Vertex Study Number: VX20-121-102

A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-121 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for *F508del* and a Minimal Function Mutation (F/MF)

ELIGIBLE MF MUTATIONS

"MF" mutations are a subset of minimal function mutations that are non-responsive to TEZ, IVA, or TEZ/IVA. A mutation is considered an MF mutation if it meets at least 1 of the following 2 criteria:

(1) biological plausibility of no translated protein (genetic sequence predicts the complete absence of CFTR protein), or

(2) in vitro testing that supports lack of responsiveness to TEZ, IVA, or TEZ/IVA

Inclusion of MF Mutations Based on In Vitro Testing

Mutations that were considered to be MF mutations based on in vitro testing met the following criteria in in vitro experiments:

- baseline chloride transport that was <10% of wildtype CFTR
- an increase in chloride transport of <10% over baseline following the addition of TEZ, IVA, or TEZ/IVA in the assay

Eligible MF Mutations

The list below represents acceptable mutations, which are detectable by an FDA-cleared genotyping assay or other method (e.g., sequencing); however, this list does not include every eligible mutation, and investigators should contact the medical monitor regarding other mutations that may also meet study eligibility criteria.

Heterozygous for *F508del* and a Minimal Function (F/MF) Mutation

Mutation 1	Mutation 2
F508del	**Minimal Function Mutations**

Examples of Eligible Minimal Function Mutations					
Nonsense mutations	C276X	K710X	Q414X	R764X	W1204X
	C524X	L1254X	Q493X	R785X	W1282X
	E1104X	L218X	Q525X	R792X	W19X
	E1371X	L732X	Q552X	R851X	W216X
	E193X	L88X	Q685X	S1196X	W401X
	E585X	Q1042X	Q715X	S1255X	W496X
	E60X	Q1313X	Q890X	S434X	W57X
	E822X	Q1330X	Q98X	S466X	W846X
	E92X	Q1382X	R1102X	S489X	W882X
	G27X	Q1411X	R1158X	S4X	Y1092X
	G330X	Q220X	R1162X	S912X	Y122X
	G542X	Q290X	R553X	W1089X	Y275X
	G550X	Q2X	R709X	W1098X	Y849X

	G673X	Q39X	R75X	W1145X	Y913X

Canonical splice mutations	185+1G→T	711+5G→A	1717-1G→A	2790-1G→C	3600+2insT
	296+1G→A	712-1G→T	1811+1G→C	3040G→C (G970R)	3850-1G→A
	296+1G→T	1248+1G→A	1811+1.6kbA→G	W846X	4005+1G→A
	405+1G→A	1249-1G→A	1811+1643G→T	3120G→A	4374+1G→T
	405+3A→C	1341+1G→A	1812-1G→A	3120+1G→A	
	406-1G→A	1525-2A→G	1898+1G→A	3121-2A→G	
	621+1G→T	1525-1G→A	1898+1G→C	3121-1G→A	
	711+1G→T	1717-8G→A	2622+1G→A	3500-2A→G	

Small (≤ 3 nucleotide) insertion /deletion (ins/del) frameshift mutations	182delT	1078delT	1677delTA	2711delT	3737delA
	306insA	1119delA	1782delA	2732insA	3791delC
	306delTAGA	1138insG	1824delA	2869insG	3821delT
	365-366insT	1154insTC	1833delT	2896insAG	3876delA
	394delTT	1161delC	2043delG	2942insT	3878delG
	442delA	1213delT	2143delT	2957delT	3905insT
	444delA	1259insA	2183AA→G[a]	3007delG	4016insT
	457TAT→G	1288insTA	2184delA	3028delA	4021dupT
	541delC	1343delG	2184insA	3171delC	4022insT
	574delA	1471delA	2307insA	3171insC	4040delA
	663delT	1497delGG	2347delG	3271delGG	4279insA
	849delG	1548delG	2585delT	3349insT	4326delTC
	935delA	1609del CA	2594delGT	3659delC	

Non-small (> 3 nucleotide) insertion /deletion (ins/del) frameshift mutations	CFTRdele1	CFTRdele16-17b	1461ins4
	CFTRdele2	CFTRdele17a,17b	1924del7
	CFTRdele2,3	CFTRdele17a-18	2055del9→A
	CFTRdele2-4	CFTRdele19	2105-2117del13insAGAAA
	CFTRdele3-10,14b-16	CFTRdele19-21	2372del8
	CFTRdele4-7	CFTRdele21	2721del11

	CFTRdele4-11	CFTRdele22-24	2991del32
	CFTR50kbdel	CFTRdele22,23	3121-977_3499+248del2515
	CFTRdup6b-10	124del23bp	3667ins4
	CFTRdele13,14a	852del22	4010del4
	CFTRdele14b-17b	991del5	4209TGTT→AA

Missense mutations that are non-responsive in vitro to TEZ, IVA, or TEZ/IVA	A46D	L1077P	R560S
	A559T	L467P	R560T
	A561E	M1101K	V520F
	G85E	N1303K	Y569D
	I507del	R1066C	
	L1065P	R347P	

IVA: ivacaftor; MF: minimal function; TEZ: tezacaftor
Source: CFTR2.org [Internet]. Baltimore (MD): Clinical and functional translation of CFTR. The Clinical and Functional Translation of CFTR (CFTR2), US Cystic Fibrosis Foundation, Johns Hopkins University, the Hospital for Sick Children. Available at: http://www.cftr2.org/. Accessed 15 February 2016.
[a] Also known as 2183delAA→G.