



Considerations for Medically Attended Visits in COVID-19 Clinical Trials

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MOVE-OUT: A phase 2/3 global study adult participants with mild-moderate COVID-19 conducted May-Oct 2021

Study Population

- Non-hospitalized adults with mild or moderate COVID-19
 - Laboratory-confirmed SARS-CoV-2 infection with sample collection ≤ 5 days prior to randomization
 - Initial onset of COVID-19 signs/symptoms ≤ 5 days prior to randomization

- All participants at increased risk for severe illness from COVID-19

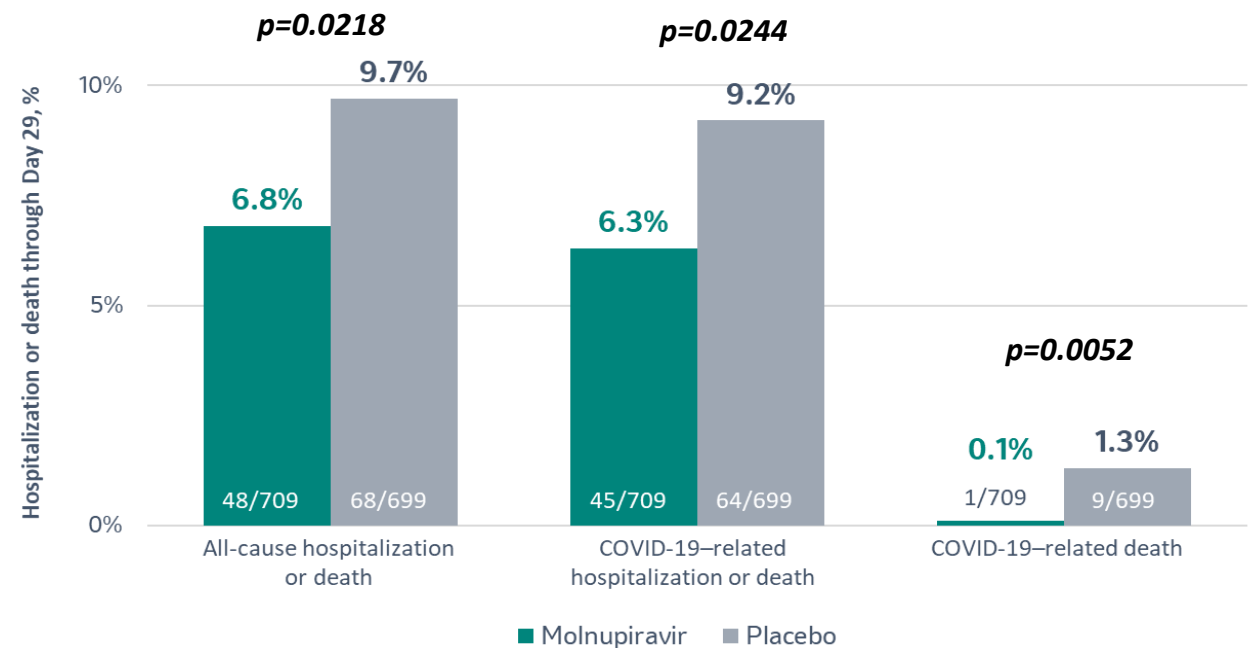
- >60 years of age
- Active cancer
- CKD
- COPD
- Obesity (BMI ≥ 30)
- Serious heart conditions (CAD, heart failure, cardiomyopathies)
- Diabetes mellitus

Stratification

- Time from symptom onset to randomization (≤ 3 days, >3 days)

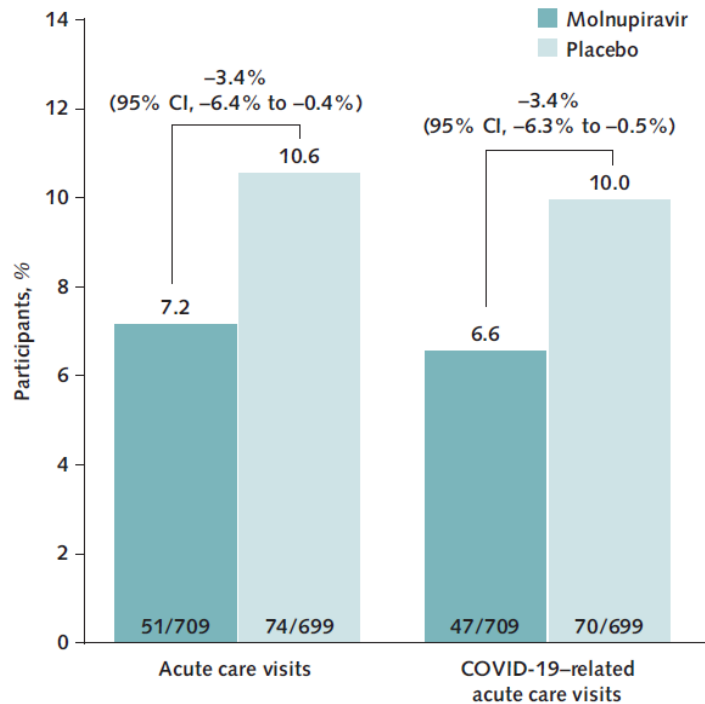
MOV reduced the risk of hospitalization or death as compared to placebo

All-cause and COVID-19-related hospitalization or death through Day 29
(All randomized MITT population)



Medically Attended Visits in MOVE-OUT

Acute care visits and COVID-19-related acute care visits were less frequent in molnupiravir versus placebo-treated participants



95% CIs were based on the Miettinen-Nurminen method, with stratification by randomization strata. MITT = modified intention-to-treat.

- Acute care visits were collected in eCRF based on sites soliciting info from patients on the following:
 - Urgent Care
 - Office or clinic visit
 - Home visit by health care provider
 - ER or facility created to address hospitalization during the COVID-19 pandemic (≥ 24 hours was considered hospitalization)
- COVID-19 relatedness was investigator-assessed and was up to their discretion

What is a Medically Attended Visit (MAV)?

Defined as an unscheduled or nonroutine visit with a healthcare provider

There are challenges associated with defining MAVs in the context of a clinical trial

- Definition of a healthcare provider can differ globally, as can healthcare settings and delivery of care
- Telemedicine is commonly used. Are all telemedicine visits acceptable?
- Does time spent in hospital or emergency room define it being an MAV (ex: <24 hours = MAV vs ≥ 24 hours = hospitalization)
- Source data collection can be challenging as MAV may occur at urgent care or healthcare facility that the investigator site does not have access to therefore access to the record of the visit can be challenging
- Frequency of study visits may impact a patient's decision to see another healthcare provider or an unscheduled visit to the investigator vs waiting for next scheduled protocol visit with site

MAVs – what are COVID-19 related interventions?

THESE ARE...

- Oxygen therapy given in an emergency room
- Antibiotic at an urgent care visit for a secondary bacterial infection
- Primary care provider giving IV fluids
- Telehealth visit with a provider that prescribes benzonatate for persistent cough that is interrupting sleep

ARE THESE??

- Phone triage nurse recommends pseudoephedrine and nasal sinus flushing for persistent congestion
- At a prescheduled wellness visit, patient complains of worsening nausea which began with COVID-19, so is given a prescription for ondansetron
- Cough suppressant recommended by a pharmacist for persistent cough

MAVs - what are exacerbations of underlying conditions due to COVID-19?

THESE ARE...

- Exacerbations of COPD or asthma
- Unusual glucose fluctuation in a diabetic patient
- Heart failure exacerbation due to inability to tolerate PO medications due to nausea
- Worsening of arthritis pain
- Worsening neurological symptoms of multiple sclerosis
- Dermatologic condition flare-up during COVID-19

ARE THESE??

- Anxiety attack due to isolation in a patient with anxiety in their medical history
- Increased sleep disturbances in a menopausal woman
- Exacerbation of psychosis in a patient diagnosed with schizophrenia

Adjudication of Medically Attended Visits (MAVs)

- Assessment of relatedness of COVID-19 is difficult to ascertain solely on the basis of objective criteria, making adjudication challenging
- COVID-19 can impact any body system so the information needed to determine relatedness (laboratory tests, imaging, prescription medication, etc.) depending on the nature of the MAV
 - Different from relatedness used in RSV where the disease burden is confined to lower respiratory tract infections
- What will an adjudication committee need to confirming MAV is related to COVID-19 persisting or worsening or if a pre-existing chronic disease exacerbated by COVID-19
- Phase 3 global studies are conducted globally so important that adjudication committee members have information they need to understand interventions used by different countries

Defining MAVs using COVID-19 signs and symptoms

Severity and/or worsening of symptoms may help to define MAVs that are COVID-related – should it be limited to visits where it is documented that there is:

- A worsening of one or more COVID-19 signs or symptoms such that it is at least moderate severity and interferes with the participant's daily activities
- A persistent COVID-19 sign or symptom that is severe and interferes with the participant's daily activities

Discussion points to consider for using COVID-19 signs and symptoms to define MAVs

- Subjectivity of patient-reported symptom severity
 - One patient may never perceive a symptom as severe, whereas another may perceive all symptoms as severe
- Timing of patient-reported worsening or persistent symptoms on the daily symptom diary may be misaligned with MAV event
 - Look at signs and symptoms on the diary for the day of MAV and day after?
 - What if the sign or symptom is reported as worsening or persistent in the source document for the MAV but not in the daily diary?
- What if the sign/symptom that is worsening or persistent at the MAV is not one that is not included on the COVID-19 daily diary
 - For example: palpitations, chest pain, or dizziness
- How to measure that the specific symptom interfered with the participant's daily activities
 - Quality-of-life questionnaires and/or validated tools are not specific to the COVID-19 sign/symptom collected in the diary
- Source data from MAV may not capture the details needed to confirm this definition is met (a challenge for adjudication purposes)

Conclusions

- After all the challenges we cite, additional endpoints are urgently needed for COVID-19 research
- To include MAVs, need to have a clear and agreed up definition
- We welcome the exploration and consideration of additional clinically-relevant endpoints considering the current impact on patients who develop COVID-19