

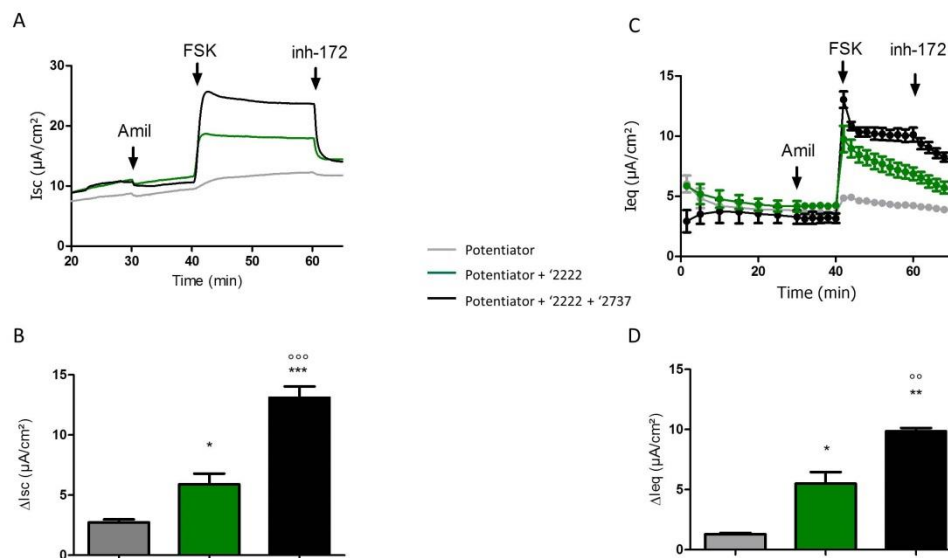
Supplementary Material

Identification of GLPG/ABBV-2737, a novel class of corrector, which exerts functional synergy with other CFTR modulators

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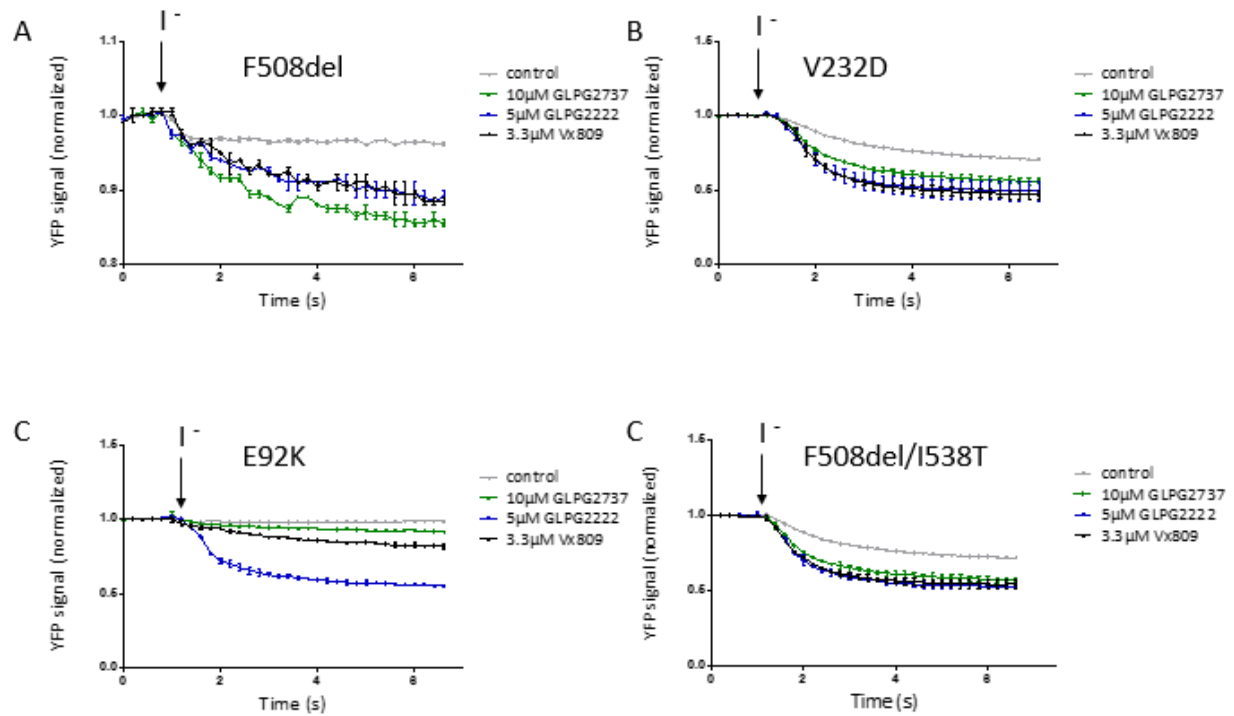
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1 Supplementary Figures



Supplementary Figure 1.

Evaluation of GLPG2737 corrector activity in Ussing chamber and TECC on F508del/F508del HBE cells (donor BCF714). **A.** Average traces of Ussing chamber data of cells treated with either 2 μM potentiator (grey); 2 μM potentiator + 0.15 μM GLPG2222 (green) or 2 μM potentiator + 0.15 μM GLPG2222 + 1 μM GLPG2737 (black). **B.** Changes in short circuit current after stimulation with forskolin for the experiment shown in A ($n = 3$ for each condition) **C.** traces of TECC data of cells treated with either Potentiator (grey); Potentiator + GLPG2222 (green) or Potentiator + GLPG2222 + GLPG2737 (black). ($n = 3$ for each condition) **D.** Area under Curve calculations. Potentiator used was GLPG2451. p values are denoted with * compared to DMSO and with $^{\circ}$ compared to GLPG2222 + potentiator (one symbol meaning $p < 0.05$, 2 $p < 0.01$ and 3 $p < 0.0001$)



Supplementary Figure 2: YHA assay using CFTR mutant overexpression in HEK293 cells. Cells were incubated for 24 hours with either DMSO (grey); 10 μM GLPG2737 (green); 5 μM GLPG2222 (blue); 3.3 μM VX-809 (black). After washing, cells were triggered with forskolin (50 μM for F508del (A), V232D (B), E92K (C) and F508del/I539T (D)) and 0.5 μM potentiator and YFP fluorescence was measured. The YFP fluorescence was recorded during 7 s, starting directly before iodide injection. The CFTR channel function was expressed using the formula $(1 - (\text{YFP fluorescence } 7 \text{ s after iodide addition (F)} / \text{YFP fluorescence before iodide addition (F}_0)))$

	EC ₅₀ (nM)	normalised efficacy (%)	n
Donor1	14.1 ± 4.5	171 ± 27	3
Donor2	27.8 ± 26.9	208 ± 40	2
Donor3	18.9 ± 7.4	172 ± 11	2
Donor4	5.9	187	1

Supplementary Table 1: Dose dependent effect of GLPG2737 on F508del CFTR function. F508del/F508del HBE cells for different donors were incubated for 24 hours with a dose response of GLPG2737 in combination with 0.15 µM GLPG2222 and 1.5 µM GLPG3067. The potency (EC₅₀) and normalized efficacy (with response of GLPG2222 and GLPG3067 set as 100%) in each donor are shown.