Vertex Study Number: VX20-121-103

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 Homozygous for *F508del*, Heterozygous for *F508del* and a Gating (F/G) or Residual Function (F/RF) Mutation, or Have At Least 1 Other Triple Combination Responsive *CFTR* Mutation and No *F508del* Mutation

1) **Homozygous for *F508del***

Mutation 1	Mutation 2
F508del	**F508del**

2) **Heterozygous for *F508del* and a Gating (F/G) or Residual Function (F/RF) Mutation**

Mutation 1	Mutation 2
F508del	**Gating Mutations***

* These mutations are characterized as “gating” for the purpose of this trial based on precedent set in prior studies

Qualifying Gating Mutations			
G1069R	G178R	R1070Q	S1255P
G1244E	G551D	R117H	S549N
G1349D	G551S	S1251N	S549R

Mutation 1	Mutation 2
F508del	**Residual Function Mutations**

Qualifying Residual Function Mutations		
2789+5G>A	D579G	R117C
3272-26A>G	E193K	R347H
3849+10kbC>T	E56K	R352Q
711+3A>G	E831X	R74W
A1067T	F1052V	S945L
A455E	F1074L	S977F
D110E	K1060T	
D110H	L206W	
D1152H	P67L	
D1270N	R1070W	

3) **Have At Least 1 Other Triple Combination Responsive *CFTR* Mutation and No *F508del* Mutation**

Mutation 1	Mutation 2
Any, <u>except</u> for F508del	**ELX/TEZ/IVA Responsive Mutations**

Qualifying ELX/TEZ/IVA Responsive Mutations		
3141del9	E403D	G576A;R668C †
546insCTA	E474K	G622D
A46D	E588V	G628R
A120T	E822K	G970D
A234D	F191V	G1061R
A349V	F311del	G1069R
A455E	F311L	G1244E
A554E	F508C	G1249R
A1006E	F508C;S1251N †	G1349D
A1067T	F575Y	H139R
D110E	F1016S	H199Y
D110H	F1052V	H939R
D192G	F1074L	H1054D
D443Y	F1099L	H1085P
D443Y;G576A;R668C †	G27R	H1085R
D579G	G85E	H1375P
D614G	G126D	I148T
D836Y	G178E	I175V
D924N	G178R	I336K
D979V	G194R	I502T
D1152H	G194V	I601F
D1270N	G314E	I618T
E56K	G463V	I807M
E60K	G480C	I980K
E92K	G551D	I1027T
E116K	G551S	I1139V
E193K	G576A	I1269N

I1366N	R74W;V201M;D1270N †	S589N
K1060T	R75Q	S737F
L15P	R117C	S912L
L165S	R117G	S945L
L206W	R117H	S977F
L320V	R117L	S1159F
L346P	R117P	S1159P
L453S	R170H	S1251N
L967S	R258G	S1255P
L997F	R334L	T338I
L1077P	R334Q	T1036N
L1324P	R347H	T1053I
L1335P	R347L	V201M
L1480P	R347P	V232D
M152V	R352Q	V456A
M265R	R352W	V456F
M952I	R553Q	V562I
M952T	R668C	V754M
M1101K	R751L	V1153E
P5L	R792G	V1240G
P67L	R933G	V1293G
P205S	R1066H	W361R
P574H	R1070Q	W1098C
Q98R	R1070W	W1282R
Q237E	R1162L	Y109N
Q237H	R1283M	Y161D
Q359R	R1283S	Y161S
Q1291R	S13F	Y563N
R31L	S341P	Y1014C
R74Q	S364P	Y1032C
R74W	S492F	
R74W;D1270N †	S549N	
R74W;V201M †	S549R	

† Complex/compound mutations where a single allele of the CFTR gene has multiple mutations; these exist independent of the presence of mutations on the other allele.