Journal Club
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Title: Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients[1]

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Background: As of January 21, 2022, SARS-CoV-2, better known as COVID-19, has caused over 336 million infections and over 5.5 million deaths.[2] The risk of developing severe COVID-19 illness can be increased with a variety of risk factors leading to hospitalization, intensive care unit admission, or death.[3] Since the emergence of COVID-19, scientists have been researching treatments that will reduce the severity and transmissibility of this virus. Molnupiravir, a novel ribonucleoside prodrug of N-hydroxycytidine (NHC), is an oral capsule that has been developed for this purpose. After administration and metabolism, NHC becomes phosphorylated intracellularly and incorporated to viral RNA. This causes viral polymerase to inappropriately incorporate guanosine or adenosine during replication to render the virus noninfectious and unable to replicate.[4,5] Prior to this trial, treatments involved infusions that could not be performed in an outpatient setting. With oral molnupiravir reducing severity and transmissibility, we can see potential decrease in stress on our healthcare system.

Primary Objective: To determine the efficacy of molnupiravir in adult outpatients at-risk of severe COVID-19 illness.

Primary Efficacy Measure: Composite of the incidence of hospitalizations for any cause or death through day 29.

Study Design: This was a phase III, randomized, double-blind, multinational, placebo-controlled study which was a component of the Phase II/III MOVe-OUT trial. After laboratory confirmation of SARS-CoV-2 infection, patients began a 29-day study period which included an initial 5-day treatment period. Patients were not allowed to use other therapies intended to treat COVID-19 including monoclonal antibodies or remdesivir through the end of the study period.

Subjects: Patients were randomized in a 1:1 fashion to receive molnupiravir or matching placebo. Randomization was stratified in blocks of four according to the time since onset of signs or symptoms ($\leq$ 3 days or > 3 days). Randomization resulted in similar groups regarding age, risk factors for severe illness, and COVID-19 severity; however, the authors noted there was a difference between groups in the distribution of sex.

Inclusion Criteria:

1. Has documentation of PCR-confirmed SARS-CoV-2 infection with sample collection ≤7 days prior to randomization.
   Note: PCR is the preferred method; however, with evolving approaches to laboratory confirmation of SARS-CoV-2 infection, other diagnostic methods are allowed if authorized for use in the country.
2. Has initial onset of signs/symptoms attributable to COVID-19 for ≤7 days prior to randomization and at least 1 of the following signs/symptoms attributable to COVID-19 on the day of randomization (Appendix 9):
   a. Cough, Sore throat, Nasal congestion, Runny nose, Shortness of breath or difficulty breathing, Muscle or body aches, Fatigue, Fever 38.0◦C, Chills, Headache, Nausea, Vomiting, Diarrhea, Loss of smell, Loss of taste
3. Has mild or moderate COVID-19 (Appendix 9); participants with mild COVID-19 must have at least 1 characteristic or underlying medical condition associated with an increased risk of severe illness from COVID-19 (Appendix 10).
4. Has oxygenation saturation of >93% (on room air OR on supplemental oxygen prior to randomization which has not increased since onset of COVID-19 signs/symptoms) obtained at rest by study staff at randomization.
5. Is willing and able to take oral medication.
6. Is male or female ≥18 years of age, at the time of providing informed consent.
7. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 90 days after the last dose of study intervention:
   a. Refrain from donating sperm PLUS either:
      i. Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
         OR
      ii. Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:
         Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.
      iii. Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
8. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
   a. Is not a WOCBP
      OR
   b. Is a WOCBP and using a contraceptive method that is highly effective (a low user dependency method OR a user dependent method in combination with barrier method) or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 7

months after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (i.e., noncompliance, recently initiated) in relationship to the first dose of study intervention.

c. A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention.
d. Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.4.
e. The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
f. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
g. If contraceptives are interrupted as standard of care management of COVID-19 patients and resumed at a later time point, such as at hospital discharge, then abstinence must be practiced for the defined period of back-up contraception per the contraceptive product labeling. After this period, contraceptive use must adhere to Appendix 5.

9. Participant (or legally acceptable representative) has provided documented informed consent for the study.

Exclusion Criteria:

1. Is currently hospitalized or is expected to need hospitalization for COVID-19 within 48 hours of randomization.
2. Is on dialysis or has reduced eGFR.
3. Has any of the following conditions:
    a. HIV with a recent viral load >50 copies/mL or CD4 <200 cell/mm^3.
    b. Chemotherapy required within 6 weeks before randomization.
    c. A neutrophilic granulocyte absolute count <500/mm^3.
    d. Autologous or allogeneic hematopoietic stem cell transplant recipient.
4. Has an active diagnosis of hepatitis due to any cause, including active HBV infection (defined as HBsAg-positive) or HCV infection (defined as detectable HCV RNA).
5. Has a platelet count <100,000/µL or received a platelet transfusion in the 5 days prior to randomization.
6. Has a history of acute pancreatitis within 3 months prior to randomization or a history of chronic pancreatitis.
7. Has a baseline heart rate of <50 beats per minute at rest.
8. Has hypersensitivity or other contraindication to any of the components of the study interventions as determined by the investigator.
9. Has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant or that could prevent, limit, or confound the protocol-specified assessments including but not limited to:
    a. Participants who are not expected to survive longer than 48 hours after randomization, or
    b. Participants with a recent history of mechanical ventilation not associated with COVID-19, or

c. Participants with conditions that could limit gastrointestinal absorption of capsule contents.

10. Is taking or is anticipated to require any prohibited therapies as outlined in Section 6.5.
11. Is unwilling to abstain from participating in another interventional clinical study through Day 29 with an investigational compound or device, including those for COVID-19 therapeutics.
12. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

Study Period: The MOVe-OUT trial was initiated on May 6, 2021, with enough patients enrolled for the prespecified interim analysis to be performed on September 10, 2021. After an independent data monitoring committee recommended recruitment be stopped early, the final participant was enrolled on October 2, 2021, and completed the day 29 follow up on November 4, 2021. After randomization, patients began a 5-day treatment phase with either molnupiravir 800 mg – supplied as four, 200 mg capsules – or matching placebo by mouth twice daily, with follow up through the 29-day study period.

Monitoring: Patients were monitored for hospitalization status, vital signs, laboratory tests, physical examination, and adverse events on days 1, 3, 5, 10, 15, and 29. Patients reported signs and symptoms as not present, mild, moderate, or severe throughout the study period using a paper dairy.

Data Analysis: Analysis of a modified intent-to-treat population was performed both at the interim analysis, 50% of expected population, and with all patients included after enrollment was stopped. The interim analysis included 385 patients assigned to molnupiravir and 377 patients assigned to placebo. The analysis of all patients enrolled included 709 and 699 patients assigned to molnupiravir and placebo respectively. Enrollment was set at 1550 patients total to achieve 95% power, with a one-sided alpha set at 0.025. For the interim analysis, superiority of molnupiravir was shown if p was less than one-sided alpha of 0.0092.

Data Analyzed	Type of Data	Statistical Test Used	Appropriate/Not Appropriate
Composite of incidence of hospitalization for any cause or death through day 29	Nominal	Miettinen and Nurminen method using Cochran-Mantel-Haenszel weights	Appropriate

Results: At the prespecified interim analysis, molnupiravir was shown to have a statically significant difference versus placebo in the incidence of hospitalization for any cause or death through day 29. This is shown by the 95% confidence interval not crossing the absolute equivalency of zero and further supported by a p value less than alpha (0.0092 for interim analysis). This result is further supported by the results of all patients enrolled, which showed a lower incidence of hospitalization for any cause or death through day 29 compared to placebo.

Interim analysis	Molnupiravir (n=385)	Placebo (n=377)	Difference (95% CI)	P value	NNT[a]
Percentage of patient with primary outcome[b] (no.)	7.3% (28)	14.1% (53)	-6.8% (-11.3 to -2.4)	0.001	15

[a]Number Needed to Treat to prevent one primary outcome
[b]Incidence of hospitalization for any cause or death through day 29

All enrolled patients	Molnupiravir (n=709)	Placebo (n=699)	Difference (95% CI)
Percentage of patient with primary outcome[a] (no.)	6.8% (48)	9.7% (68)	-3.0% (-5.9 to -0.1)

[a]Incidence of hospitalization for any cause or death through day 29

Tolerability: Overall, the number of patients experiencing at least one adverse event and an adverse event related to the assigned treatment regimen were similar. There were more serious adverse events (67 vs. 49) and deaths (12 vs. 2) in the placebo group. The most common reported adverse events related to treatment in both groups were diarrhea, nausea, and dizziness.

Author's Conclusion: The MOVe-OUT trial showed that 5-day treatment with molnupiravir, initiated within 5 days of symptom onset, was superior to placebo in reducing the risk of hospitalization for any cause or death through 29 days.

Strengths:

- Planned interim analysis used a stricter alpha than full analysis
- Treatment was appropriate and accepted
- Length of study was appropriate to show affect
- Inclusion and exclusion criteria were appropriate
- Blinding was present
- Biostatistical test was present
- Primary outcome is appropriate
- Authors' conclusion supported by results
- Survival status at day 29 was confirmed for all but a single patient in the mITT population, this missing data was inputted as having a primary outcome

Limitations:

- Power set but not met
- Randomization produced groups with different characteristics
- Because interim analysis showed superiority, analysis of all enrolled patients did not have a calculated p value, with an unknown, noticeable drop in treatment difference
- Only included non-vaccinated patients

Level of Evidence: Level II – interventional, placebo-controlled, randomized trial that did not power with Major Limitations

Recommendation: I recommend the use of molnupiravir in adult outpatients, at risk of severe COVID-19 illness, if initiated within 5 days of symptom onset versus no treatment for the following reasons:

- Efficacy
  - At the preset interim analysis, molnupiravir was associated with a statistically significant decrease in incidence of hospitalization for any cause or death through 29 days
    - Further supported by the results of all enrolled population
- Safety
  - The number of patients experiencing adverse events were similar between groups
  - Most common adverse events were diarrhea, nausea, and dizziness
- Cost
  - The US purchased molnupiravir treatments at an estimated cost of ≈$700/patient[6]
- Special Considerations/Populations
  - There is currently no data comparing molnupiravir to other oral or injectable treatments for COVID-19
  - Currently, molnupiravir is available through an emergency use authorization[7]
  - Molnupiravir is an oral agent, making it an option for patients who may not prefer injections
  - National Institutes of Health COVID-19 treatment guideline recommends molnupiravir as fourth line option for use[8]
  - Most common risk factors for severe illness were obesity, age >60, and diabetes mellitus
  - Larger clinical trials are needed to further establish efficacy and safety
  - Vaccinated patients were excluded limiting generalizability to use in breakthrough infections
  - Mechanism of action is independent of mutations in spike protein allowing molnupiravir to work across different variants of COVID-19
  - Does not replace the need for vaccination against COVID-19

Grade of Recommendation: B

References:

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