Table S1 Common potential interactions between the CFTR modulators and concomitant therapies (please refer to the individual product's SPC for more information):

Product	CYP pathway involvement	Common interactions	Comments
Ivacaftor	Ivacaftor is a substrate of CYP3A4 AND CYP3A5. May exhibit weak inhibition towards CYP3A AND CYP2C9.	*Strong CYP3A inducers:* Rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine	Exposure to Ivacaftor expected to be reduced. Combination should be avoided.
		Strong CYP3A inhibitors: Azoles (e.g. voriconazole), clarithromycin *Moderate CYP3A inhibitors:* Fluconazole, erythromycin	Exposure to Ivacaftor expected to be increased. Dose reductions of ivacaftor would be required.
		Food or drink containing grapefruit	Exposure to Ivacaftor expected to increase. Grapefruit to be avoided.
Orkambi (Lumacaftor/Ivacaftor)	Lumacaftor is a strong CYP3A inducer. See above for Ivacaftor.	*Strong CYP3A inducers:* Rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine	Exposure to Orkambi expected to be reduced. Combination should be avoided.
		CYP3A inhibitors	No dose adjustment required when CYP3A inhibitors are initiated in patients already on existing Orkambi therapy. When initiating Orkambi in patients taking CYP3A inhibitors,

			dose adjustments of Orkambi required.
			Lumacaftor may induce metabolism of CYP3A substrates (decreased exposure to these substrates).
		Interactions with transporters (P-gp substrates): Digoxin, ciclosporin, sirolimus, tacrolimus, ranitidine, fexofenadine	Lumacaftor can both induce and inhibit P-gp so close monitoring of P-gp substrates is required.
		CYP2B6 substrates: Bupropion	In vitro studies have shown that lumacaftor may induce CYP2B6 substrates potentially reducing exposure to them.
		CYP2C substrates: Warfarin (CYP2C9 substrate) Citalopram, sertraline (CYP3A/2C19 substates) Methylprednisolone, prednisolone (CYP3A substrates) PPIs (CYP3A/2C19 substrates)	In vitro studies have shown that Lumacaftor may induce CYP2C8, CYP2C9 AND CYP2C19 but inhibition of CYP2C8 AND CYP2C9 has been documented. In vitro studies suggest possible inhibition of CYP2C9 by Ivacaftor. Lumacaftor may induce metabolism of CYP3A substrates (decreased exposure to these substrates).

		Hormonal contraceptives (CYP3A substrate) Midazolam (CYP3A substrate) Ibuprofen (CYP3A/2C8/2C9 substrate) Montelukast (CYP3A/2C8/2C9 substrate)	Summary: Orkambi may increase OR decrease exposure of CYP2C8 and 2C9 substrates and decrease exposure of CYP2C19 substrates.
Symkevi (Tezacaftor/ Ivacaftor)	Tezacaftor is a substrate for CYP3A4 and CYP3A5. See above for Ivacaftor.	*Strong CYP3A inducers:* Rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine	Exposure to Elexacaftor, Tezacaftor and Ivacaftor is expected to be reduced (particularly Ivacaftor.) Combination should be avoided.
		Strong CYP3A inhibitors: Azoles (e.g. voriconazole), clarithromycin *Moderate CYP3A inhibitors:* Fluconazole, erythromycin	Exposure to Elexacaftor, Tezacaftor and Ivacaftor is expected to be increased. Dose reductions of Symkevi and Kaftrio would be required.
		Food or drink containing grapefruit	Exposure to Elexacaftor, Tezacaftor and Ivacaftor is expected to be increased. grapefruit to

			be avoided.
		CYP2C9 substrates: Warfarin	Close monitoring of INR recommended.
		Interactions with transporters (P-gp substrates): Digoxin, ciclosporin, sirolimus, tacrolimus	Exposure to the P-gp substrates may be increased and so close monitoring required.
Kaftrio (Elexacaftor/Tezacaftor/ Ivacaftor)	Elexacaftor is a substrate for CYP3A4 and CYP3A5. See above for Tezacaftor and Ivacaftor.	As above – see Symkevi section.	As above – see Symkevi section.