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Olgotrelvir: A New Generation Oral Antiviral for Treatment of COVID-19

Can Jin, Xiao Xu and Long Mao*

ACEA Therapeutics, Inc., California, USA

About the Study

Severe Acute Respiratory Syndrome Coronavirus 2 (SARA-CoV-2) and its variants have caused Corona Virus Disease 2019 (COVID-19) over a more than 3-year-long pandemic with millions of reported deaths worldwide. Despite the unprecedented speed of development and approval of SARS-CoV-2 vaccines and oral antivirals including Paxlovid (co-administered Nirmatrelvir with Ritonavir), there remain concerns on emerging Variants of Concern (VOCs) with increased virulence and infectivity and clinical challenges especially for population at risk who cannot benefit from existing drugs due to potential Drug-Drug Interactions (DDIs) (https://www.pfizer.com/products/product-detail/paxlovidtm) [1].

Olgotrelvir (STI-1558), a dual inhibitor of SARS-CoV-2 M^{pro} and human cathepsin L., is a novel antiviral drug with improved antiviral potency and safety profiles designed to address above concerns and clinical challenges [2]. Olgotrelvir is a highly oral-bioavailable prodrug that is converted in plasma to its active form AC1115 in a non-enzymatic process. AC1115 inhibits all tested M^{pro} from variants including WA-1 and Omicron (IC_{50}=2.7 nM and 14.3 nM, respectively). Importantly, AC1115 demonstrated potent activity against the M^{pro} *E166* mutants which are resistant to Nirmatrelvir. AC1115 also inhibits host CTSL (IC_{50}=27.4 pM) [3]. The dual inhibition was confirmed by co-crystal structures of AC1115 with SARS-CoV-2 M^{pro} and human CTSL (Figure 1).

In Vero E6 cells, antiviral EC_{50} values of AC1115 were 1 uM against WA-1 and 0.8 uM against Omicron BA.5. In differentiated normal human bronchial epithelial cell system, the antiviral EC_{50} value is below 41 nM against Omicron BA.5. Consistent with potent inhibition of CTSL, olgotrelvir blocked viral entry into cells using SARS-CoV-2 S protein pseudotyped ΔG-luciferase rVSV (IC_{50}=54.5-81.4 nM). In k18-hACE2 mouse model, olgotrelvir at oral dose of 500 and 1000 mg/kg twice daily BID significantly reduced mice lung virus load, cytokine release or lung pathology and prevented mice body weight loss. Olgotrelvir showed enhanced oral bioavailability in animal models and in humans, with significant plasma and lung tissue exposures without the need for co-administration of Ritonavir, a CYP3A4 inhibitor.

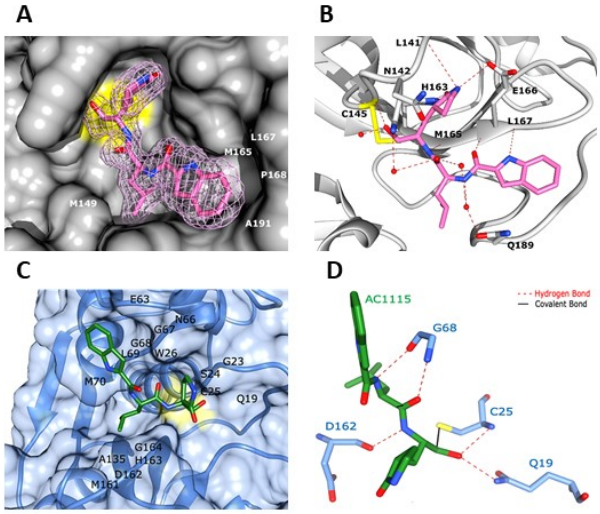

Figure 1. Co-crystal structure of SARS-CoV-2 M^{pro} or human cathepsin L complexed with AC1115. A) SARS-CoV-2 M^{pro} (gray surface) bound with AC1115 (pink sticks). Electron density corresponding to AC1115 is shown in pink mesh. Hydrophobic residues of the M^{pro} catalytic pocket are labeled; with the active site cysteine (Cys145) shown in yellow; B) Hydrogen bond interactions between AC1115 and M^{pro} (black lines). AC1115 forms 7 direct hydrogen bonds with M^{pro} residues, with additional polar interactions mediated by water molecules (red spheres); C) CTSL protein (blue surface) with covalently bound AC1115 (green sticks). Amino acid residues contacting AC1115 are labeled; the catalytic cysteine (Cys25) shown in yellow; D) AC1115 forms covalent bond with the Cys25 side chain sulfur atom (black line) and additional hydrogen bonds with CTSL amino acids (red dashed lines). The two structures were deposited to PDB with IDs of 8UAB and 8UAC.

Phase I trials data indicated no Serious Adverse Event (SAE) or dose related AE for olgotrelvir at single oral doses up to 2000 mg or multiple doses up to 800 mg BID for 7.5 days. AC1115 plasma concentration peaked around 0.5-2 hours post oral administration and the plasma exposure increased linearly with increasing dose of olgotrelvir. No obvious accumulation was observed for AC1115 after 7.5 days administration. For COVID-19 patients in phase I study, oral

***Address for Correspondence**: Long Mao, ACEA Therapeutics, Inc., California, USA; E-mail: lmao@aceatherapeutics.com*

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treatment with olgotrelvir at 300, 600 or 800 mg BID demonstrated fast reductions of viral RNA copies compared with placebo control at D3 (two days of treatment) in each dose group.

Recently, clinical phase III trial was completed [4]. The study (double-blind, randomized, placebo-controlled) evaluated the efficacy and safety of olgotrelvir in 1212 eligible adult patients recruited from 25 hospitals in China. All 1212 non-hospitalized COVID-19 patients with mild-to-moderate symptoms irrespective of risk factors, were randomly assigned to receive either 600 mg of olgotrelvir or placebo BID orally for 5 days. The primary and key secondary endpoints were time to sustained recovery of 11 COVID-19 symptoms and the viral RNA load. The incidence of adverse events was the safety endpoint. The study results are shown below in Figure 2.

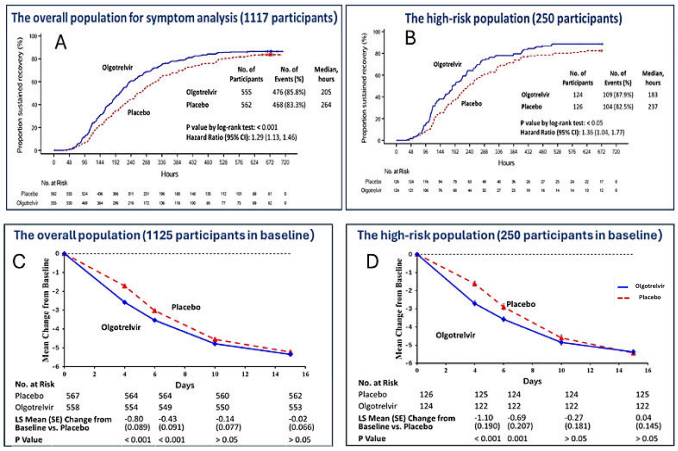

Figure 2. Efficacy of olgpotrelvir in phase III study. A) Symptom recovery analysis in overall modified Intent to Treatment set (mITT) population; B) Symptom recovery analysis in high-risk population; C) Viral load reduction in overall mITT population; D) Viral load reduction in overall high-risk population.

The baseline characteristics of 1212 patients recruited between 08 Feb, 2023 and 26 Jun, 2023 were similar in the two groups. Most patients (98.7%) were either vaccinated or previously infected with SARS-CoV-2, which is different from previously reported clinical trials (in which most participants were either unvaccinated or COVID-19-naive participants) [5]. In the modified Intent to Treatment set (mITT), 1125 patients were assessed for efficacy (567 in placebo and 558 in olgotrelvir). Compared to placebo, olgotrelvir shortened time to sustained recovery of 11 COVID-19 symptoms by 2.4 days (Hazard Ratio (HR), 1.29; 95% Confidence Interval (CI), 1.13 to 1.46; p=0.0001) and reduced viral RNA load by 0.8 log10/mL (p<0.0001) at day 4. In patients at-risk, the clinical recovery time was shortened by 2 days-3 days (HR, 1.36; 95% CI, 1.04 to 1.77; p=0.026) and viral RNA load was reduced by 1.1 log10/mL (p<0.0001) at day 4 in the olgotrelvir group, compared to the placebo group. Most reported Treatment-Emergent Adverse Events (TEAEs) were mild and balanced between two groups. Mild skin rash (2.5%) and mild nausea (1.3%) were more frequent drug-related TEAEs for olgotrelvir than placebo. No drug related serious AEs and death were reported.

The successful completion of phase III clinical trials, which showed significant improvement in clinical recovery and reduction in viral load, paves the way for regulatory approval. With its robust antiviral properties, reduced potential for drug-drug interactions and emerging resistance, Olgotrelvir as a standalone treatment represents a promising next-generation therapeutic option for treating COVID-19 and potentially other coronavirus-related illnesses.

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