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Advancing Therapeutic Development for COVID-19 Treatment

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Introduction

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Background

- Three antiviral treatments are currently available in the U.S. (approved or authorized) for the treatment of outpatients with COVID-19 who are at high risk of progression: nirmatrelvir/ritonavir, remdesivir, and molnupiravir.

Background

- Clinical trials in support of currently available therapeutics were conducted when:
  - Immunity rates, natural or vaccine-mediated, were lower.
  - Overall risk of hospitalization and death for patients with mild-moderate COVID-19 was higher.
  - No other active agents were available.

Current State

- Unmet need remains for alternative options to treat mild-moderative COVID-19.
  - Prevention of symptomatic COVID-19 disease in people unlikely to respond to immunization is another priority but not our focus today.
- Risk factors for disease progression is a key consideration in patient selection criteria for enrollment in trials of new treatments for mild-moderate COVID-19.
- In the U.S., it has not been considered acceptable to enroll a patient with mild-moderate COVID-19 considered “high risk” for disease progression to participate in a placebo-controlled trial unless standard of care is offered.
- FDA has looked to CDC to describe "high risk" patient characteristics.
- Data concerning estimates of risk associated with certain underlying medical conditions would be expected to continue to change.

Current Challenges in Conducting Clinical Trials for COVID-19

“High-risk” population

- Given availability of treatment options, placebo-controlled trials are not considered acceptable in "high-risk" patients without offering standard of care (SOC).
- Only a SOC add-on design is currently acceptable in this population.
- Noninferiority trials are not possible (constancy assumption is not maintained).
- Endpoints of hospitalization or death are now less frequently observed.

“Standard-risk” population

- Trials with outpatients are no longer anticipated to have a significant number of events (hospitalization or death).
- Endpoints based on symptom resolution seem most suitable for this population but demonstrating a clinically meaningful effect has been challenging.

Summary of Current Challenges

	High Risk Population	High Risk (<1%?)	Standard Risk
Trial Design	• Placebo-controlled trial: not considered acceptable • Placebo-controlled with add-on to SOC design: difficult to demonstrate treatment difference • Non-inferiority trials: not possible (constancy assumption not maintained)	• Limited updated estimates of risk for progression to severe COVID-19 • Need to determine a population that can be acceptably enrolled in a placebo-controlled trial	• Placebo-controlled trials are feasible
Endpoints	• Endpoints of hospitalization/death now less frequently reported • Clinically meaningful events, which if deemed appropriate, may include medically-attended visits (MAVs) could be part of a composite symptom-based and/or hospitalization/death endpoint.		• Trials with symptom endpoints are feasible • Incorporate MAVs?

Potential Strategies

Is it possible to define a population who could acceptably be enrolled in a placebo-controlled trial and observe enough clinically meaningful events to feasibly assess the effectiveness of the study drug?

1. Identify a sub-population of "high risk" patients that are appropriate for randomization to placebo without SOC (e.g., "intermediate risk" with <1% absolute risk of progression to severe COVID-19).
2. Consider additional or alternative clinically meaningful events (e.g., MAVs) to incorporate as part of a composite with hospitalization/death or symptoms.

Goals for Session 1

- Discuss estimates of risk associated with certain baseline factors and underlying conditions.
- Discuss outpatient population baseline risk criteria that may be suitable for randomization to a placebo control without standard of care.

Goals for Session 2

- Determine if COVID-19 related medically attended visits (MAVs) can serve as a part of a clinically meaningful composite endpoint that also includes hospitalization and death.
- Define criteria for COVID-19 related MAVs and adjudication of these events.


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