A novel corrector for F508del-CFTR that complements existing CFTR modulators in vitro

INTRODUCTION

Deletion of phenylalanine 508 (F508del) in the cystic fibrosis transmembrane regulator (CFTR) is the most common mutation associated with cystic fibrosis (CF). As a result of the F508del mutation, the vast majority of CFTR protein is co-translationally ubiquitinated and degraded through the proteasome, resulting in deficiency of functional CFTR and thereby a deficiency of chloride ion flux. Pharmacologic intervention strategies, such as treating with the corrector lumacaftor, have been shown to facilitate the chaperoning of a portion of the mutant F508del CFTR to the cell surface where a potentiator, or PTI corrector, lumacaftor and ivacaftor significantly increases chloride transport, suggesting the PTI overall level of steady-state F508del-CFTR protein compared to lumacaftor alone. PTI-C1811 provides a concentration-dependent increase in F508del-CFTR maturation in CFBE cells overexpressing F508del-CFTR with sub-micromolar potency.

RESULTS

PTI-C1811 Corrector Increases F508del-CFTR Maturation and Activity in Cell Lines

PTI-C1811 Has Superior in vitro Efficacy to Lumacaftor in F508del/F508del Donor HBE Cells

PTI-C1811 is Additive with Lumacaftor, Indicating a Novel Mechanism of Action

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CONCLUSIONS

PTI-C1811 provides in vitro F508del-CFTR maturation superior to lumacaftor.

In combination with potentiator and amplifier, PTI-C1811 provides in vitro efficacy superior to lumacaftor in functional readouts.

PTI-C1811 adds to lumacaftor, consistent with a distinct mechanism of action for this corrector.

PTI-C1811-mediated correction and functional rescue are maintained under conditions where lumacaftor correction is abrogated by ivacaftor destabilization.

Molecular modeling suggests a plausible binding site distinct from lumacaftor at the MSD1-MSD2 interface for PTI-C1811 that will be confirmed by mutational analysis of the residues involved in the domain-domain and compound interactions.