ACTIV-6: COVID-19 Outpatient Randomized Trial to Evaluate Efficacy of Repurposed Medications

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ACTIV-6 – Why?

- There is no FDA approved standard of care for COVID-19 patients with mild-to-moderate disease
- Current treatment options require infusion
- Vaccine hesitancy remains high
- Vaccine access globally is low
Viral Evolution

The genetic code for each of these variants is slightly different.

UK “Kent” variant B.1.1.7

- N501Y

South Africa variant B.1.351

- N501Y
- E484K

Brazil variant P.1

- N501Y
- E484K

mAbs with EUA

Convalescent plasma

Vaccinee sera

medRxiv preprint doi: https://doi.org/10.1101/2021.02.23.21252259;
Rationale

• > 80% of COVID-19 cases are diagnosed as an outpatient
• Testing “on the shelf” drugs has advantages during fast-paced pandemic:
  • Expedited timeline
  • Existing knowledge of safety profile
  • Possibly less expensive than newly developed drugs

• Question: Are there medications currently approved for other conditions that improve symptoms in non-hospitalized patients with mild to moderate COVID-19 symptoms?
Key Questions Facing Clinicians, Patients and Caregiver

How to help someone feel better faster with newly diagnosed mild-moderate COVID-19?

How to prevent hospitalizations or death in someone with newly diagnosed mild-moderate COVID-19?
Primary Objective

• To evaluate whether repurposed medications can:
  • Make outpatient participants with mild-to-moderate COVID-19 symptoms feel better faster
  • Reduce death and hospitalization, with the following evaluated from baseline through 14 days:
    • Hospitalization
    • Death
    • Time to symptom freedom
    • Symptom count
Secondary Objectives

• To evaluate clinical outcomes in a study drug arm versus placebo arm
  • Using Modified COVID Ordinal Outcomes Scale on Days 1-14, Day 21, Day 28, and Day 90

• To describe symptom resolution (3 consecutive days without symptoms)

• To describe participants’ quality of life (QOL)
  • Using Patient-Reported Outcomes Measurement Information System (PROMIS)-29 at baseline, Day 7, Day 14, Day 28, and Day 90 follow-up
### ACTIV-6 Repurposed Agents | Scoring Criteria

<table>
<thead>
<tr>
<th>Scoring Criteria</th>
<th>No Go</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Triage &amp; Must-Have</strong></td>
<td></td>
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<tr>
<td>Safety</td>
<td>Not approved for any other</td>
<td>Previously approved for other</td>
<td>Adequate safety profile with</td>
<td>Strong safety profile [previously</td>
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<tr>
<td></td>
<td>disease indication in</td>
<td>disease indication, but lacks</td>
<td>suitable benefit/risk profile (with</td>
<td>approved for other indication in</td>
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<tr>
<td></td>
<td>proposed formulation</td>
<td>safety data in proposed dose</td>
<td>safety warning that needs to be</td>
<td>broad patient populations (i.e., elderly, and/or patients</td>
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<td></td>
<td></td>
<td></td>
<td>adjudicated)</td>
<td>with co-morbidities) and adequate amount of historical safety data]</td>
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<tr>
<td>Route of Administration</td>
<td>Difficult to administer (e.g., IV or store (e.g., requiring specialized equipment)</td>
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<td><strong>Must-Have</strong></td>
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<tr>
<td>Rationale for MOA to be relevant to COVID-19</td>
<td>Unknown</td>
<td>Weak</td>
<td>Moderate</td>
<td>Strong (reasonable rationale for use with COVID-19 and appropriate for outpatient setting)</td>
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<tr>
<td>Relevant Clinical Trial Data for Early COVID-19</td>
<td>Majority of clinical data</td>
<td>No data from outpatient trials</td>
<td>Data from one or more outpatient</td>
<td>Mixed / inconclusive results from</td>
<td>Overall promising initial results from</td>
<td>Overall highly promising initial results including data from one or more outpatient RCTs for SARS CoV-2 or related virus</td>
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<td></td>
<td>shows no effect in</td>
<td></td>
<td>trials in mechanistically relevant</td>
<td>outpatient uncontrolled trials and/or RCTs in SARS CoV-2 or related virus</td>
<td>Overall promising initial results from outpatient uncontrolled trials for SARS CoV-2 or related virus</td>
<td>Overall highly promising initial results including data from one or more outpatient RCTs for SARS CoV-2 or related virus</td>
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<tr>
<td></td>
<td>outpatient setting</td>
<td></td>
<td>disease with promising initial results</td>
<td>RCTs in SARS CoV-2 or related virus</td>
<td>for SARS CoV-2 or related virus</td>
<td>for SARS CoV-2 or related virus</td>
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<tr>
<td>Real World Evidence</td>
<td>No evidence of efficacy from</td>
<td>Valid data from one RWE case study</td>
<td>Valid data from multiple RWE case series</td>
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<tr>
<td></td>
<td>use in the clinical setting /</td>
<td>suggesting clinical efficacy</td>
<td>suggesting clinical efficacy</td>
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<td></td>
<td>no data to judge</td>
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<tr>
<td>Drug-drug Interaction</td>
<td>Major concern (clinically</td>
<td>Insufficient / no data to judge</td>
<td>Minor concern / manageable drug</td>
<td>None</td>
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<td>significant DDIs)</td>
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<td>interactions</td>
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<td>Preclinical Data</td>
<td>No preclinical data / shows no effect</td>
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<td>In vivo data in appropriate animal model</td>
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<td>PK / PD</td>
<td>No PK/PD data / insufficient plasma levels</td>
<td></td>
<td>Sufficient plasma and / or tissue levels</td>
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<tr>
<td>Need for Scientific Clarity (i.e., strong public interest)</td>
<td>No expressed interest from the public / scientific community</td>
<td></td>
<td>Significant interest from the public / scientific community, with no current plans to study the agent in an adequately powered trial</td>
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</table>

*Note: Availability / scalability will be assessed after prioritization of any agent before official entry into the trial*
ACTIV-6

Study Design
Study Design

• Platform Protocol
  • Quickly test different medications using the same infrastructure
  • Used in wide range of settings
  • Integrated into routine COVID-19 testing programs and treatment plans

• Remote Study Visits
  • Participants use online system to complete study surveys and report adverse events or changes in clinical status
  • Unplanned in-person or remote study visits possible if deemed necessary by study investigator
Overall Goal:
ACTIV-6 access in every state via sites or remotely
Randomization

• If only one study drug under study, patients randomized 1:1 between study drug and placebo
• If multiple study drugs, patients randomized among study drugs for which they are eligible and placebo with equal probability (1:1)
  • 2-step randomization process:
    • Participant randomized 1:m, placebo to active study drugs. Participants carry this “placebo” versus “study drug” randomization into the next step.
    • Participant randomized among the m active study drugs for which they are eligible.
• Sites will be informed of participants’ study drug arm but not whether participant is allocated to placebo or study drug
Overall Flow:
Direct to Participant via Site or Anywhere

Eligible adult testing positive for SARS-CoV-2

Health system referral

Eligibility for study arms determined

Randomized 1:m placebo to study drug
(m is number of open, eligible study drug arms)

Placebo
  - Placebo 1
  - Placebo ...
  - Placebo m

Randomized 1/m to open, eligible study drug arm

Study Drug
  - Study Drug 1
  - Study Drug ...
  - Study Drug m

Health system, pharmacies, community testing offering education and trial engagement
Inclusion Criteria

- Willing and able to provide informed consent
- ≥30 years
- Confirmed SARS-CoV-2 infection by any authorized or approved PCR or antigen test collected within 10 days of screening
- Two or more current symptoms of acute infection for ≤7 days. Symptoms include the following:
  - Fatigue, dyspnea, fever, cough, nausea, vomiting, diarrhea, body aches, chills, headache, sore throat, nasal symptoms, new loss of sense of taste or smell
- Willing and able to complete study questionnaires for up to 90 days
Exclusion Criteria

• Prior COVID-19 diagnosis (>10 days from screening)
• Hospitalization for COVID-19
• Known allergy/sensitivity or any hypersensitivity to components of the study drug or placebo
• Known contraindication to study drug, including prohibited concomitant medications
# Objectives and Endpoints

<table>
<thead>
<tr>
<th><strong>OBJECTIVES</strong></th>
<th><strong>REPORTED ENDPOINTS</strong></th>
</tr>
</thead>
</table>
| To evaluate the effectiveness of repurposed medications [(study drug(s)] in non-hospitalized participants with mild to moderate COVID-19 | • The OR describing the overall treatment effect on symptoms and clinical events over the 14 days  
• The overall risk difference for hospitalization and death  
• Mean and median time to symptom freedom |
Primary Analysis

SYMPTOM BURDEN SCALE

- Fatigue
- Dyspnea
- Fever
- Cough
- Nausea
- Vomiting
- Diarrhea
- Body aches
- Chills
- Headache
- Sore throat
- Nasal symptoms
- New loss of sense of taste or smell
- Other COVID-related symptom

ASSESSING EFFECTIVENESS

- Overall effect for each study drug versus placebo will be quantified using the common odds ratio (cOR) from a proportional odds model
- The following will be reported, regardless of efficacy signal:
  - Mean and median time to symptom freedom (for quantifying benefit on symptoms)
  - Mean and median time to hospitalization or death (secondary outcomes)
MAIN RESULTS

The figure shows symptom freedom and event rates over the first fourteen days of observation. Overall, participants in the treatment group experienced significantly fewer symptoms, hospitalization and mortality (cOR=0.7, CI 0.6-0.8, p=0.0003). Specifically, median time to being free of symptoms was 2 days (CI 1.8 to 2.2) shorter in the treatment group than the control group, and the risk of hospitalization and mortality at day 14 was 0.9% lower (CI 0.1% to 1.4%).
# Objectives and Endpoints

<table>
<thead>
<tr>
<th>Secondary</th>
<th>OBJECTIVES</th>
<th>REPORTED ENDPOINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>To evaluate the <strong>clinical outcomes</strong> in participants in a study drug arm versus those in the placebo arm</td>
<td>• The OR describing the overall difference in clinical progression</td>
<td>• The overall risk difference for hospitalization or death</td>
</tr>
<tr>
<td>To evaluate <strong>effects on acute care needs</strong></td>
<td>• The OR describing the difference in clinical progression at each measured time point.</td>
<td>• The overall risk difference for any of urgent care, emergency care, hospitalization or death</td>
</tr>
<tr>
<td>To describe <strong>symptom resolution</strong></td>
<td>• The overall risk difference for hospitalization, hospitalization or death</td>
<td>• Time to first urgent care, emergency care, hospitalization or death</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Risk and time to event for each component of the composite</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Directly measured mean and median time to 3 consecutive days symptom free</td>
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</tbody>
</table>
## Objectives and Endpoints

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<thead>
<tr>
<th><strong>OBJECTIVES</strong></th>
<th><strong>REPORTED ENDPOINTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary</strong></td>
<td><strong>For each scale, the overall OR</strong></td>
</tr>
<tr>
<td>To describe the <strong>quality of life (QOL)</strong> in participants in a study drug arm versus those in the placebo arm</td>
<td><strong>For each scale, the OR and mean difference at D7, D14, D28, D90</strong></td>
</tr>
<tr>
<td><strong>Exploratory</strong></td>
<td><strong>Directly measured mean and median symptom count</strong></td>
</tr>
<tr>
<td>To describe <strong>long-term COVID-19-related symptoms</strong> in participants in a study drug arm versus those in the placebo arm</td>
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</table>
Independent Data and Safety Monitoring Decision Framework

Stopping thresholds for efficacy, safety, and futility after each 200 participants enrolled in an agent-specific arm based on overall benefit and clinical efficacy

- Stopping for efficacy, inferiority or equivalence will be based on the posterior probabilities, stopping for futility

- If overall efficacy is observed but there is no clear benefit on clinical events, a futility analysis on clinical benefit will be undertaken and the trial may continue if the predicted probability of success on clinical events is optimistic within the resources available to the platform in the context of external environmental factors (external data on available drugs; evolution of the pandemic)

- All futility analysis will use projected accrual at a defined calendar time
ACTIV-6

Patient Engagement
Stakeholder Engagement

• COVID-19 has affected people in many ways

• Overall goal—Understand and incorporate the lived experience to address:
  • Meaningful outcomes
  • Recruitment and retention
  • Dissemination of results
Stakeholder Advisory Committee Charge

To provide input into critical elements and key areas of ACTIV-6 protocol and processes in order to support high-quality, efficient, patient-centered research that:

- Includes representative populations
- Is feasible and minimally burdensome for participants
- Drives higher rates of retention and compliance through enhanced value and improved participant experience
- Improves data quality through minimizing patient dropout and enhancing participant adherence to networks’ protocols
- Enables dissemination of what’s most important from different points of view
Stakeholder Advisory Committee is Going!

<table>
<thead>
<tr>
<th>PCORnet Affiliation</th>
<th>Member Name</th>
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</thead>
<tbody>
<tr>
<td>CAPriCORN</td>
<td>Florence Thicklin</td>
</tr>
<tr>
<td>GPC</td>
<td>Kirk T. Phillips</td>
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<tr>
<td>GPC</td>
<td>Andrew Vasey</td>
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<tr>
<td>INSIGHT</td>
<td>Matthew William McCarthy</td>
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<tr>
<td>OneFlorida</td>
<td>Talethia O. Edwards</td>
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<tr>
<td>OneFlorida</td>
<td>Danielle Nelson</td>
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<tr>
<td>PaTH</td>
<td>Greg Merritt</td>
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<td>PaTH</td>
<td>Jonathan Arnold</td>
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<tr>
<td>REACHnet</td>
<td>Jeannie Nguyen</td>
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<tr>
<td>REACHnet</td>
<td>Joshua Denson</td>
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Facilitators

Megan Hamm, PaTH
Kathleen McTigue, PaTH
Conclusion: What does success look like?

• Informing and changing care!

• Any clear, proven answer for study drugs
  • Do any of the study drugs help participants feel better, faster, when compared with placebo?

AND

• Do any of the study drugs also improve clinical outcomes such as emergency department visits, hospitalization, and death?

• Does early treatment of mild to moderate COVID-19 in the outpatient setting impact post-acute sequelae of COVID?