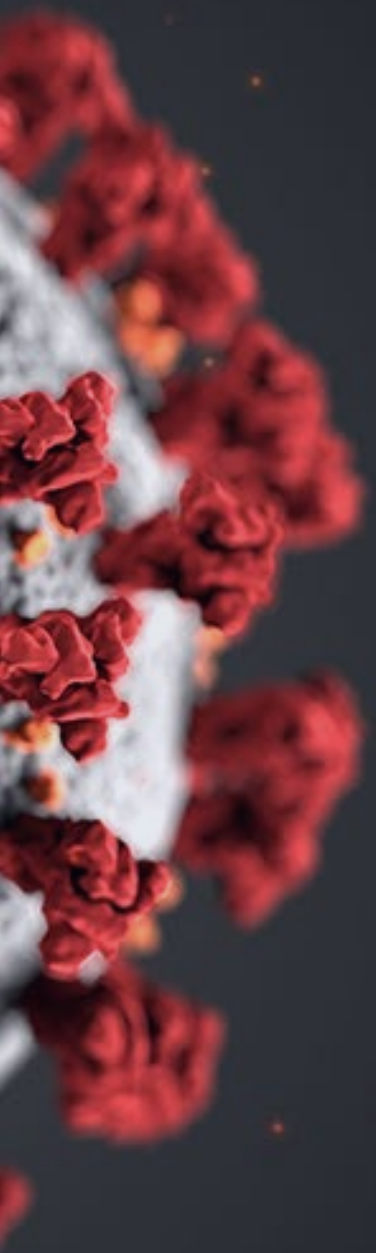

ACTIV-1 IM

Randomized Master Protocol for
Immune Modulators for Treating COVID-19

Study Overview

National Center
for Advancing
Translational Sciences

ACTIV

LAUNCH

On April 17, NIH announced the launch of a public-private partnership, **Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)**

MISSION

Develop a coordinated research response to **speed COVID-19 treatment and vaccine options**

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ACTIV-1 Objectives and Patient Population

Study Objectives

ACTIV-1 is a master protocol designed to evaluate **multiple therapeutic agents** for the treatment of **moderately or severely ill** patients infected with SARS-Cov-2.

The research objectives are to evaluate each agent with respect to **speed of recovery, mortality, illness severity, and hospital resource utilization**. Each agent will be evaluated as **add-on therapy to the local standard of care** including remdesivir (provided) as well as convalescent plasma and dexamethasone per guidelines

Patient Population

Hospitalized adults (≥18 years old) with COVID-19, including patients both in and out of the ICU.

ACTIV-1 Design

Number of Agents

Infliximab, abatacept, cenicriviroc selected for initial testing; additional 2-3 could enter later

Standard of Care (SoC)

Local standard management (remdesivir provided)
CP, dexamethasone allowed

Placebo

Injection or pill

Comparisons

(Drug X + SOC) vs. (Placebo + SOC)

- Double-blinded trial
- Placebo patients pooled across drugs, regardless of mode of administration

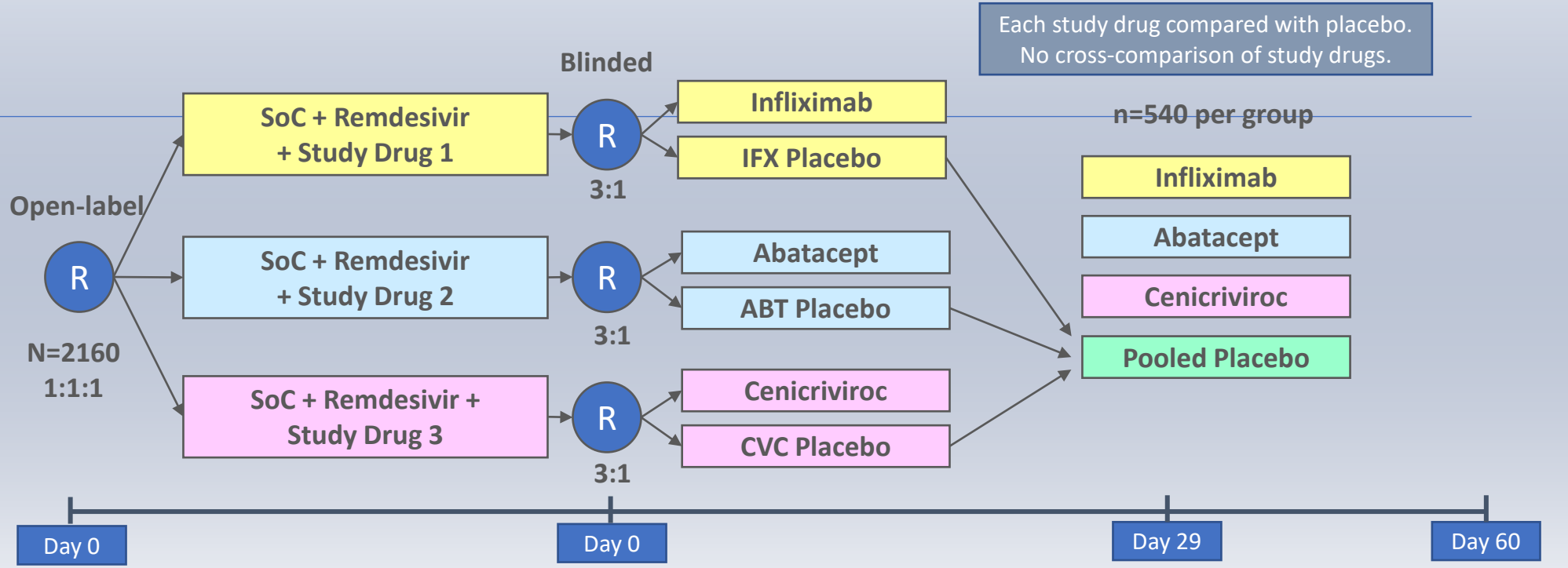
Randomization

- Step 1: Drug infliximab vs. abatacept vs. cenicriviroc in 1:1:1 ratio
- Step 2: Active drug X vs. Placebo in 3: 1 ratio
- → Randomization ratio across all 3 agents = 1:1:1:1

ACTIV-1 Schema

Moderate-severe, hospitalized COVID-19 with positive PCR test of any duration and:

Lung infiltrates (chest imaging)
or
SpO2 ≤ 94%
or
Requiring supplemental O2
or
Requiring mechanical ventilation/ECMO



Dosing regimens of study drugs:

- **Remdesivir**: 200mg IV loading dose on Day 1, 100mg once daily IV maintenance up to 10 days
- **Infliximab:** single 2 hour infusion of 5 mg/kg
- **Abatacept:** single 30 minute infusion of 10 mg/kg up to max of 1000 mg
- **Cenicriviroc:** tablet q12 hours with food for 28 days (450 mg on day 1; 300 mg on days 2-28)

Primary Endpoint:
Time to Recovery, defined as hospitalized without need for O2 or not hospitalized, at Day 29

Last follow-up

Sites from the US and Latin America are participating.
Enrolment began in October 2020.

https://www.nih.gov/research-training/medical-research-initiatives/activ/covid-19-therapeutics-prioritized-testing-clinical-trials#activ1
https://www.nih.gov/news-events/news-releases/nih-begins-large-clinical-trial-test-immune-modulators-treatment-covid-19
https://www.clinicaltrials.gov/ct2/show/NCT04593940?term=activ-1&cond=Covid19&draw=2&rank=1

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NIH National Center for Advancing Translational Sciences

SoC = Standard of Care

ACTIV-1 Objectives and Endpoints

PRIMARY ENDPOINT

Time to Recovery by Day 29

Day of recovery is defined as the first day on which the subject satisfies one of the following three categories from the ordinal scale:

- Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care;
- Not hospitalized, limitation on activities and/or requiring home oxygen;
- Not hospitalized, no limitations on activities.

KEY SECONDARY ENDPOINTS

Clinical Status on Day 14 and Day 28

Clinical status is defined by the 8-point ordinal scale:

8 - Death;
7 - Hospitalized, on invasive mechanical ventilation or ECMO;
6 - Hospitalized, on non-invasive ventilation or high flow oxygen devices;
5 - Hospitalized, requiring supplemental oxygen;
4 - Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise);
3 - Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care;
2 - Not hospitalized, limitation on activities and/or requiring home oxygen;
1 - Not hospitalized, no limitations on activities.

14-day and 28-day Mortality

ACTIV-1 Study Population | Selected Inclusion Criteria

1. Admitted to a hospital or awaiting admission in the ED with symptoms suggestive of COVID-19
2. Male or non-pregnant female adults ≥ 18 years of age at time of enrollment
3. Has laboratory-confirmed SARS-CoV-2 infection
4. Illness of any duration, and at least one of the following:
    - Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
    - SpO2 ≤ 94% on room air, OR
    - Requiring supplemental oxygen, OR
    - Requiring mechanical ventilation or ECMO

ACTIV-1 Study Population | Selected exclusion Criteria

1. ALT or AST > 5 times the upper limit of normal
2. Neutropenia
3. Lymphopenia
4. Pregnancy or breast feeding
5. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72hrs
6. Allergy to any study medication
7. Cytotoxic or biologic treatments within 4 weeks

7. Have suspected clinical diagnosis of current active tuberculosis (TB) or, if known, latent TB treated for less than 4 weeks
8. *Active* Hepatitis B or HIV
9. Suspected serious, active bacterial, fungal, viral infection
10. Have received any live vaccine within 3 months before screening, or intend to receive a live vaccine during the study
11. Current severe heart failure [NYHA III-IV]
12. Estimated glomerular filtration rate < 30 ml/min (under review)

ACTIV-1 Sample Size

PRIMARY ENDPOINT

Time to Recovery in 28 Days

Consistent with ACTT-1 and ACTT-2 | Assessed via log-rank Test

Powered for an 85% chance to detect a recovery rate ratio (RRR) = 1.25

- 2,160 patients overall (3 agents)
- Interim analysis at 25%, 50%, 75% enrolled
- Aggressive test for futility
- Moderately aggressive test for efficacy
- Blinded sample size re-estimation at 50% analysis

ACTIV-1 | Schedule of Assessments

Inpatient

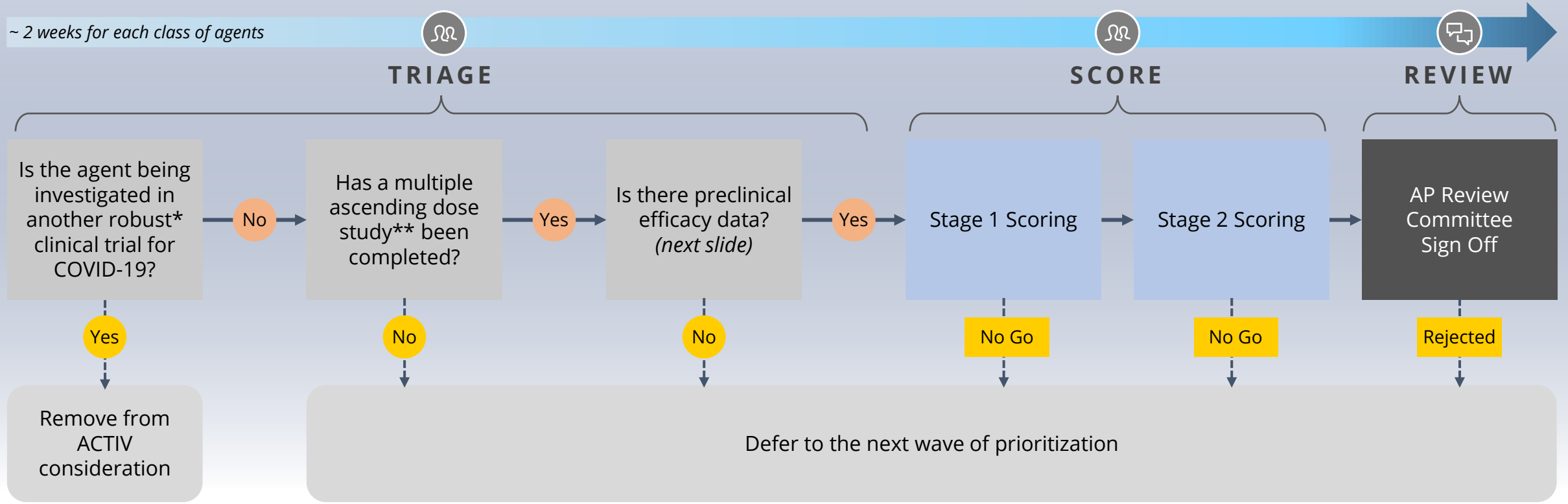
- Daily assessments
- Direct contact unnecessary
- Co-enrollment with ACTIV-4 OK

Outpatient

- Visit preferred on days 8, 11, 15, & 29
  - Phone can be substituted if necessary
- Phone follow-up on days 22 and 60

Agent Prioritization | Triage and Scoring Process

Candidate agents are triaged based on concurrent clinical trials, completion of a multiple ascending dose study, and availability of preclinical data before being scored based on predefined criteria.



NOTES

**Criteria for "robust trial" (to be defined by Prioritization Team)*
*** Sufficient safety data to support 14-day exposure*

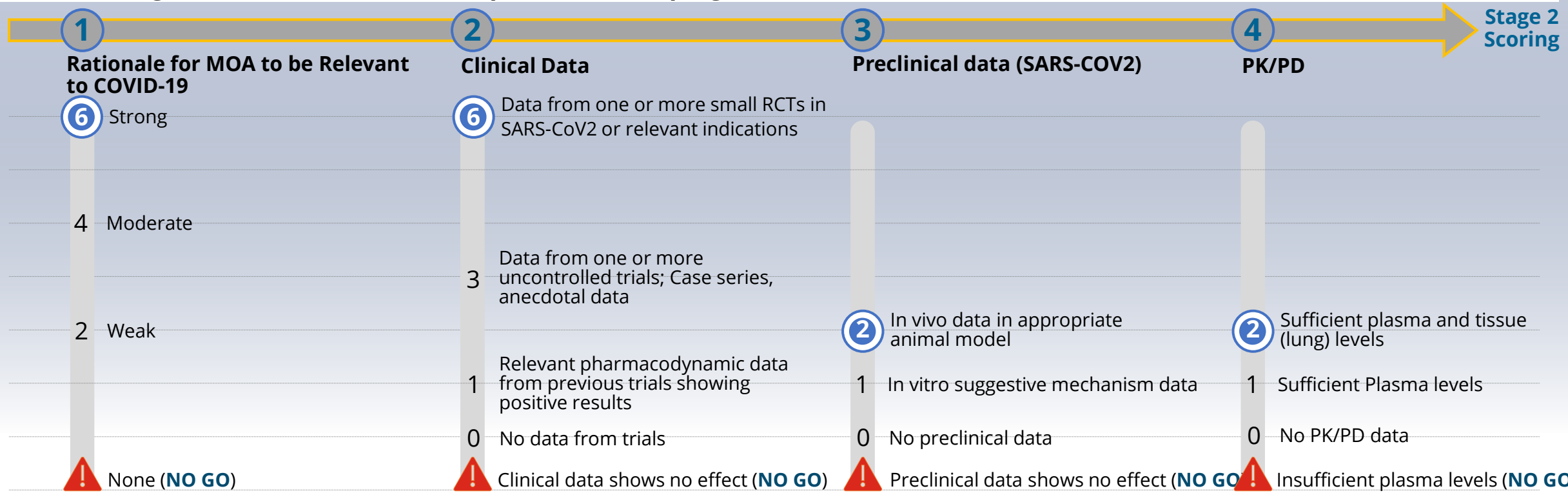
Small Group Assessment (a few compounds per group)

Large Group Discussion & Alignment

Scoring Criteria | Immunomodulators

- Immunomodulators and Symptomatic / Supportive Therapies Prioritization Team members will conduct a first stage of scoring with a greater emphasis on rationale for MOA, SARS-CoV-2 trials, and preclinical data (including PK)

Criteria in Stage 1 will be reviewed in order. If the reviewer determines an agent is a NO GO for a given criteria, then other criteria will go unreviewed, and the compound will not progress further.



NOTES

Criteria 1: Rational needs to include proof of target engagement. Strong rationale alone, without additional supporting preclinical/clinical data, is not sufficient to prioritize an immune modulator or symptomatic / supportive therapy candidate.

Criteria 2: SARS-CoV-2 Trials refer to the quality of clinical data from smaller completed / ongoing trials (Phase 1 or 2), NOT the existence of ongoing Phase 3 trials for an agent or another in the same class. The existence of Phase 3 trials with an agent should be considered during triage. Appropriate reference population (e.g. critical care patients) needs to be defined when evaluating clinical data.

ACTIV-1 | Agent Selection

Overall N agents evaluated	>400
N clinically ready	~170
N scored	39
N immunomodulators scored	14
Selected immunomodulators	Infliximab, abatacept, cenicriviroc

Selection criteria:

- Timeliness- speed to clinic
- Robust science – strong evidence for use against inflammatory reaction and cytokine storm
- Availability – ability to manufacture quickly at scale

ACTIV-1 Agents Selected for Inclusion | Infliximab (Remicade)

TARGET

TNFα **(tumor necrosis factor α)**

AGENT-SPECIFIC EXCLUSION CRITERIA

History of HSTCL or other lymphoma within 5 years before screening; history of or current diagnosis of MS or other significant demyelinating condition (e.g., optic neuritis)

DOSAGE

A single dose of 5mg/kg (IV) on Day 1 in addition to standard of care

SAFETY CONSIDERATION

- Some risk of immune suppression, which could allow for secondary infection
- **Should not be administered to patients with known moderate to severe heart failure (NYHA Functional Class III/IV)**

RATIONALE / MECHANISM OF ACTION

- It has been well documented for many years that infection by several members of the *Coronaviridae* family both in vitro and in vivo in humans and animals is associated with increases in the production of TNFα.
- **Elevated serum levels of TNF consistently shown to be associated with COVID-19 infection vs. healthy normals**
- Elevated TNF levels in the fluid of the lungs have been associated with a poor prognosis for individuals with ARDS.
- **Infliximab neutralizes the biological activity of** TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits the binding of TNFα to both of its receptors, TNFR1 and TNFR2.
- **Infliximab inhibits the functional activity of TNFα in a wide variety of in vitro bioassays using human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes, and epithelial cells.**
- The safety of anti-TNF therapy in patients with COVID-19 was evaluated from analysis of COVID-19 patients with inflammatory bowel disease (IBD) who were already on anti-TNF treatment. IBD patients with COVID-19 on anti-TNF therapy appear to have better outcomes than those treated with other IBD drugs - only 2% (**18/935**) of IBD patients with COVID-19 have experienced ICU/MV/deat. **(SECURE-IBD registry).**
- **RA patients with COVID-19 on anti-TNF therapy appear to have decreased odds of hospitalization compared to those with no RA treatment (Global Rheumatology Alliance registry).**

HSCTL = hepatosplenic T cell lymphoma MS = multiple sclerosis

ACTIV-1 Agents Selected for Inclusion | Abatacept (Orencia)

TARGET

CTLA-4-Ig

AGENT-SPECIFIC EXCLUSION CRITERIA

None

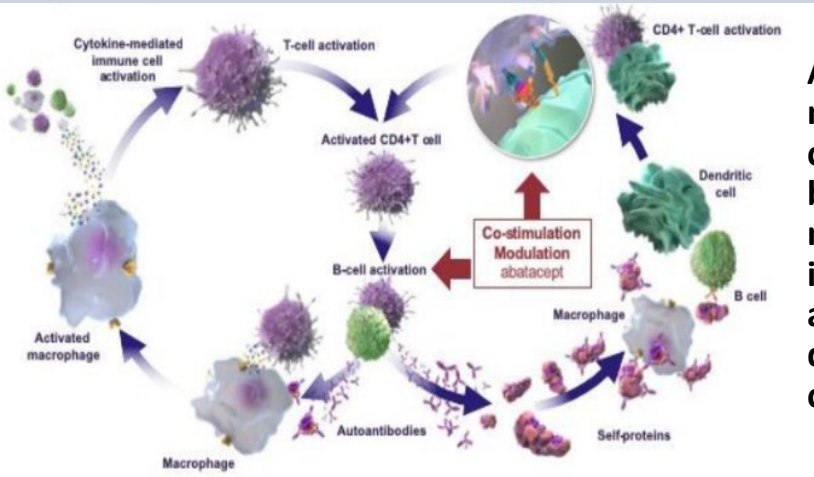
DOSAGE

A single dose of 10mg/kg with a maximum dose of 1000mg (IV) on Day 1 in addition to SoC

SAFETY CONSIDERATION

- COPD patients may develop more frequent respiratory adverse events
- Risk of primary anti-viral suppression response and secondary infection that may result from the use of a T-cell directed agent

RATIONALE / MECHANISM OF ACTION



Abatacept binds to CD80/CD86 receptors on antigen-presenting cells, thereby inhibiting their binding to the costimulatory molecule CD28 on T cells. By inhibiting full T cell activation, abatacept also affects the downstream inflammatory cascade.

Abatacept has demonstrated the ability to modulate the maladaptive immune response in multiple models of cytokine storm.

- In a mouse model of flu-induced pneumonia, treatment with CTLA4-Ig decoupled the protective and immunopathological memory T cell responses following secondary infection without affecting viral clearance.
- In a large case series of patients undergoing haploidentical HSCT, addition of abatacept to a conventional post-transplant cyclophosphamide regimen resulted in a dramatic reduction in the incidence of cytokine release syndrome and its severity.
- In a small case series of sJIA patients with macrophage activation syndrome (MAS) addition of abatacept to anakinra resulted in significant attenuation of symptoms and improvements in inflammatory markers.
- Abatacept treatment has recently been shown to be highly effective in hyper-inflammatory states, such as myocarditis, induced by treatment with immune checkpoint inhibitors for malignant disease.

ACTIV-1 Agents Selected for Inclusion | Cenicriviroc (CVC)

TARGET

Dual CCR2 / CCR5 Inhibitor

AGENT-SPECIFIC EXCLUSION CRITERIA

None

DOSAGE

Administered with food as a 450mg oral loading dose on Day 1, followed by a 300mg (150mg BID) maintenance dose for the duration of the study, in addition to standard of care

SAFETY CONSIDERATION

- Potential drug-drug interaction with strong CYP3A4 inhibitors
- Pregnancy should be avoided during CVC administration

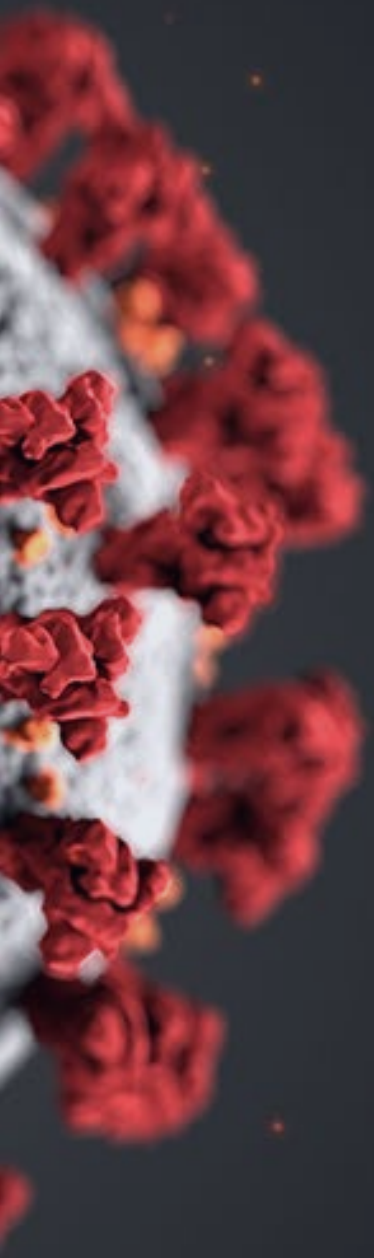
RATIONALE / MECHANISM OF ACTION

- Severe pneumonia and pneumonitis caused by coronaviruses are often associated with massive inflammatory cell infiltration and elevated pro-inflammatory cytokine and chemokine responses.
- Patients with this cytokine storm have been observed to have high levels of CCL2 (MCP1) and CCL5 (RANTES), likely caused by feedback from SARS-CoV upregulating CCR2 and CCR5.
- Effects off-set by dual antagonism of CCR2/5 has been shown to be operative in: CoV infection; ARDS; and influenza-caused lung inflammation, tissue destruction, and fibrosis.

- **Cenicriviroc (CVC) is a novel small-molecule, orally active, well-tolerated, potent and selective antagonist of CCR2 and CCR5 with anti-inflammatory and anti-fibrotic activity.**
- In a mouse model of acute liver injury, administration of CVC significantly decreased the numbers of monocyte-derived macrophages and associated inflammation and tissue damage. Lung disease models demonstrating infiltrating monocyte-derived interstitial macrophages have a similar inflammatory phenotype, including CCR2/5 based processes, as in the liver disease models.
- **ACTIV hypothesizes that CVC will decrease recruitment of infiltrating monocyte-derived interstitial macrophages** known to be operative in respiratory tissues in coronavirus infections, thus preventing the respiratory injury, ARDS, and cytokine storm patients with COVID-19.

ACTIV-1 | Sites

- Criteria
  - N cases, capacity, experience, management of competing trials, priority of ACTIV-1
- Number
  - US: 60+ geographically distributed sites
  - Latin America: 40+ sites in 3-5 countries



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