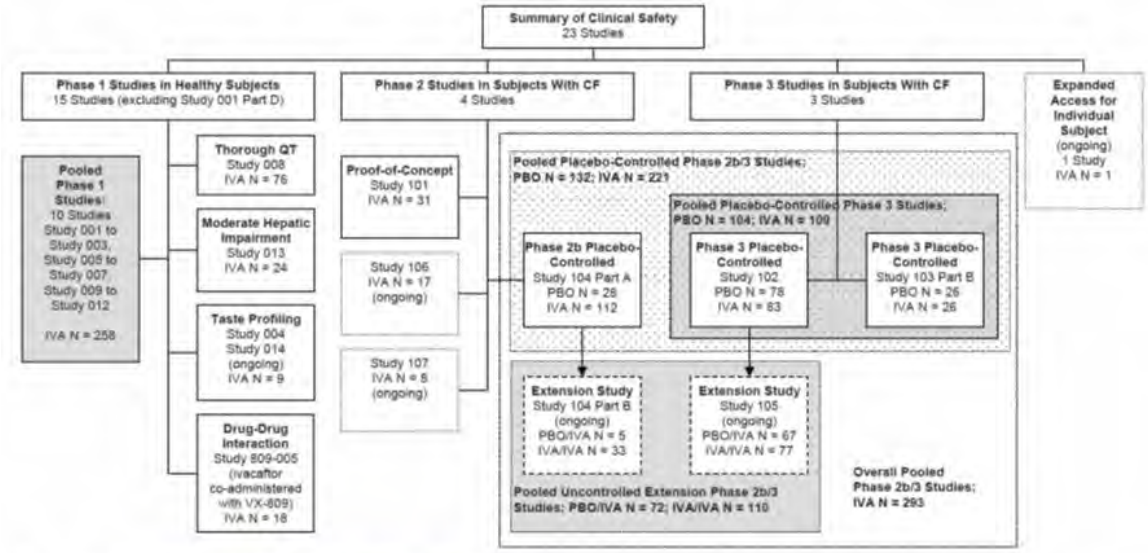
evidenced by the achievement of clinically meaningful and statistically significant effects in the primary and key secondary endpoints, and by the reproducibility of these effects in the placebo group of Study 102 that enrolled in Study 105 These data support the chronic use of ivacaftor as treatment of CF in patients age 6 years and older who have a *G551D* mutation in the *CFTR* gene.

Safety

Studies providing evaluable safety data

The ivacaftor development program consists of a total of 23 clinical studies, with 17 completed clinical studies and 6 ongoing studies. In addition, an expanded access program was initiated in the US to make ivacaftor available to patients in need. Studies in the Summary of Clinical Safety are shown in Figure 2.

Figure 2. Overview of studies and poolings in the Summary of Clinical Safety (SCS).



Source: Appendix 1, Section 11.1, Module 5.3.5.3/VX-770 ISS/Tables 1.1.1 and 2.1.1.1

CF: cystic fibrosis; IVA N: number of subjects who received at least 1 dose of ivacaftor; PBO N: number of subjects who received at least 1 dose of placebo; PBO/IVA N: number of subjects who received placebo in a placebo-controlled study and then received ivacaftor in an uncontrolled extension study; IVA/IVA N: number of subjects who received ivacaftor in a placebo-controlled study and then received ivacaftor in an uncontrolled extension study

Note: The number of subjects in this figure is based on the cut-off date of 01 July 2011. Studies with multiple parts (e.g., Part A and Part B) appear more than once in this figure based on the methodology within that phase of the study; however, these studies are only counted once toward the total number of studies investigating ivacaftor. Study 001 Part D enrolled 6 subjects (PBO N = 2 and IVA N = 4 subjects) with CF. Study 013 includes subjects with moderate hepatic impairment and healthy subjects. Study 103 Part A was designed to evaluate a single dose of ivacaftor to confirm the dose for Study 103 Part B and is therefore not included in this figure. Subjects in the long-term follow-up period (no administration of ivacaftor) of Study 102, Study 103 Part B, and Study 104 are not included in this figure. Shaded boxes denote analysis pooling for safety analyses.

Drug exposure

Overall 324 patients with CF and 364 healthy subjects were exposed to ivacaftor (Table 6).

Table 6. Number of subjects exposed to ivacaftor, any dose and duration.

Study Type (Population)	Subjects Exposed to Ivacaftor
Pooled Studies	
Pooled Phase 1 (10 studies in healthy subjects: Studies 001 [excluding Part D] through 003, 005 through 007, 009 through 012)	258
Pooled Phase 2b/3 studies (Studies 102, 103 Part B, 104, and 105 in subjects with CF)	293
Non-Pooled Studies	
Non-pooled Phase 1 (Study 008 in healthy subjects)	76
Non-pooled Phase1 (Study 809-005 in healthy subjects)	18
Non-pooled Phase 1 (Study 013 in 12 hepatic impaired subjects and 12 healthy subjects)	24[a]
Non-pooled Phase 1 (Study 001, Part D in subjects with CF)	4
Non-pooled Phase 2a (Study 101 in subjects with CF)	31[b]
Non-pooled Phase 3 (Study 103 Part A in subjects with CF)	9[c]
Total Exposure: Subjects With CF	**324[b,c,d]**
Total Exposure: Healthy Subjects	**364[a]**
Total Exposure: All Subjects	**700[e]**

CF: cystic fibrosis
Note: This table includes unique subjects who have received at least 1 dose of ivacaftor (any dose or duration). This table does not include 2 taste profiling studies (Studies 004 and 014 [ongoing]; no systemic exposure to ivacaftor), 2 ongoing Phase 2 studies in subjects with CF (Studies 106 and 107; studies are ongoing), and 1 expanded access for an individual subject.
a Of the 24 subjects in Study 013, 12 were hepatic impaired subjects. These subjects were not included in the "Total of Healthy Subjects" row.
b Of the 31 subjects in Study 101, 11 subjects enrolled in Study 102. Ten of the 11 subjects received ivacaftor in both Studies 101 and 102, and 1 subject received placebo in both Studies 101 and 102. Safety data for these 11 subjects are included in the Phase 2b/3 poolings. The 10 subjects who received ivacaftor in Study 102 were only counted once in this table; counted in Study 102 because that is where they had the longest exposure to ivacaftor.
c Of the 9 subjects in Study 103 Part A, 2 subjects did not enroll in Study 103 Part B, and 7 subjects enrolled in Study 103 Part B (3 subjects received ivacaftor in Study 103 Part B and 4 subjects received placebo in Study 103 Part B). Study 103 Part B was included in the Phase 2b/3 pooling; therefore, the 3 subjects that enrolled in Study 103 Part B after completing Study 103 Part A are included in the total of 293 subjects exposed to ivacaftor in Phase 2b/3 studies.
d The total of 324 subjects is comprised of 293 subjects in the Phase 2b/3 poolings, 4 subjects with CF in Study 001, 21 subjects in Study 101 who did not receive ivacaftor in another study, and 6 subjects who received ivacaftor in Study 103 Part A (2 subjects who did not enrol in Study 103 Part B, and 4 subjects who enrolled in Study 103 Part B but received placebo).
e The enumeration of all subjects exposed to ivacaftor includes the total of subjects with CF, the total of healthy subjects, and 12 subjects with hepatic impairment.

Evaluator's overall summary and conclusions on clinical safety

A total of 683 subjects were exposed to ivacaftor in the ivacaftor clinical development program: 364 healthy subjects (including 12 subjects with hepatic impairment) and 307 subjects with CF who have a *G551D* mutation in the *CFTR* gene or who are homozygous for the *F508del* mutation in the *CFTR* gene. A total of 293 subjects with CF (*G551D* or *F508del* mutations in the *CFTR* gene) received the proposed dose of ivacaftor 150 mg q12h in the Phase IIb/III studies. Ivacaftor was well tolerated and most subjects completed treatment (93.7% and 87.9% of subjects in the ivacaftor and placebo groups, respectively). The mean treatment duration in the pooled placebo-controlled Phase IIb/III studies was 218.1 days for subjects in the ivacaftor group. A total of 101 subjects were treated with ivacaftor for 48 weeks and 63 subjects were treated for 60 weeks.

In the pooled Phase IIb/III studies, the majority (89.8%) of subjects who received at least 1 dose of ivacaftor had an AE. In the placebo-controlled studies, nearly all subjects in the ivacaftor (92.3%) and placebo (97.0%) groups had AEs. The incidence of AEs considered

by the investigator to be related to the study drug was similar between the ivacaftor (33.5%) and placebo (34.1%) groups (Table 7).

Table 7. Adverse events related to study drug with an incidence of at least 3% in any treatment group and Preferred Term: Pooled Phase 2b/3 studies, Safety set.

	Placebo-Controlled Studies (102, 103 Part B, 104 Part A)		Uncontrolled Extension Studies (104 Part B and 105)		Overall Phase 2b/3 Studies
Preferred Term	Placebo (N = 132) n (%)	Ivacaftor (N = 221) n (%)	Placebo/ Ivacaftor (N = 72) n (%)	Ivacaftor/ Ivacaftor (N = 110) n (%)	All Ivacaftor (N = 293) n (%)
Rash	4 (3.0)	9 (4.1)	0	0	9 (3.1)
Cystic fibrosis lung	12 (9.1)	8 (3.6)	0	1 (0.9)	9 (3.1)
Headache	6 (4.5)	8 (3.6)	0	0	8 (2.7)
Aspartate aminotransferase increased	2 (1.5)	7 (3.2)	0	4 (3.6)	9 (3.1)
Alanine aminotransferase increased	7 (5.3)	7 (3.2)	0	2 (1.8)	8 (2.7)
Diarrhoea	5 (3.8)	5 (2.3)	1 (1.4)	0	6 (2.0)
Nausea	5 (3.8)	4 (1.8)	0	1 (0.9)	5 (1.7)
Abdominal pain	1 (0.8)	3 (1.4)	3 (4.2)	0	6 (2.0)
Cough	9 (6.8)	3 (1.4)	1 (1.4)	1 (0.9)	5 (1.7)
Productive cough	4 (3.0)	3 (1.4)	2 (2.8)	0	5 (1.7)

Source: Module 5.3.5.3/VX-770 ISS/Table 2.1.3.7

Note: A subject with multiple events within a preferred term is counted only once within the preferred term. This table is sorted in descending frequency of the ivacaftor column preferred term in the placebo-controlled studies. Preferred terms are coded using MedDRA, Version 12.0. Related includes related and possibly related to study drug categories.

There were no deaths in any of the pooled Phase IIb/III studies. In the placebo-controlled studies, the incidence of SAEs was lower in the ivacaftor group than the placebo group (17.6% versus 34.8%), as was the incidence of AEs leading to study drug discontinuation (1.8% versus 5.3%). The incidence of AEs leading to study drug interruption in these studies was similar between the ivacaftor and placebo groups (7.2% versus 7.6%).

The majority of AEs were mild or moderate in severity and not serious. Interruption or discontinuation of study drug due to AEs was uncommon; discontinuation of study drug was less common in subjects receiving ivacaftor than subjects receiving placebo. There was no one dominant event that led to discontinuation. The most common AEs in the ivacaftor group were cough, CF lung (preferred term for pulmonary exacerbation), headache, upper respiratory tract infection (URTI), nasal congestion, oropharyngeal pain, pyrexia, productive cough, nausea, and rash. Based on the higher incidence in the ivacaftor group than the placebo group, URTI events, dizziness, rash, headache, bacteria in sputum, diarrhoea, and abdominal pain were identified as likely to represent adverse drug reactions (ADRs).

The safety profile in the subjects receiving ivacaftor for 60 weeks was similar to that of the first 48 weeks which supports the safety of chronic administration of ivacaftor. This population will be followed for up to 144 weeks of total treatment in the uncontrolled extension study.

The most common severe AEs and SAEs were CF lung and hemoptysis, both of which are common manifestations of CF and occurred with a lower frequency in subjects receiving ivacaftor. There were no deaths in any of the ivacaftor studies

Treatment with ivacaftor was not associated with an increased incidence of clinically significant cardiac arrhythmias, including supraventricular and ventricular ectopy, or with a prolonged QT as measured by 12-lead standard ECGs and 24 h ambulatory ECGs. Thus, the non-clinical signal for supraventricular tachycardia in animal studies was not confirmed in the human clinical studies. Administration of ivacaftor at the therapeutic

dose (150 mg q12h) or a supratherapeutic dose (450 mg q12h) had no effect on QTc interval.

Serious AEs of hypoglycemia were reported as possibly related to ivacaftor; these were most likely related to complications of treatment for diabetes, which is a well-known manifestation of CF. Overall there was no effect of ivacaftor on blood glucose concentrations.

Elevations of transaminases occurred in a small number of subjects in both the placebo and ivacaftor groups. The incidence of these elevations was similar between subjects in the ivacaftor and placebo groups. The clinical features, including time to onset, concomitant factors (co-illnesses, medications), progression, and resolution of these events were similar between the ivacaftor and placebo groups. The role of ivacaftor in contributing to transaminase elevations is uncertain. In all instances, the elevations in transaminases were reversible. However, due caution is still advised in patients with hepatic impairment. Overall, treatment with ivacaftor was not associated with clinically meaningful changes in laboratory parameters.

The safety profile of ivacaftor was similar across the different age and gender subgroups. The pattern of AEs was similar across the subgroups by severity of lung disease and the most common AEs within each FEV1 subgroup are common manifestations of CF. As expected, subjects with more severe disease had a higher incidence of AEs compared to other subgroups, but ivacaftor was well tolerated even in this most severely compromised group. The pattern of AEs was similar in subjects homozygous for *F508del-CFTR* and subjects who have the *G551D-CFTR* mutation. The most common AEs in both populations were pulmonary exacerbations, cough, headache, oropharyngeal pain, nasal congestion, and fatigue.

After a single dose of 150 mg of ivacaftor, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had similar ivacaftor C_{max}, but an approximately 2-fold increase in $AUC_{0-\infty}$ compared with healthy subjects matched for demographics. A reduced dose of 150 mg once a day is recommended for these patients. The sponsor's statement that 'Patients with mild hepatic impairment (Child-Pugh Class A) do not require dose adjustment because the effects on clearance are expected to be smaller than in Child-Pugh Class B patients' is not justified as ivacaftor was not evaluated in patients with mild hepatic impairment.

The safety profile of ivacaftor was adequately evaluated in an appropriate number of patients in line with the size of the targeted patient population. Administration of ivacaftor 150 mg orally every 12 hours (q12h) for up to 48 weeks was well tolerated, as evidenced by an evaluation of AEs, SAEs and AEs leading to premature discontinuation of treatment, clinical laboratory evaluations, ECG results, vital signs, and physical examinations. Available data through 60 weeks of ivacaftor treatment did not identify new clinically important safety concerns.

First round benefit-risk assessment

First round assessment of benefits

The benefits of ivacaftor in the proposed usage are:

- Ivacaftor acts by targeting the underlying cause of cystic fibrosis by increasing the CFTR channel opening to enhance chloride transport. Currently in Australia, there are no marketed drugs which target the dysfunctional CFTR channel.
- Ivacaftor 150 mg twice daily (every 12 h) showed a substantial and durable effect on absolute change in percent predicted FEV1 through Week 24 (10.6 to 12.5 percentage

points) that was highly significant (P<0.0001) compared with placebo. Improvements in FEV1 were rapid in onset and durable through the 48 week treatment period in the placebo-controlled Phase III studies.

- Durable improvements in other pulmonary outcomes were observed, including the risk of experiencing a pulmonary exacerbation, as well as the frequency and duration of pulmonary exacerbations, and respiratory symptoms as measured by CFQ-R. Durable improvements in measures of nutritional status were observed, including weight and BMI.
- Ivacaftor led to sustained improvements in CFTR function, evidenced by the substantial and durable reduction in sweat chloride concentration. The overall pattern of improvement in CFTR function was consistent with that of FEV1, demonstrating that modulation of CFTR by ivacaftor is associated with clinical benefit.
- The pattern and magnitude of the treatment effects of ivacaftor observed in subjects 6 to 11 years of age was consistent with the clinical benefit observed in subjects 12 years of age and older. Treatment effects were observed in subjects with all degrees of disease severity (baseline percent predicted FEV1 ranging from 32% to 134%) and were observed in subjects while continuing on their prescribed CF therapies.
- The clinical benefits observed in the placebo-controlled Phase III studies were confirmed in the open-label rollover Study 105 (currently for up to 60 total weeks of ivacaftor treatment) by the maintenance of the treatment effect in subjects initially treated with ivacaftor, and by the replication of rapid and substantial improvements in clinical endpoints in subjects initially treated with placebo.
- Ivacaftor treatment was well tolerated for at least 60 weeks. The most common AEs were typical manifestations of CF disease; these occurred at a lower incidence in the ivacaftor than the placebo group. The incidence of SAEs was lower in the ivacaftor than the placebo group. The frequency of discontinuations due to AEs was lower in the ivacaftor than the placebo group. The most common risks associated with ivacaftor treatment have been characterised, can be readily monitored and recognised, and may be managed without treatment discontinuation.

First round assessment of risks

The risks of ivacaftor in the proposed usage are:

- Compared to placebo, treatment with ivacaftor was associated with a higher incidence of URTI events (including URTI, nasal congestion, pharyngeal erythema, oropharyngeal pain, rhinitis, sinus congestion, and nasopharyngitis), headache, abdominal pain, rash, diarrhoea, dizziness, and bacteria in sputum.
- Elevations in transaminases were observed in subjects with CF that were common in both the ivacaftor and placebo groups, which is consistent with the natural history of CF liver disease. Patients with elevated transaminases at baseline were more likely to show clinically relevant elevations in transaminases during ivacaftor treatment compared with placebo; however, interpretation was confounded by higher proportion of patients with elevated transaminases at baseline in the ivacaftor group. Since the role of ivacaftor in these events is uncertain, monitoring, and management recommendations was included in the product labelling.
- Safety of ivacaftor was not evaluated in patients with mild and severe hepatic impairment. It was only evaluated in patients with moderate hepatic impairment, who showed doubling of exposure to ivacaftor.

First round assessment of benefit-risk balance

Overall, ivacaftor was highly effective in the treatment of CF, shown by improvement in CFTR function and substantial, durable improvements in important clinical outcomes, including FEV1, pulmonary exacerbations, respiratory symptoms, and nutritional status. Thus, ivacaftor is expected to have broad and meaningful clinical benefit in patients 6 years of age and older who have a *G551D* mutation in the *CFTR* gene.

The safety of ivacaftor was also well-established in over 290 patients (appropriate sample size for the target patient population) and the risks associated with ivacaftor were reversible, not serious and easily managed.

Hence, the benefit-risk balance of ivacaftor given the proposed usage is favourable.

Recommendation regarding authorisation

It is recommended that ivacaftor 150 mg bid (given 12 hourly) be approved *for 'Treatment of cystic fibrosis in patients age 6 years and older who have a G551D mutation in the CFTR gene.'* However, the approval is subject to incorporation of suggested changes to the proposed PI.[13]

Clinical questions

None.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU RMP Version 1.4, dated 24 May 2012 [Data Lock Point 15 March 2012], including Annex 8-Australian Specific Annex) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the non-clinical aspects of the Safety Specification (SS) by the Toxicology area of the Office of Scientific Evaluation (OSE) and the clinical aspects of the SS by the Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows:

Table 8. Summary of Ongoing Safety Concerns

Important identified risks	None

[13] Recommendations regarding product literature are beyond the scope of the AusPAR.

Important potential risks	Effects on liver function tests Cataract Concomitant use of ivacaftor with potent CYP3A4 inhibitors or inducers Cardiac arrhythmias Off-label use in children less than 6 years of age and in patients with other mutations (non-G551D CFTR gating mutations and non class III mutations)
Important missing information	Use in Pregnant and Lactating Women Pulmonary exacerbations and bacterial sputum colonization with long term ivacaftor treatment Use in children between 6 to 11 years old Patients with FEV1 <40 % Safety in patients with cardiac diseases Long-term safety Clinical relevance of P-glycoprotein inhibition by ivacaftor Patients with moderate or severe hepatic impairment

Pursuant to the evaluation of the non-clinical and clinical aspects of the SS, it is recommended that the above summary of the Ongoing Safety Concerns is considered acceptable.

Pharmacovigilance plan

The sponsor proposes routine and additional pharmacovigilance activities as part of the pharmacovigilance plan.

Pharmacovigilance activities are proposed to address potential risks, including liver function, cataract and concomitant use of ivacaftor with potent CYP3A4 inhibitors or inducers. Additional pharmacovigilance activities consist of both ongoing and proposed activities (including post-market studies) and are proposed to monitor the following safety concerns:

Important potential risks

- Cardiac arrhythmias
- Off-label use in children less than 6 years of age and in patients with other mutations (non-*G551D CFTR* gating mutations and non class III mutations)

Important missing information

- Use in Pregnant and Lactating Women
- Pulmonary exacerbations, and bacterial sputum colonisation with long term ivacaftor treatment
- Use in children between 6 to 11 years old

- Patients with FEV1<40 %
- Safety in patients with cardiac diseases
- Long-term safety
- Safety in patients with moderate or severe hepatic impairment
- Clinical relevance of P-glycoprotein inhibition by ivacaftor

Risk minimisation activities

The sponsor has provided the following in regards the need for risk minimisation activities in Australia:

Based on the detailed evaluation in Chapter 3 of the identified and potential risks, no additional risk minimization measures are considered necessary. The routine risk minimization activities include product labelling, as well as, analyses of ongoing studies including the studies mentioned above that were conducted in Australia. In addition, analyses for long-term safety are planned using the US and United Kingdom (UK) CF patient registry studies. By working with these patient registries, we expect to be able to analyse data representing more than half of the patients with G551D in the world.

OPR reviewer comment

Routine risk minimisation activities (that is, PI and CMI) are considered acceptable to mitigate the risks associated with Kalydeco.

Summary of round 1 recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; the submitted EU-RMP is applicable without modification in Australia unless so qualified; and the draft product information and consumer medicine information documents should not be revised until the Delegates Overview has been received:

- Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated request for information and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.
- It is recommended that the sponsor provide study milestones for *Study 109: A Phase 3, Open-Label, Roll-Over Study to Evaluate the safety of ivacaftor in Paediatric Subjects with Cystic Fibrosis and a CFTR Gating Mutation*.
- It is recommended the Delegate consider adding the statement or similar to the Australian PI "*Kalydeco contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine*", as Kalydeco tablets contains lactose.

Final conclusions and recommendation

The sponsor's response to the first round RMP evaluation report adequately addressed all issues identified by the OPR with the exception of revisions to certain PI statements. It was noted that at this stage PI negotiations had not been completed.

Issues raised in the nonclinical evaluation report

The nonclinical evaluator has provided the following comments on the RMP Safety Specification:"*… The draft RMP should be updated to reflect the finalisation of the juvenile rat toxicity study (including the outstanding histopathological assessment [VX-770-TX-025]) in which cataracts were observed in treated animals. There is no alteration to the preliminary conclusion though (that is, that relevance to humans 6 years of age and older is unlikely).*"

OPR reviewer comment

It is noted in EU RMP Version 1.4 the sponsor states *"Histopathology data, which could help determine the etiology of ivacaftor-induced cataract development in the juvenile rats, will be available in late April 2012. The final report for Study VX-770-TX-025 will be available in June 2012."*

It is recommended to the Delegate that the sponsor commits to including the results from Study VX-770-TX-025 in the RMP. This may be included in an RMP update submitted to the TGA.

Should this application be approved, it is recommended to the Delegate that the following be imposed:

- Implement EU RMP Version 1.4, dated 24 May 2012 [Data Lock Point 15 March 2012], including Annex 8-Australian Specific Annex and any future updates as a condition of registration.
- Standard requirements for submission of Periodic Safety Update Reports (PSURs)

VI. Overall conclusion and risk/benefit assessment

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

This application is to register ivacaftor 150 mg tablets (Kalydeco) for the proposed therapeutic indications:

> *The treatment of cystic fibrosis (CF) in patients age 6 years and older who have G551D mutation in the CFTR gene.*

Kalydeco (ivacaftor) was granted orphan drug designation on the 14th of March 2012 for *"treatment of cystic fibrosis in patients who have a gating or an R117H mutation in the CFTR gene".* Orphan designation is only for the purpose of waiving the fees.

Quality

All chemistry and quality control issues have been resolved to the satisfaction of the TGA.

The evaluator notes that there are no bioavailability data and this was justified by the sponsor on the basis of the poor aqueous solubility of the drug substance and the inclusion of a study comparing tablets to an oral solution.

The evaluator discusses 4 biopharmaceutic studies (VX05-770-001, VX06-770-002, VX08-770-007 and VX10-770-012). These studies showed an increased exposure (2-4 times) of ivacaftor when administered with food containing fat. Steady state was reached 3-5 days after 12 hourly dosing, with an accumulation ratio of 2.2 to 2.9. The pharmacokinetics was similar in healthy subjects and patients with cystic fibrosis.

The PSC recommendations included the following: *'Attention is drawn to ACPM and the clinical Delegate that optimal absorption of the product requires ingesting with a high fat diet and this may not be clinically appropriate in the setting of people with cystic fibrosis.'*

Nonclinical

The evaluator mentions that there was an adequate set of studies to characterise the toxicology profile. All pivotal safety studies complied with GLP.

Ivacaftor *in-vitro* was shown to be a CFTR potentiator. The drug was active at *G551D-GFTR* and numerous other GFTR forms. *In vivo* PD studies were not performed due to lack of validated CF animal models.

There were 11 metabolites characterised. Of these, two were major metabolites (M1and M6). They were less potent than the parent compound. Based on potency and exposure data, M1 was considered to be active and to contribute to the pharmacological activity in patients.

Secondary PD studies showed that ivacaftor inhibited the competitive-binding of typical substrates or enzyme activities of only two targets with nanomolar potency of more than 140 enzymes and receptors tested in radioligand binding assays: the monoamine transporter and serotonin 5-HT2C. It also showed inhibitory activity against $Ca_V1.2$ and $K_V1.5$ ion channels. It is noted that tissue distribution studies in rats did not show significant crossing of the blood brain barrier; thus, it is unlikely to interact with CNS targets in humans.

The evaluator states that safety pharmacology studies encompassed CNS, cardiovascular, respiratory and gastrointestinal systems. There were no significant cardiovascular effects. Gastric emptying and GI motility were reduced by ivacaftor in rats. No effects on CNS or respiratory function were observed. Ivacaftor showed a concentration-dependent inhibitory effect on hERG tail currents, producing a total inhibition of in hERG tail current of 34.6% at 8 μM.

In relation to PK, the evaluator summarises: "moderate oral bioavailability was demonstrated in laboratory animal species. Tissue distribution of radioactivity following oral administration of ^{14}C-ivacaftor was rapid and wide; CNS penetration was minimal. Plasma protein binding was high. Metabolism of ivacaftor was shown to be mainly through CYP3A4, with some contribution from CYP3A5. Inhibition of CYP2C8, CYP2C9, CYP3A and P-glycoprotein was observed *in vitro* with ivacaftor and/or M1. Excretion was predominantly via the faecal route, with minimal renal excretion".

Ivacaftor demonstrated a low potential for acute toxicity in mice and rats.

Repeat dose toxicity studies were conducted in rats (3 and 6 months). There was hepatotoxicity seen at high doses (≥ 200 mg/kg/day). This was also seen in mice (≥ 600 mg/kg/ day).

A three month study was also conducted in dogs (60 mg/kg/day).

Overall, the nonclinical evaluator mentions that "the liver (hepatocellular necrosis; inflammation), gastrointestinal tract (enteropathy; vomiting and stool abnormalities), heart (atrioventricular block; supraventricular premature complex; cardiomyopathy and coronary artery medial degeneration) and kidney (convoluted basophilic tubular epithelia; chronic progressive nephropathy) were identified as the major targets for toxicity. Cataracts were seen to develop in very young rats treated with ivacaftor". Human eye development is recognised to be more complete at time of birth as compared to rats; therefore the risk of developing of cataracts is not expected in young children (children less than 6 years of age) and is believed to be not relevant for children aged 6 years and older.

In relation to hepatotoxicity this appeared to be confined to lethal doses of ivacaftor used in three month studies in rats and mice and was not seen in the 6 month studies with rats or in dogs. This was attributed to rodent-specific hepatic drug accumulation. The cardiac and renal findings were attributed to an exacerbation of age related findings in rats. The finding of cataracts in very young rats is considered to be of little relevance to the proposed patient population (≥ 6 years of age) given that treatment evidently requires drug exposure at a very early stage of lens development.

Ivacaftor was not genotoxic in the standard battery of tests and not carcinogenic in 2-year oral studies conducted in mice and rats.

The evaluator states that impairment of (male and female) fertility was noted in rats. Treatment with ivacaftor during gestation was associated with a decrease in fetal weight and an increased incidence of minor fetal skeletal variations in rats. The drug was not teratogenic in either rats or rabbits. Pup birth weight, survival and postnatal body weight gain were decreased in rats in a pre- and post-natal development study. The observed effects all occurred in conjunction with general toxicity.

Local tolerance: Ivacaftor did not exhibit skin irritation, eye irritation or skin sensitization potential after topical administration.

PI amendments are recommended.

The evaluator recommends approval of ivacaftor for the proposed indication.

Clinical

Pharmacokinetics

There are 14 studies which include studies in healthy adults, in hepatic impairment (n=1) and one study in children. Of these, there were six PK interaction studies and one population PK study.

Absolute bioavailability: This has not been determined as it is stated that ivacaftor has low solubility.

The bioequivalence studies, VX06-770-002 and VX08-770-007 are discussed in the CER (see Attachment 2 of this AusPAR). These studies compared the formulation used in the Phase III studies with those of the earlier Phase I studies. The bioequivalence of these formulations was generally similar. The Phase III studies were conducted with the formulation intended for marketing.

Influence of food is examined in three studies (002, 007 and 012). The evaluator mentions that food consistently increased ivacaftor exposure with the tablet formulation having a more marked effect compared to the solution formulation. The T_{max} was also delayed from 3 to 5 h. The following observations were also made. [In these studies, DL-SDD refers to development formulations].

- A high-fat breakfast resulted in higher $AUC_{0-\infty}$ (Geometric Least Square Mean ratio (GLSMR) 2.06) and higher C_{max} (GLSMR 2.28), when compared to the fasted state using 50%DL-SDD tablets in healthy subjects (VX06-770-002).
- Using either T1 or T2 80%DL-SDD tablets in healthy subjects, a high-fat breakfast resulted in an increase in $AUC_{0-\infty}$ of ivacaftor (GLSMRs 2.34 to 2.55) and C_{max} of ivacaftor (GLSMRs 2.38 to 2.83) when fed and fasted states were compared (VX08-770-007).

- Similarly using film-coated 150 mg tablet in healthy subjects, a high-fat breakfast significantly increased the $AUC_{0-\infty}$ (GLSMR 2.98) and C_{max} (GLSMR 3.89) (VX10-770-012).

Dose proportionality: There was dose proportionality seen in a single dose study (VX05-770-001) where a range of 25 mg to 800 mg dose range of ivacaftor solution was examined.

Volume of distribution: The evaluator mentions that non-compartmental PK analysis in healthy subjects in the fed state determined a mean (SD) Vz/F of ivacaftor after a single dose of 275 mg of ivacaftor as a solution formulation was 220 (61) L and after multiple-dose administration of ivacaftor 250 mg q12h was 206 (47) L (VX05-770-001).

Protein binding: Ivacaftor, M1, and M6 were highly bound to proteins in human plasma at all concentrations tested *in vitro* (>98%). Serum albumin was the main plasma component involved in the binding of ivacaftor and its metabolites in human plasma.

Metabolism: Ivacaftor is extensively metabolised. A ^{14}C labelled study on 6 healthy male volunteers showed that 2 metabolites M6 and M1 accounted for approximately 65% of total dose excreted; ^{14}C ivacaftor was mainly excreted as metabolites via faeces; renal route plays a minimal role. A majority of the administered dose was recovered in the faeces in the first 7 days. The evaluator mentions that the major metabolic pathway involved oxidation of ivacaftor to M1 (hydroxymethyl-ivacaftor) and M6 (ivacaftor carboxylate). The M1 metabolite is active, but about a sixth of that of ivacaftor, the parent drug. M6 is considered inactive (>50-fold less potent than ivacaftor). The metabolite to parent ratio ($AUC_{0-tlast}$ for metabolite/$AUC_{0-tlast}$ for ivacaftor) for M1 and M6 at steady state was 4.89 and 1.73, respectively.

Elimination: Elimination in the faeces was the predominant route (with minimum renal excretion). Following administration of a single oral dose of 133 mg ^{14}C-ivacaftor in healthy subjects, mean recovery of total radioactivity was 95% (88% in faeces and 6.6% in urine).

Pharmacokinetics in the target population: Pharmacokinetics in adults with CF was similar to the PK in healthy adults (in a study of 275 mg single dose). Pharmacokinetics in 9 subjects (6-11 years) with CF was similar to that of adults (study 103).

Steady state (when ivacaftor was administered as a twice daily dose ranging from 125 mg to 150 mg) was achieved in 3 to 7 days where the accumulation ratio was 2.2 to 2.9.

There were no studies conducted in renal impairment subjects.

Pharmacokinetics in hepatic impairment: One study examined the effect of hepatic impairment on systemic exposure (VX10-770-013). The PK of ivacaftor after a single dose of 150 mg was compared in moderate hepatic impairment versus healthy controls. The C_{max} was similar between groups but the $AUC_{0-\infty}$ GLSMR for ivacaftor was 1.96 (90% CI: 1.43; 2.67) was about double that of the healthy controls. The exposure in relation to the metabolites showed similar trends. Other degrees of hepatic impairment (mild or severe) were not investigated.

Pharmacokinetic interaction studies: The evaluator observes the following:

The effects of multiple doses of the CYP3A inhibitor ketoconazole on the single-dose PK of 150 mg of ivacaftor in the fasted state were evaluated in 24 healthy male volunteers (VX08-770-006). Ketoconazole increased ivacaftor $AUC_{0-\infty}$ by about 8.5-fold and C_{max} by 2.7-fold. The M1 metabolite AUC increased 1.7-fold while C_{max} was decreased by 77%, and decreased both the AUC and C_{max} of M6 by approximately 70% and 94%, respectively.

A similar study examined the effects of multiple doses of fluconazole on the multi-dose PK profile of ivacaftor in the fed state (VX09-770-010). Ivacaftor $AUC_{0-12\,h}$ increased approximately 3-fold and C_{max} approximately 2.5-fold; M1 $AUC_{0-12\,h}$ increased

approximately 1.9-fold and C_{max} approximately 1.5-fold, and M6 $AUC_{0\text{-}12\,h}$ decreased by approximately 17% and C_{max} by approximately 16%.

Co-administration of ivacaftor with the strong inducer of CYP3A rifampicin reduced ivacaftor exposure.

The effect of steady-state ivacaftor on the PK parameters of a single dose of midazolam and its metabolite 1'-hydroxy-midazolam was investigated in healthy male volunteers (VX09-770-010;). Ivacaftor increased midazolam $AUC_{0\text{-}\infty}$ about 1.5-fold and C_{max} 1.4-fold.

There was no evidence that ivacaftor inhibited CYP2C8 or CYP2D6.

The potential interaction between ivacaftor (150 mg q12h for 28 days) and a hormonal oral contraceptive containing ethinyl estradiol [EE] (35 µg) and norethisterone [NE], (500 µg) was evaluated in healthy female volunteers (VX08-770-0050). There was no significant interaction.

Pharmacodynamics

Two studies are submitted (VX06-770-101 and VX09-770-008).

The first study used 75 mg to 250 mg 12 hourly for 14 days in adult subjects with CF and *G551D-CFTR* mutation in at least one allele. There was a decrease in sweat chloride and NPD values and increased FEV1. These were seen by Day 3 and were sustained at Day 14. All three PD endpoints showed a statistically significant linear trend of increasing response with increasing dose. The evaluator mentions that this was confirmed by a PK/PD modelling study which included data from 400 CF adults and children.

Cardiac safety was also assessed in study VX09-770-008. This was a randomised, placebo- and active-controlled, 4-treatment, double-blind, 4-period crossover study conducted in 72 healthy male and female subjects. The dose of ivacaftor was 150 mg q12h or 450 mg q12h for 5 days. The evaluator states that, "ivacaftor was not associated with a clinically significant effect on QTcF or QTcB[14] intervals at either dose used. For both doses, the upper limits of the 90% 2-sided confidence interval (CI) were below 10 msec at all postdose time points on Day 5. There no differences in effect for male and female subjects. A linear mixed-effect model demonstrated no statistical significant correlation of QTcF changes with concentrations of ivacaftor and its metabolites".

Dose finding studies

This was a PD study (101) which was a two part, double blind, placebo controlled, cross over randomised study of 28 days of dosing in 39 subjects. The doses used were 25 mg, 75 mg, 150 mg or 250 mg every 12 h.

The evaluator mentions that statistically significant changes from baseline in FEV1, sweat chloride levels and NPD with ivacaftor 75 mg and 150 mg q12h compared with placebo (Part 1 of the study where dosing was administered for 14 days) were observed. Statistically significantly greater improvement with ivacaftor 150 mg and 250 mg (Part 2- 28 day duration) was also seen with the above mentioned endpoints. The evaluator states that this Phase 2a study "established proof of concept for ivacaftor" and was the basis for dose selection for the Phase III studies.

Efficacy studies

There are 2 pivotal efficacy studies submitted.

[14] QT interval corrected for heart rate using Bazett's formula

Study 102

This was a Phase III, randomised, double blind, placebo controlled, parallel group, multicentre study that evaluated the efficacy of ivacaftor in subjects with CF and a *G551D-CFTR* mutation.

The main inclusion criteria: Male and female subjects with confirmed diagnosis of CF, 12 years of age and older, who have the *G551D-CFTR* mutation in at least 1 allele; mild or moderately impaired lung function (FEV1 40% to 90% of predicted normal for age, gender, and height (Knudson standards). The exclusion criteria are described in detail in the CER (Attachment 2 of this AusPAR). In essence, those with unstable disease, "normal" lung function or pulmonary exacerbation were excluded.

Study treatments: Ivacaftor 150 mg tablet or matching placebo tablet was administered orally 150 mg q12h (recommended to take study drug 30 minutes after the start of a standard "CF" high-fat, high calorie meal or snack). Study drug was administered q12h for 48 weeks (24 weeks in the treatment period and 24 weeks in the extension period).

The primary efficacy endpoint was the absolute change in percent predicted FEV1 through week 24 of treatment. The secondary efficacy endpoints were absolute change from baseline in percent predicted FEV1 through week 48, absolute change from baseline in CFQ-R score, absolute change from baseline in sweat chloride, time to first pulmonary exacerbation, absolute change from baseline in weight. Tertiary efficacy endpoints are included.

The evaluator also mentions the methods used to maintain the blinding and randomisation. Subjects were randomised in a 1:1 ratio to groups of ivacaftor and placebo, stratifying for age (< 18 versus ≥ 18 years of age) and FEV1 (< 70% versus ≥ 70% predicted) at screening. The subjects, study site personnel, study monitors and the study team of the sponsor were blinded for treatment allocation. Most of them were blinded also for sweat chloride, bioanalysis and spirometry results. Emergency un-blinding procedures were defined.

The Full Analysis Set (FAS) and the Per Protocol analysis are adequately defined.

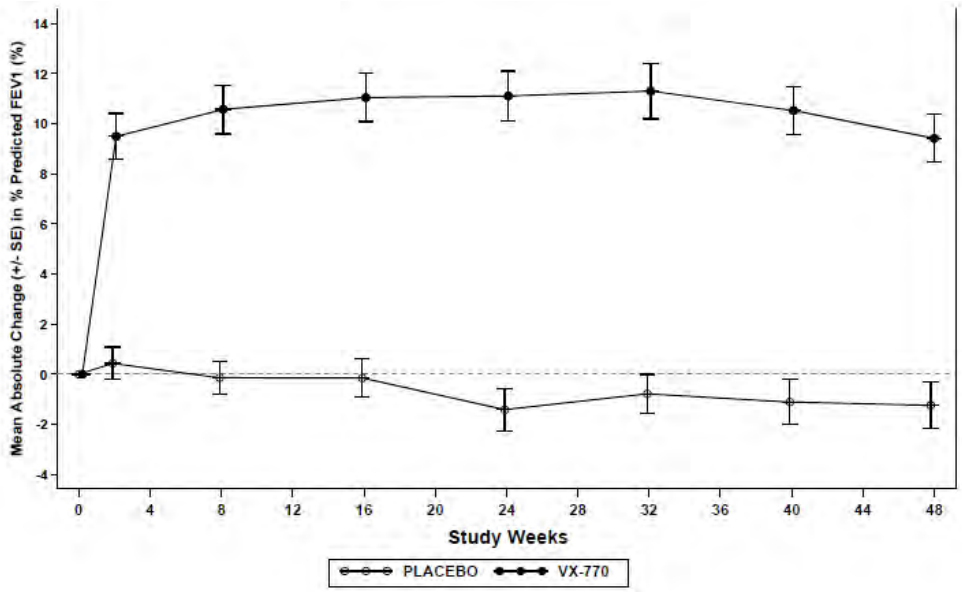
Sample size calculations are discussed. In essence, a minimum of 80 subjects were planned to be randomised to either ivacaftor or placebo. This calculation was aimed at having at least 80% power to detect an expected treatment effect of 4.5% in absolute change from baseline in percent predicted FEV1. Statistical methods used are described.

Numbers analysed: A total of 167 subjects were randomised, of which 84 subjects were randomised to ivacaftor and 83 subjects were randomised to placebo treatment. Full Analysis Set consisted of subjects who received at least 1 dose of the study drug: 83 subjects in the ivacaftor group and 78 subjects in the placebo group. The Per Protocol Set at Week 24 included 138 subjects (74 subjects in the ivacaftor group and 64 subjects in the placebo group), and at Week 48, 133 subjects (69 subjects in the ivacaftor group and 64 subjects in the placebo group). This set was defined as all subjects without major protocol violations having at least 80% overall study drug compliance and having completed at least 80% of the analysis period as well as having necessary predefined FEV1 measurements available.

Demographic details of the FAS. Overall, there were 48% males; 98.1% were White. Mean age (SD) was 25.5 years (9.54). Those less than 18 years were 22.4%. 62% were from North America. The percent predicted FEV1 < 70% was 58%. Mean weight was 61 kg (14). Mean sweat chloride mmol/L 100.24 (10.27); oxygen saturation (%) was 97% (1.72).

Results for the primary efficacy endpoint are given below.

Figure 3. Mean absolute change from baseline in percent predicted FEV1 by treatment, Full Analysis Set.



As seen above, there was a statistically significant difference, favouring ivacaftor over placebo. The evaluator mentions that the treatment effect was sustained during the treatment period and that the robustness of the analysis was supported by the results of the sensitivity analysis.

The primary and selected secondary efficacy endpoints: FAS.

Table 9. Study 102. Primary and selected secondary efficacy endpoints: FAS

Endpoint	Treatment Difference[a] (95% CI)	*P* value
Absolute Change from Baseline in Percent Predicted FEV_1 (percentage points)		
Through Week 24 (Primary Endpoint)	10.6 (8.6, 12.6)	<0.0001
Through Week 48	10.5 (8.5, 12.5)	<0.0001
Change from Baseline in CFQ-R Respiratory Domain Score (points)[b]		
Through Week 24 (Key Secondary Endpoint)	8.1 (4.7, 11.4)	<0.0001
Through Week 48	8.6 (5.3, 11.9)	<0.0001
Change from Baseline in Sweat Chloride (mmol/L)		
Through Week 24 (Key Secondary Endpoint)	-47.9 (-51.3, -44.5)	<0.0001
Through Week 48	-48.1 (-51.5, -44.7)	<0.0001
Time to First Pulmonary Exacerbation		
Through Week 24	0.40 (0.23, 0.71)[c]	0.0016
Through Week 48 (Key Secondary Endpoint)	0.46 (0.28, 0.73)[c]	0.0012
Change from Baseline in Weight (kg)		
At Week 24	2.8 (1.8, 3.7)	<0.0001
At Week 48 (Key Secondary Endpoint)	2.7 (1.3, 4.1)	0.0001

The evaluator also mentions the results of the tertiary efficacy endpoints. These are related to measures of pulmonary exacerbation, sinopulmonary signs and symptoms. There was a statistically superior response with ivacaftor (versus placebo).

Study 103.

This was a Phase III, 2-part, randomised, double-blind, placebo-controlled, parallel-group study to evaluate the PK, efficacy, and safety of ivacaftor in subjects aged 6 to 11 years with CF and the *G551D* mutation. Part A was a PK study of ivacaftor and its metabolites and is discussed in the attached. Part B is the efficacy study and is discussed here.

Inclusion criteria: This study recruited subjects aged 6 to less than 12 years with 40 to 105% of FEV1 of predicted normal for age, gender, and height (Knudson standards) and weight ≥15 kg at screening. Other inclusion criteria, as well as exclusion were in general similar to those in study 102.

Study treatments: Ivacaftor 150 mg tablet or placebo was to be administered orally in the fed state (30 minutes after the start of a standard "CF" high-fat, high calorie meal or snack) q12h for 48 weeks (24 weeks in the Treatment Period and 24 weeks in the Extension Period).

Efficacy endpoints: The primary efficacy endpoint was the absolute change from baseline in percent predicted FEV1 through 24 weeks of treatment. The main secondary endpoints were the absolute change from baseline in CFQ-R, absolute change from baseline in sweat chloride, time to first pulmonary exacerbation, absolute change from baseline in weight and absolute change from baseline in percent predicted FEV1 through Week 48.

The evaluator mentions that the sample size of a minimum of 30 subjects to be enrolled in Part B was based on the availability of the subject population and not on any statistical consideration. Therefore, the study was not powered to detect a statistically significant treatment effect.

A total of 52 subjects were randomised: 26 subjects were randomised to ivacaftor and 26 subjects were randomised to placebo treatment. All of these subjects received at least 1 dose of study drug and were included in the FAS.

48% were male; 86.5% were White. The mean age was 8.9 years (1.91). 48% were between the ages of 6 to 8; and 44% between the ages of 9-11. The % predicted FEV1 < than 70 was 23%. Sweat chloride was 104.55 m mol/L (11.919).

The following changes are observed. There was statistically significant superiority of ivacaftor over placebo in relation to the primary and key secondary efficacy endpoints.

Table 10. Study 103. Primary and selected secondary efficacy endpoints: FAS

Endpoint	Treatment Difference[a] (95% CI)	*P* value
Absolute Change from Baseline in Percent Predicted FEV_1 (percentage points)		
Through Week 24 (Primary Endpoint)	12.5 (6.6, 18.3)	<0.0001
Through Week 48	10.0 (4.5, 15.5)	0.0006
Change from Baseline in CFQ-R (Children Ages 6 to 11) Respiratory Domain Score (points)		
Through Week 24 (Key Secondary Endpoint)	6.1 (-1.4, 13.5)	0.1092
Through Week 48	5.1 (-1.6, 11.8)	0.1354
Change from Baseline in Sweat Chloride (mmol/L)		
Through Week 24 (Key Secondary Endpoint)	-54.3 (-61.8, -46.8)	<0.0001
Through Week 48	-53.5 (-60.9, -46.0)	<0.0001
Change from Baseline in Weight (kg)		
At Week 24 (Key Secondary Endpoint)	1.9 (0.9, 2.9)	0.0004
At Week 48	2.8 (1.3, 4.2)	0.0002

a: Treatment difference is ivacaftor to placebo (LS mean absolute change)

Other efficacy studies

Study 104

Study 104 was a Phase II, randomised, double-blind, placebo-controlled, parallel-group study (Part A) with an open-label extension (Part B) of orally administered ivacaftor in 140 subjects with CF (aged ≥12 years). The main objectives of Part A of this study were to evaluate the safety, efficacy and PK following 16 weeks of treatment with ivacaftor in subjects with CF who are homozygous for the *F508del-CFTR* mutation. The main objectives of the open-label Part B were to evaluate safety and efficacy of long-term treatment with ivacaftor for 96 weeks.

The adjusted mean absolute change from baseline through Week 16 in percent predicted FEV1 was greater in the ivacaftor group (1.54%) than in the placebo group (-0.183%) but the treatment difference was not statistically significant.

The evaluator mentions that "as the treatment effect for the primary efficacy endpoint was not statistically significant, any observed statistical significance in other efficacy endpoints was reported nominally". Effect on respiratory symptoms, oxygen saturation did not show any significant change.

Long term efficacy: Study 105

This was an open label study in patients > 6 years with CF. This was a rollover study and planned to enrol those from Studies 102 and 103. 192 subjects were enrolled: 144 subjects from Study 102, and 48 subjects from study 103.

For patients treated with ivacaftor in the pivotal studies 102 and 103 the maximum length of exposure in study 105 is 96 weeks (study 102) and 72 weeks (study 103). For placebo-treated patients, maximum length of exposure in study 105 is 48 weeks (study 102) and 24 weeks (study 103).

The evaluator mentions that "for subjects in the ivacaftor group, the improvements in FEV1, CFQ-R respiratory domain scores and weight observed in the previous study were sustained in the current study; for subjects in the placebo/ivacaftor group, the improvements in FEV1, CFQ-R respiratory domain scores and weight in the current study were similar to those observed in the previous study for subjects in the ivacaftor/ivacaftor group. Results relating to pulmonary exacerbations revealed conflicting results.

Efficacy in subgroups

The evaluator states that the improvements in primary and secondary endpoints were not affected by age, sex or disease severity (measured by percent predicted FEV1 at screening). Among the subgroup of subjects with the *G551D* mutation in 1 allele and the *F508del* mutation in the second allele, mean (SD) change in percent predicted FEV1 baseline to Week 24 was -0.7 (5.95) percentage points in the placebo group and 11.1 (9.11) percentage points in the ivacaftor group.

Overall efficacy conclusions

The evaluator concludes that ivacaftor was highly effective in the treatment of CF as evidenced by improvement in CFTR function and substantial, durable improvements in important clinical outcomes, including FEV1, pulmonary exacerbations, respiratory symptoms and nutritional status. The dose used is supported by a Phase II study. The inclusion criteria specified CF age 6 years and older who have a *G551D* gating mutation in the *CFTR* gene. Subject demographics and baseline characteristics were, in general, representative of the population of patients with CF for whom ivacaftor is intended. Both studies have been adequately powered to detect clinically significant difference between ivacaftor and placebo. The studies also used an appropriate endpoint, FEV1 as the primary endpoint, which the evaluator endorses. There were clinically meaningful improvement in CF lung disease and nutritional measures. It also demonstrates an effect on CFTR function.

The endpoints measured also were sustained up to 48 weeks. In the open label study, 105, the effect on FEV1 was generally sustained.

Safety

The evaluator mentions that safety data are included from 23 clinical studies: 17 completed and 6 ongoing studies.

The Phase I studies generally included healthy subjects and the safety data have been pooled; in these studies, the maximum duration of exposure to ivacaftor was 18 days.

Overall, the data includes 324 patients with CF and 364 healthy subjects who have been exposed to ivacaftor. However, the majority of safety data came from 293 patients exposed to ivacaftor in placebo-controlled Phase IIb/III studies. The proportion by sex in this pooling was similar (male: 48.5% and female 51.5%) and the majority of subjects were white (97.3%) and aged 18 years or older (64.2%). In this pooling, only 109 patients had the *G551D* mutation in the CFTR gene (for whom ivacaftor is applied for).

There were only 23 patients with age from 6 to 11 years-old (Study 103 part B) who received ivacaftor in these studies. The following table captures the safety data set presented in this submission.

Table 11. Safety data set.

Study Type (Population)	Subjects Exposed to Ivacaftor
Pooled Studies	
Pooled Phase 1 (10 studies in healthy subjects: Studies 001 [excluding Part D] through 003, 005 through 007, 009 through 012)	258
Pooled Phase 2b/3 studies (Studies 102, 103 Part B, 104, and 105 in subjects with CF)	293
Non-Pooled Studies	
Non-pooled Phase 1 (Study 008 in healthy subjects)	76
Non-pooled Phase1 (Study 809-005 in healthy subjects)	18
Non-pooled Phase 1 (Study 013 in 12 hepatic impaired subjects and 12 healthy subjects)	24[a]
Non-pooled Phase 1 (Study 001, Part D in subjects with CF)	4
Non-pooled Phase 2a (Study 101 in subjects with CF)	31[b]
Non-pooled Phase 3 (Study 103 Part A in subjects with CF)	9[c]
Total Exposure: Subjects With CF	**324[b,c, d]**
Total Exposure: Healthy Subjects	**364[a]**
Total Exposure: All Subjects	**700[e]**

The evaluator includes discussion of all AEs (irrespective of relationship to study treatment). In the pivotal placebo-controlled studies, nearly all subjects in the ivacaftor (92.3%) and placebo (97.0%) groups had AEs. The most common AEs (at least 10% incidence) in the ivacaftor group were cough, CF lung (preferred term for pulmonary exacerbation), headache, URTI, nasal congestion, oropharyngeal pain, pyrexia, productive cough, nausea, and rash.

Those of lesser frequency are also discussed and no significant trends were seen, except for rash (5.3% in placebo and 10.4% in the ivacaftor treated patients).

The AEs were of mild to moderate severity except for 4 reports of severe (or life threatening) events: 3 subjects who received ivacaftor had life threatening events (hypoglycaemia; hepatic enzyme increase and fatigue; depression, and suicidal ideation) and one placebo-treated subject had a life-threatening event that was also an SAE of respiratory failure.

The evaluator also mentions that "The incidence of AEs considered by the investigator to be related to the study drug was similar between the ivacaftor (33.5%) and placebo (34.1%) groups. In the placebo-controlled studies, CF lung and cough occurred at a lower incidence (at least 3% difference) in the ivacaftor group than the placebo group".

There have been no deaths reported in the Phase IIb/III studies. The SAEs in at least 2 subjects in any treatment group were listed: there are no undue trends identified. Discontinuations due to AEs were 1.8% in the ivacaftor group versus 5.3% in the placebo group.

There were no clinically meaningful changes in relation to laboratory investigations. The evaluator discusses liver function tests in detail as there were 5 subjects (2.3%) in the ivacaftor group versus 3 (2.3%) in the placebo group whose treatment was interrupted due to high liver function tests (LFTs) in the ivacaftor group in the Phase IIb/III studies (in addition, there was a toxicology data set in rats).

Overall, the evaluator mentions that a similar proportion of subjects in the ivacaftor and placebo groups had maximum transaminase levels exceeding a range of thresholds including ≥ 2 ×, ≥ 3 ×, ≥ 5 ×, and ≥ 8 × the upper limit of normal (ULN). The incidence of elevations of ALT or AST between ≥ 2 × to < 3 × ULN and ≥ 3 × to < 5 × ULN were similar. The incidence of ALT or AST increases was similar between the ivacaftor and placebo group across the different ranges: 6.3% (≥ 3 × ULN) in the ivacaftor group and 8.4% (≥ 3 × ULN) in the placebo group; 2.7% (≥ 5 × ULN) in the ivacaftor group and 2.3% (≥ 5 × ULN) in the placebo group; 1.8% (≥ 8 × ULN) in the ivacaftor group and 1.5% (≥ 8 × ULN) in the placebo group.

The population with hepatic impairment was not included in main pivotal studies; therefore no safety analysis on this population was conducted. The proportion of patients with "history" of liver enzyme elevation was similar in both groups (approximately 15%). In this subgroup of patients, a higher proportion of subjects in the ivacaftor group had maximum on-treatment ALT or AST elevation compared to those in the placebo group. The evaluator mentions that "the significance of this observation is uncertain due to the limited number of subjects involved, and the presence of a higher proportion of subjects randomised to the ivacaftor group who had a history of elevated liver enzymes and had elevations at baseline compared to the placebo group".

Standard 12 lead ECG monitoring was done at baseline and at last scheduled visit in the Phase IIb/III placebo controlled studies. The incidence of AEs associated with ECG abnormalities in the ivacaftor group was similar to placebo group.

The evaluator also discussed AEs in subgroups. The numbers are too small to yield meaningful results.

Overall, the evaluator is of the opinion that "the safety profile of ivacaftor was adequately evaluated in an appropriate number of patients in line with the size of the targeted patient population. Administration of ivacaftor 150 mg orally every 12 hours (q12h) for up to 48 weeks was well tolerated, as evidenced by an evaluation of AEs, SAEs and AEs leading to premature discontinuation of treatment, clinical laboratory evaluations, ECG results, vital signs, and physical examinations. Available data through 60 weeks of ivacaftor treatment did not identify new clinically important safety concerns".

Overall conclusion and recommendation of the evaluator

Overall, the evaluator recommends that ivacaftor be approved for the treatment of cystic fibrosis in patients age 6 years and older who have the G551D mutation in the *CFTR* gene.

Risk management plan

The OPR evaluator states that the RMP is supportive to the application.

It is stated that the EU–RMP is applicable here in Australia. Study milestones for Study 109 (*A Phase 3, Open-Label, Roll-Over Study to Evaluate the safety of ivacaftor in Pediatric Subjects with Cystic Fibrosis and a CFTR Gating Mutation*) was requested by the evaluator. Some PI changes were recommended.

Risk-benefit analysis

Delegate considerations

There are two pivotal Phase III studies (102 and 103, Part B) that support the proposed indication: *the treatment of CF in patients age 6 years and older who have G551D mutation in the CFTR gene*. Study 102 included patients who were 12 years and older; Study 103

included patients aged 6-11 years of age. Data on children, however, is limited: in Study 103, those treated with ivacaftor are: 12 in the 6-8 year group; 11 in the 9-11 year group and 3 in the > 11 year group. In Study 102 there were 19 in the 12-18 year age group and 64 in the > 18 year age group.

The primary efficacy endpoint, FEV1 is a clinically meaningful endpoint which showed statistically significant superiority of ivacaftor over placebo. The secondary efficacy endpoints supported the effect seen with the primary endpoint.

This data set only supports ivacaftor in patients with *G551D CFTR* mutation. Ivacaftor administered at 150 mg q12h for 16 weeks resulted in no improvement in FEV1 relative to placebo in patients with CF who are homozygous for the *F508del-CFTR* mutation (Study 104).

The data on children (aged 6-11 years) are limited. Whilst efficacy and safety were observed in Study 103, ongoing surveillance through routine pharmacovigilance practices of ongoing studies should provide further evidence of efficacy and safety. The relevant studies are 105, 110, 111, 112 and the 2 years follow up study of those who prematurely discontinued from Study 103.

It is noted that data on hepatic impairment is inadequate. However, this deficiency is addressed in the draft PI.

Ivacaftor has a high potential for drug interaction when concomitantly administered with drugs inhibiting CYP3A. The proposed statements in the PI are satisfactory in this regard.

Long term data in study 105 shows sustained efficacy and safety. The numbers are limited. This study is currently ongoing and the completed report should be submitted for review. Also, there is a 5 year observational study that is planned (included in the RMP evaluation). The results should also be disclosed to the TGA when other regulatory agencies are informed.

PI amendments: In relation to LFTs, the statement included in the US Product monograph, "dosing should be interrupted in patients with ALT or AST of greater than 5 times the ULN" should be included. Other proposed revisions to the product literature are beyond the scope of the AusPAR.

Proposed action

The Delegate proposed to register ivacaftor (Kalydeco) 150 mg tablet for the *treatment of cystic fibrosis in patients age 6 years and older who have a G551D mutation in the CFTR gene*.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM.

Response from sponsor

Sponsor comments on the delegate's overview

The comments in the Delegate's Overview that represent the concerns of the PSC *"that optimal absorption of the product requires ingesting with a high fat diet and this may not be clinically appropriate in the setting of people with cystic fibrosis"* are noted. Vertex wishes to clarify that the advice in the Kalydeco PI is consistent with both the optimal absorption of the product and the current standard of care in CF.

CF patients are known to have higher metabolic demands (in part at least due to their lung disease) and since CF patients can have difficulties with consuming sufficient calories to

maintain an adequate body weight, it is standard advice for patients to consume a high calorie diet which contains fat in the meals and snacks taken (Stapleton DR *et al*, 2006[15]). The *Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis* state: "…a diet high in energy, fat and protein is required to achieve optimal nutritional status." Further similar advice is readily found on CF web-sites (for example, <https://www.cysticfibrosis.org.au/all/learn/>). It is therefore considered to be appropriate that Kalydeco is consumed with a fat-containing meal or snack and that it is not associated with any additional risk or concern for the patient.

Sponsor comments on the PI/CMI

These are beyond the scope of the AusPAR

Nonclinical evaluation report [Use in pregnancy]

While Vertex accepts the Category change from B1 to B3 and the related text edits, the sponsor notes that the term "fetal damage" is not a scientifically accurate description of the findings in the rat embryofetal development (EFD) study. These types of findings, which are commonly observed in the presence of significant maternal toxicity in EFD studies, are more accurately termed "fetal effects."

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered this product to have an overall positive-benefit risk profile for the indication as proposed;

> *Kalydeco is indicated for the treatment of cystic fibrosis in patients age 6 years and older who have a G551D mutation in the CFTR gene.*

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Subject to satisfactory negotiation of the RMP.
- Negotiation of PI and CMI to the satisfaction of the TGA
- Monitoring procedures to be developed for possible cataract formation in children.

Proposed PI and CMI amendments:

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI.

The ACPM advised that the 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, TGA approved the registration of Kalydeco (ivacaftor) 150 mg film coated tablets, indicated for:

[15] Stapleton, DR., Ash *et al*. (2006). Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis. Sydney, Australia, Cystic Fibrosis Australia Publication.

the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the CFTR gene.

Specific conditions applying to these therapeutic goods

- The implementation in Australia of the Kalydeco (ivacaftor) 150 mg film-coated tablet Risk Management Plan (included with submission PM-2012-01491-3-5) identified as the EU RMP Version 1.4, dated 24 May 2012 [Data Lock Point 15 March 2012], including Annex 8-Australian Specific Annex, and any subsequent revisions as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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