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INTRODUCTION:

Molnupiravir (MOV, MK-4482) is the 5′-isobutyrate prodrug of the broadly active, antiviral ribonucleoside analog N-hydroxycytidine (NHC).

MOV is metabolized to NHC which distributes into cells where it is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP acts by a mechanism known as viral error catastrophe. NHC-TP incorporation into viral RNA by the viral polymerase results in an accumulation of errors in the viral genome leading to inhibition of replication.

MOV has been shown to be active in several preclinical models of SARS-CoV-2 infection; additionally, preclinical and clinical data have shown MOV to be active against the most common SARS-CoV-2 variants.

Coronavirus disease 19 (COVID-19) is caused by the coronavirus SARS-CoV-2. COVID-19 was declared a global pandemic by the World Health Organization on 11-MAR-2020. As of late Mar 2022, there have been over 460 million confirmed cases of COVID-19 globally, including 6 million deaths

MOV was evaluated in safety pharmacology studies, a battery of in vitro and in vivo genotoxicity studies (including Ames assays, in vitro and in vivo micronucleus assays, an in vivo Pig-a assay in rats, and an in vivo mutation assay in Big Blue® transgenic rats), tolerability/DRF studies in mice, rats, and dogs, repeat-dose toxicity studies of up to 3 months in rats and 1 month in mice and dogs, fertility studies in male and female rats, embryo-fetal developmental toxicity studies in rats and rabbits, and a pre- and post-natal developmental toxicity study in rats. Additional non pivotal short-term tolerability and/or TK studies were conducted in mice, rats, rabbits, and monkeys.

This new drug application includes results from 6 clinical studies supporting the use of MOV for treatment of COVID-19 in adults: MK-4482-002 (Phase 2/3); MK-4482-006 (Phase 2a); MK-4482-001 (Phase 2); MK-4482-007 (Phase 2a); MK 4482-005 (Phase 1/2); and MK-4482-004 (Phase 1).

At the planned interim analysis of Part 2 (Phase 3) of MK-4482-002, a randomized, placebo-controlled, double-blind study of non-hospitalized adult patients with mild to moderate COVID-19, at least one risk factor associated with poor disease outcomes, and symptom onset within five days prior to randomization, MOV significantly reduced the risk of hospitalization or death by approximately 50%; 7.3% of patients who received MOV were hospitalized or died through Day 29 following randomization (28/385), compared with 14.1% of placebo-treated patients (53/377); p=0.0012. Through Day 29, no deaths were reported in patients who received MOV, as compared to 8 deaths in patients who received placebo.

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The results for all participants randomized in Part 2 support the benefit observed at the interim analysis for MOV compared with placebo in reducing the incidence of hospitalization or death through Day 29. The percentage of participants who were hospitalized or died through Day 29 in the MOV group (6.8%, 48/709) was lower compared with the placebo group (9.7%, 68/699). Treatment with MOV resulted in a 3.0 percentage point reduction [95% CI: -5.9, -0.1] in the incidence of hospitalization or death through Day 29 compared with placebo (approximately 30% relative risk reduction). Nine participants in the placebo group and 1 participant in the MOV group died through Day 29.

MOV is being proposed for the treatment of COVID-19 in adults. The proposed dosing regimen for MOV is 800 mg (administered as four 200 mg capsules) taken orally every 12 hours (Q12H) with or without food for 5 days.