Pfizer Inc.	PF-05416266 (senicapoc; ICA-17043)
Mechanism of Action	Calcium-activated potassium channel blocker (KCa3.1), intermediate-conductance http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=384 http://www.ncbi.nlm.nih.gov/gene/3783
Overview	Senicapoc is a potent and selective blocker of the human KCa3.1 channel. Potency: IC_{50} = 6.2 nM for K^+ current through human KCa3.1 expressed in CHO cells or native KCa3.1 in human lung mast cells; 11 nM through Gardos channels in human red blood cells (RBCs); and 20 nM for increase hemoglobin concentrations in human RBCs. Selectivity: IC_{50} > 1 uM for Kv1.5, hERG, Na (TTX sensitive), IKs, KvLQT, and h-H1.
Safety/Tolerability	Senicapoc was safe and generally well tolerated at 10 mg QD for 52+ weeks (mean plasma concentration ~100 ng/ml). Non-sickle cell crisis-related adverse events (Aes) that occurred in ≥ 5% of subjects, and more often in senicapoc treated, included urinary tract infection, nausea, arthralgia, pain in extremity, and cough. Nonclinical toxicology data support clinical studies up to at least 1 year in duration and include genetic, reproduction, and carcinogenicity studies.
Additional Information	Senicapoc has a mean human plasma half-life of 12.8 days, so a loading dose followed by daily maintenance doses provide near constant plasma concentrations. Pharmacodynamic (PD) evidence of channel block was demonstrated in humans by increases in hemoglobin and decreases in indicators of hemolysis [lactate dehydrogenase (LDH), reticulocyte count and indirect bilirubin]. E_{MAX} model fitting revealed 50% maximal inhibition of the Gardos channel at a plasma concentration of 54 ± 8 ng/ml. Senicapoc is a modest inducer of CYP3A4 with no or minimal effect on 7 other human CYP450 enzymes.
Suitable for and Exclusions	There are no known contraindications for senicapoc. One pharmacokinetic (PK) and PD study has been performed in pediatric subjects (6 – 15 years of age). No study has included subjects > 65 years old.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=PF-05416266+OR+senicapoc+OR+ICA-17043
Publications	http://www.ncbi.nlm.nih.gov/pubmed?term=senicapoc%20OR%20ICA-17043 http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2010.08520.x/pdf