**Discovery and Development of Atilotrelvir (GST-HG171) for the Treatment of COVID-19.**

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The coronavirus 3C-like (3CL) protease has become a validated therapeutic target for developing new COVID-19 therapeutics with the clinical success of Paxlovid (nirmatrelvir/ritonavir) in treating high-risk COVID-19 patients. Although symptoms associated with the recent Omicron infections are generally less severe than the preceding strains, the risk of disease progressing to hospitalization and deaths remains, especially in elderly population with chronic diseases. In addition, the risk of long-term consequence (i.e., long COVID) caused by continuously emerging variants is unpredictable. Therefore, broad-spectrum, and more effective and safer antiviral drugs targeting the intrinsic and more conserved viral replication cycle are still in urgent need for treating COVID-19 patients across all risk levels. Here we report the discovery and development of Atilotrelvir (GST-HG171), a potent, broad-spectrum, orally bioavailable small-molecule 3CL protease inhibitor that has demonstrated greater potency and efficacy compared to Nirmatrelvir in pre-clinical studies in vitro and in vivo. Further, GST-HG171 exhibits more favorable pharmacokinetic characteristics and has demonstrated an excellent safety profile in both pre-clinical and phase 1 clinical studies. Finally, in a pivotal phase 2/3 study, we evaluated efficacy and safety of Atilotrelvir (GST-HG171) plus Ritonavir in mild to moderate COVID-19 patients (n = 1246) infected with emerging Omicron XBB and non-XBB variants. Subjects received GST-HG171 plus Ritonavir showed both shortened median time to sustained recovery of clinical symptoms compared to placebo (P = 0.031), and negative conversion of SARS-CoV-2 nucleic acid vs. placebo (P < 0.0001) with the LS mean difference in viral load change from baseline reaching the largest at day 5 of 1.75 log10 copies/mL (P < 0.0001). Consistent results were observed in SARS-CoV-2 XBB (45.7% of mITT population) and non-XBB variants (54.3% of mITT population) subgroups. Incidence of adverse events was similar in Atilotrelvir (GST-HG171) plus Ritonavir and placebo groups. Based on the results of the pivotal study, Atilotrelvir (GST-HG171) plus Ritonavir was conditionally approved by the Chinese National Medical Products Administration (NMPA) for treating adult patients with mild to moderate COVID-19 in November, 2023..