COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

SLV213: A Novel Orally-available Cathepsin Inhibitor In Development For Potential Treatment Or Prophylaxis Against Coronaviruses, Filoviruses And Paramyxoviruses

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Cathepsins are a group of proteolytic enzymes with a broad spectrum of substrates and functions both inside and outside of cells. Many viruses use host cathepsins to facilitate cell entry. For example, the endosomal cysteine protease cathepsin L mediates cleavage of the coronavirus SARS-CoV-2 spike (S) protein to enable the endosomal escape of the virus and entry into the host cytoplasm, a mechanism increasingly utilized by recent variants such as Omicron. To address this gap SLV213 (K777) is a novel, orally available cathepsin L inhibitor that exhibits potent in vitro activity against a range of viruses including coronaviruses, filoviruses and paramyxoviruses. In cell culture studies of SLV213 against a panel of viral pathogens, EC50 values of <0.1 uM were measured against Marburg, Ebola, Sudan, SARS-CoV-2, MERS-CoV and Nipah viruses. Preclinical studies have demonstrated the potent antiviral activity, safety, and pharmacokinetics after oral administration in several in vivo models. In a non-human primate model of SARS-CoV-2, SLV213 reduced viral load and prevented severe lung disease in both the prophylactic and therapeutic settings. A single-dose Phase 1 clinical study was completed in volunteers, where five cohorts of 8 subjects (6 active, 2 placebo) received a single oral (capsule) dose of SLV213 or placebo at sequential dose levels of 50 mg, 100 mg, 200 mg, 400 mg, or 800 mg. SLV213 was safe and well-tolerated at all doses tested with no dose limiting toxicities. All adverse events were of mild severity except one clinically significant severe AE (orthostatic syncope) noted at the 200mg dose, although this was not repeated at subsequent times or at increased dose levels. Plasma pharmacokinetic analysis indicated that SLV213 was rapidly absorbed after oral administration. A multiple ascending dose Phase 1 clinical study is ongoing to demonstrate safety and tolerability of SLV213 over repeat dosing and to select a maximum tolerated dose for subsequent Phase 2 clinical trials. Three cohorts of 12 subjects (8 active, 4 placebo) per cohort are receiving oral doses of 400 mg, 600 mg or 800 mg SLV213 or placebo twice daily for 7 days. The clinical trials and preclinical studies completed to date support the further exploration of SLV213 as a potential broad-spectrum, host-directed intervention for use as treatment or prophylaxis against emerging viral pathogens.

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