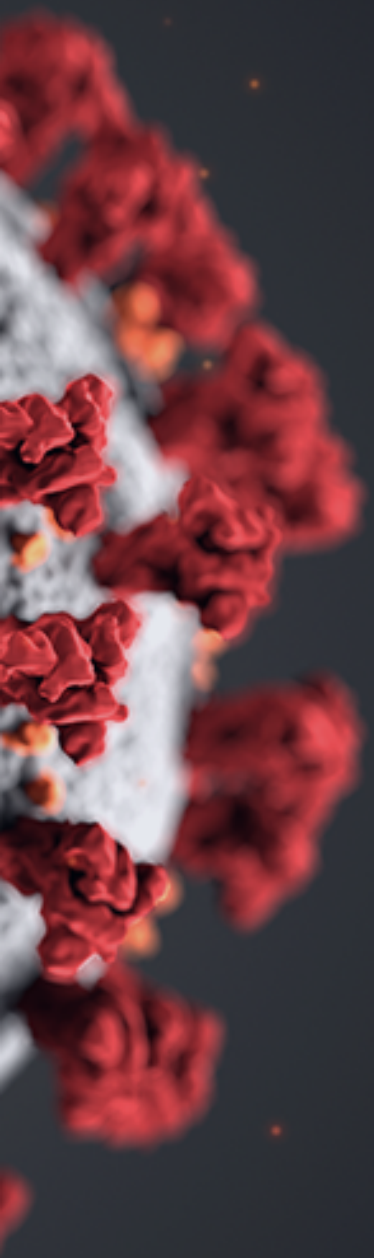


ACTIV-1 IM

Randomized Master Protocol for
Immune Modulators for Treating COVID-19

Administration of abatacept or infliximab reduces mortality in hospitalized patients with COVID pneumonia.

On behalf of ACTIV-1 team:
Emily Ko, MD/PhD
Duke Health System

(No financial disclosures to report)

National Center for Advancing Translational Sciences

ACTIV-1 Master Protocol Overview

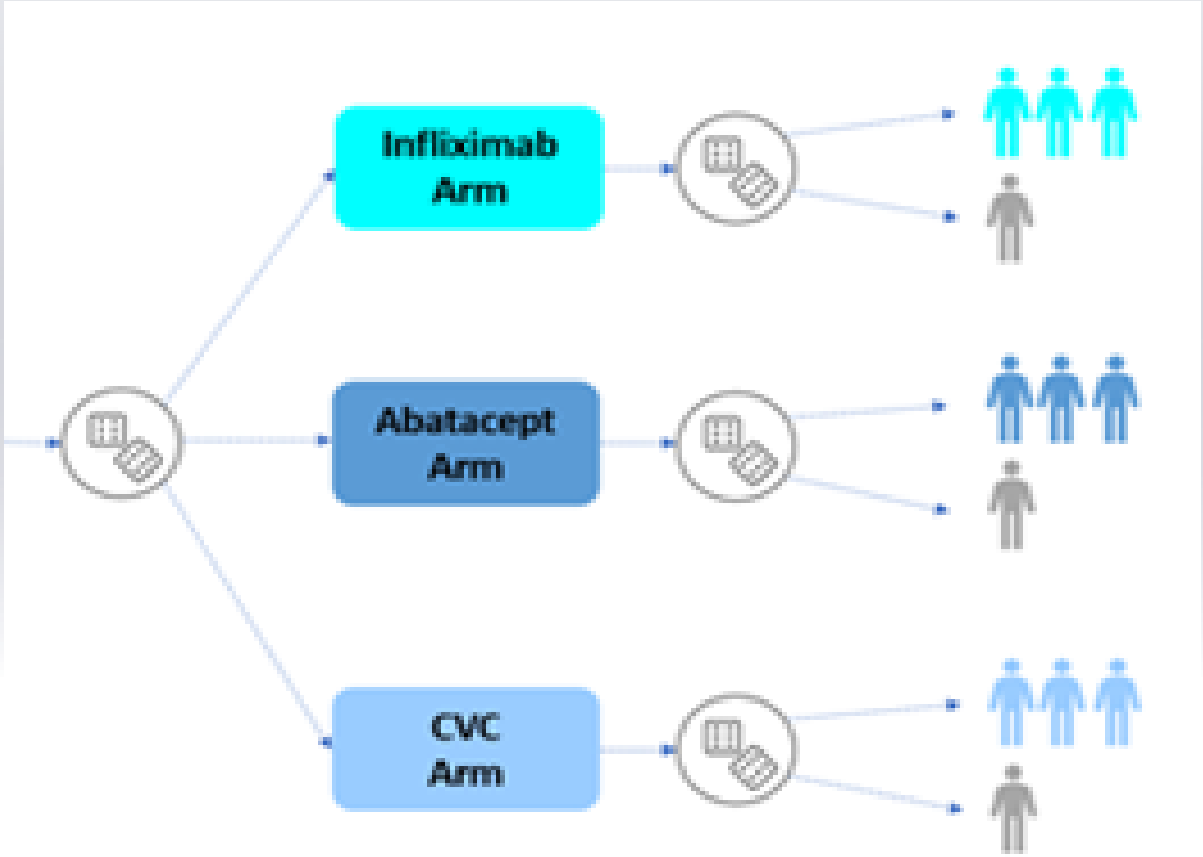
Study Objectives

- Evaluate **multiple immunomodulatory agents** for the treatment of moderate to severe COVID-19.
- Assess each agent **compared to placebo as add-on therapy to the local standard of care** in accordance with national guidelines (Remdesivir provided).

Agents Studied

- **Infliximab:** TNFa inhibitor. Single dose of 5mg/kg IV infusion on Day 1.
- **Abatacept:** Costimulatory modulator. Single dose of 10mg/kg (max 1000mg) IV infusion on Day 1.
- **Cenicriviroc (CVC):** Dual CCR2 / CCR5 Inhibitor. 450mg oral loading dose on Day 1; then 300mg (150mg BID) PO for 28 days → *DSMB recommended discontinuation for futility Sept 2021.*

ACTIV-1 Master Protocol Design



Randomization

- 1st: Assigned with equal probability to a sub-study in open label design.
- 2nd: Randomization to drug vs placebo is blinded. Performed in n:1 ratio, where n = # of agents patient eligible for.

Shared Placebo

- ONLY participants eligible for that agent were part of that sub-studies shared placebo.

ACTIV-1 Study Population

MAJOR INCLUSION CRITERIA

- Admitted to a hospital or awaiting admission in the ED with symptoms suggestive of COVID-19
- ≥ 18 years of age
- Laboratory-confirmed SARS-CoV-2 infection
- 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

KEY EXCLUSION CRITERIA

- ALT or AST > 10 times ULN
- Estimated GFR<30 ml/min (stable CKD with GFR<30 ml/min allowed)
- Neutropenia, lymphopenia
- Pregnancy or breast feeding
- Anticipated discharge from hospital within 72hrs
- Receipt of cytotoxic or biologic treatments within 4 weeks prior to screening
- Clinical diagnosis of current active tuberculosis or, if known, latent TB treated for less than 4 weeks
- Suspected serious, active bacterial, fungal, viral infection
- Current severe left heart failure [NYHA III-IV]

Primary and Key Secondary Endpoints

Primary endpoint – time-to-recovery

- Recovery rate ratio and associated confidence interval from Fine-Gray model
- Stratified by region and severity
- Covariants included age and sex

Two key secondary endpoints

- Day 14 clinical status by 8-point ordinal scale
- 28-day all cause mortality

Data analysis

- Modified intent-to-treat population.

Participant characteristics

Baseline Characteristics	Infliximab		Abatacept	
	Agent n = 517	Placebo n = 516	Agent n = 509	Placebo n = 510
Age, mean (SD)	54.7 (14.9)	54.9 (14.7)	54.7 (14.6)	54.9 (14.7)
Male sex, n (%)	62.9%	57.8%	63.1%	57.8%
Race / Ethnicity, n (%)				
▪ White	61.7%	64.5%	62.5%	63.1%
▪ Black or African American	14.9%	13.2%	13.8%	13.7%
▪ Hispanic or Latino	48.7%	48.4%	42.0%	46.3%
Symptom duration, Mean days (SD)	-9.9 (4.4)	-9.9 (5.61)	-9.2 (4.22)	-9.9 (5.58)
BMI, Kg/m^2, M (SD)	32.1 (8.0)	32.7 (8.1)	32.6 (8.2)	32.7 (8.2)
Comorbidities, n/N (%)				
▪ Hypertension	40.0%	40.5%	41.8%	41.2%
▪ Obesity (>= 30 kg/m^2)	52.9%	59.6%	57.1%	60.0%
▪ Diabetes Mellitus	26.7%	27.9%	28.7%	27.6%
▪ Cardiovascular disease	10.4%	7.9%	9.6%	8.4%

Participant characteristics (cont.)

Baseline Characteristics	Infliximab		Abatacept	
	Agent n = 517	Placebo n = 516	Agent n = 509	Placebo n = 510
Concomitant Medication				
• Remdesivir (day 1 – day 5)	94.0%	94.8%	95.1%	94.3%
• Corticosteroid (day 1 – day 5)	90.5%	93.4%	90.2%	93.5%
Ordinal scale at baseline				
5 - Hospitalized, not requiring supplemental oxygen, ongoing care	4.1%	3.7%	4.5%	3.5%
4 - Hospitalized, supplemental oxygen	51.8%	52.3%	52.3%	52.9%
3- Hospitalized, noninvasive ventilation or high-flow oxygen	32.9%	33.7%	34.0%	33.5%
2 - Hospitalized, IMV or ECMO	11.2%	10.3%	9.2%	10.0%

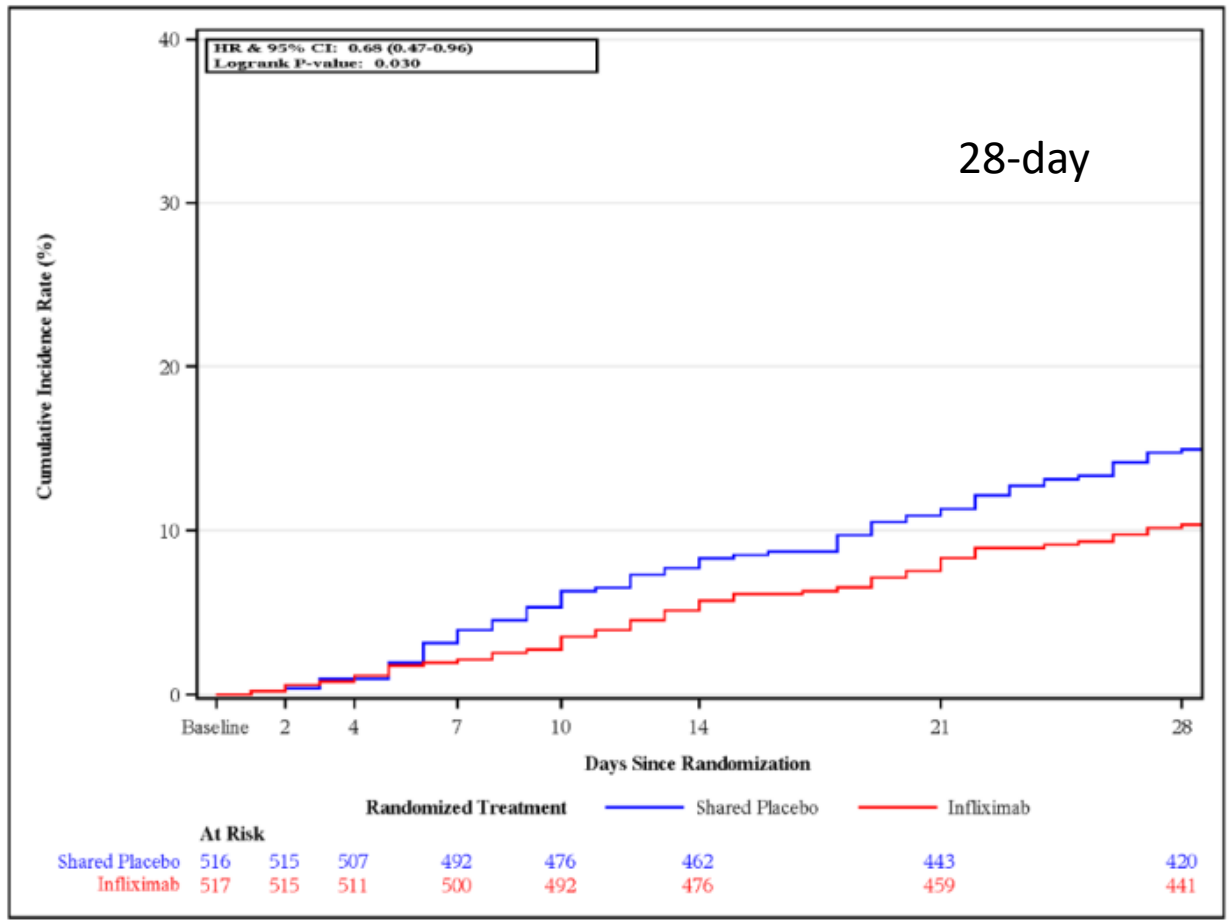
ACTIV-1: Results for Infliximab vs Placebo in Hospitalized COVID-19

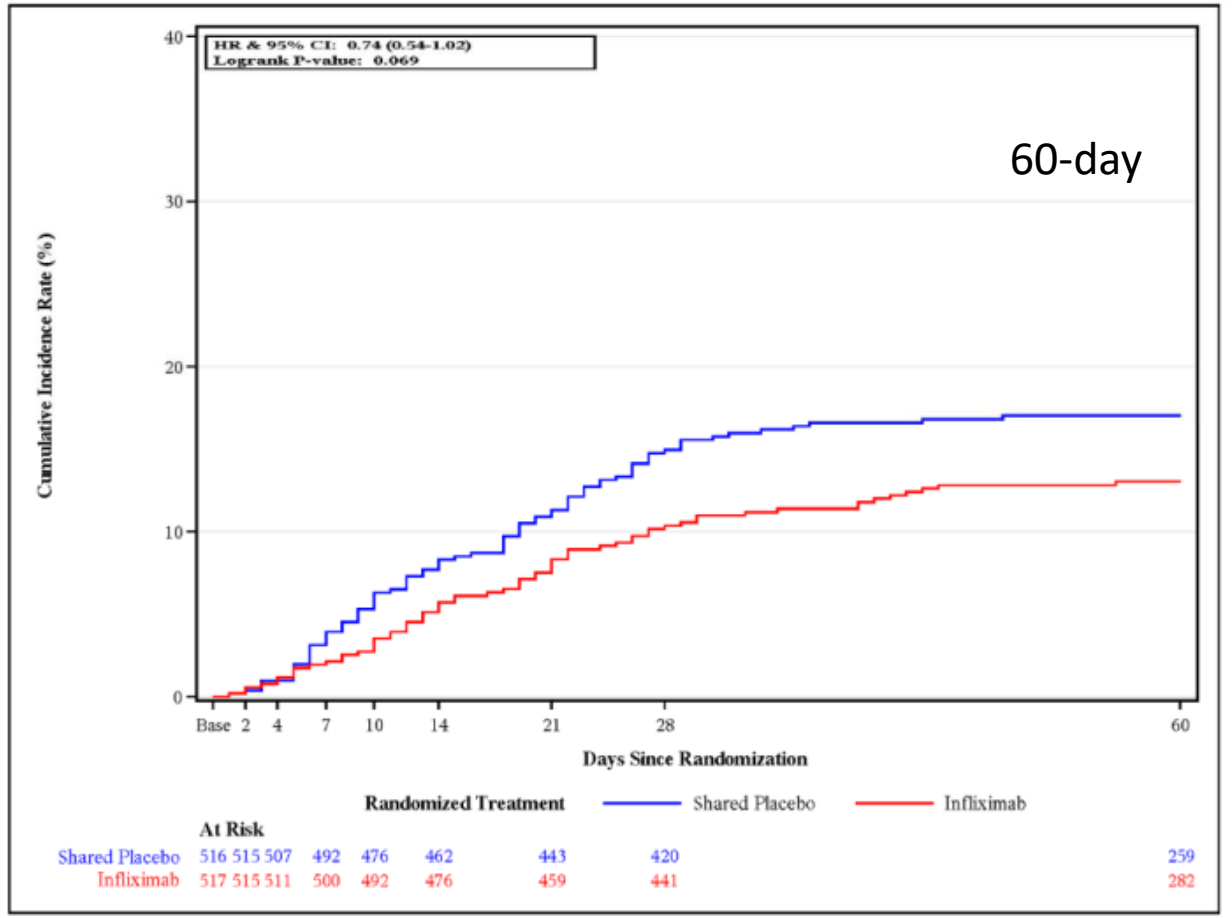
- **Primary endpoint or time to recovery did not meet statistical significance, but there was a trend toward improvement**
- **32% higher odds of improvement in clinical status at Day 14 (according to ordinal scale) with infliximab vs placebo.**
- **41% lower odds of dying by Day 28 with infliximab vs placebo.**

Outcome	Infliximab	Placebo	Rate Ratio for Recovery or OR* (95% CI)	*P* Value
Median time to recovery (primary endpoint), Days	8	9	1.13 (0.99-1.29)	0.063
Clinical Status, Day 14	n/a	n/a	1.32 (1.05-1.66)	
28-Day mortality	10.1%	14.5%	0.59 (0.39-0.90)	
**60-Day mortality	12.6%	16.5%	0.68 (0.46-1.00)	

*Rate ratio for time to recovery endpoints, Odds Ratio for clinical status and mortality.
**60-Day mortality was done as part of safety data and not a key secondary outcome

Infliximab: Cumulative incidence of time to death





Infliximab: Day 60 Safety assessment

- No statistically significant difference in serious adverse events, or grade 3 & 4 adverse events was found.
- Relative number of secondary infections for infliximab was similar to placebo.

Secondary Infections	Infliximab n=516	Placebo n=517
Any secondary infection/Superinfection	15.3%	14.0%
Confirmed	4.6%	5.0%
Probable	10.6%	8.9%
Any bacterial	13.7%	10.7%
Bacterial pneumonia	9.5%	7.0%
Bloodstream infections	3.3%	2.9%
Tuberculosis	0.2%	0.0%
Any fungal	2.7%	4.5%
Invasive candidiasis	0.8%	1.0%
Mold infection (Aspergillus species, mucormycosis or other)	0.4%	0.4%

ACTIV-1: Results for Abatacept vs Placebo in Hospitalized COVID-19

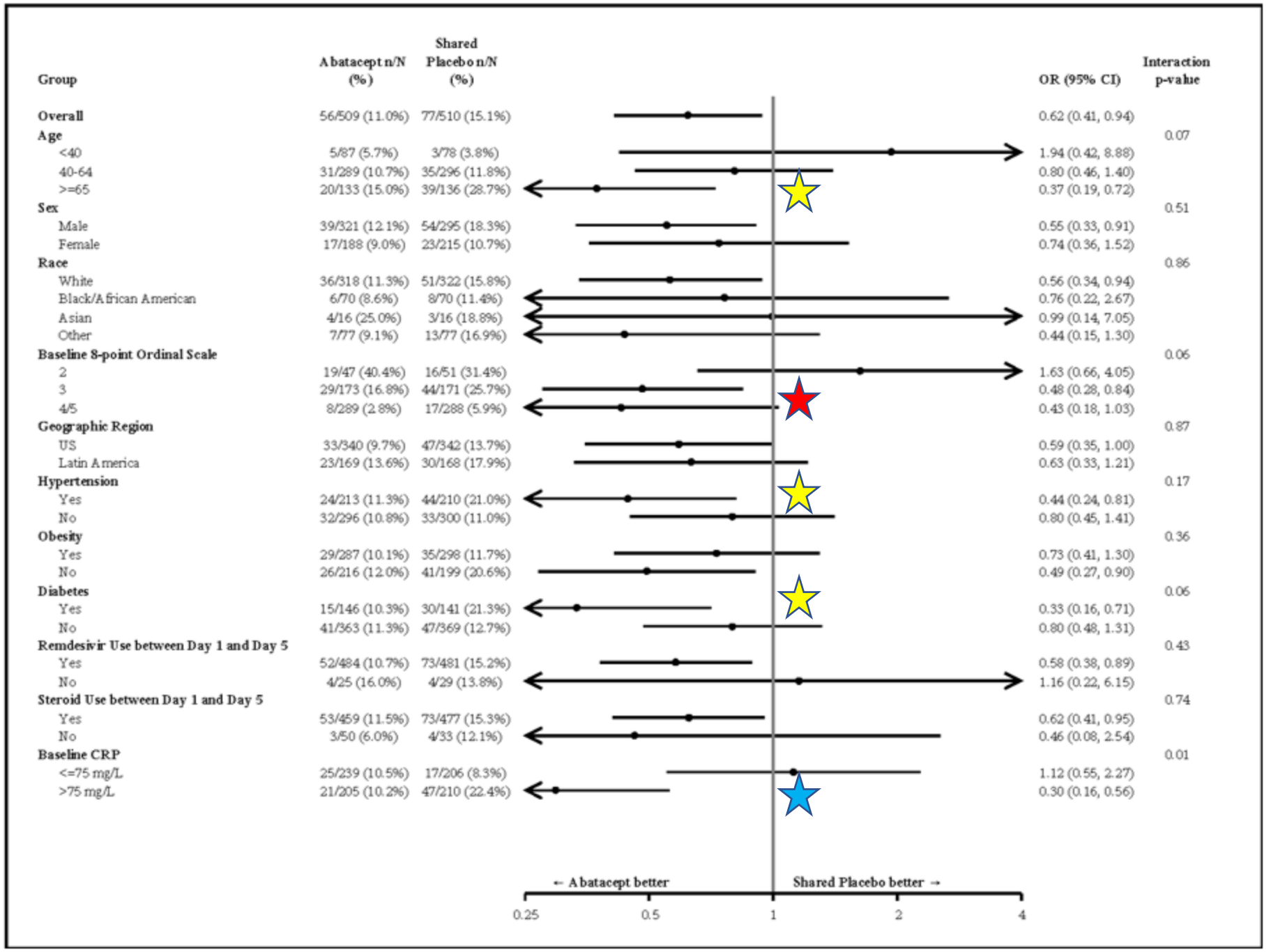
- **Primary endpoint of time to recovery was not statistically significant, but there was a trend toward improvement with abatacept**
- **38% lower odds of dying by Day 28 with abatacept vs placebo.**

Outcome	Abatacept	Placebo	Rate Ratio for Recovery or OR* (95% CI)	*P* Value
Median time to recovery (primary endpoint), Days	9	9	1.14 (1.00-1.29)	0.057
Clinical Status, Day 14	n/a	n/a	1.19 (0.94-1.50)	
28-Day mortality	11.0%	15.1%	0.62 (0.41-0.94)	
**60-Day mortality	14.5%	17.1%	0.74 (0.50-1.08)	

*Rate ratio for time to recovery endpoints, Odds Ratio for clinical status and mortality.
**60-Day mortality performed as part of safety data and not a key secondary outcome

Forest Plot of 28-Day Mortality Abatacept vs Placebo

- Patients on low-flow oxygen, high-flow oxygen, or noninvasive ventilation had the greatest benefit
- Stronger benefit for:
  - ≥ 65
  - Diabetes
  - HTN
- Patients with CRP > 75mg/L were more likely to benefit



ACTIV-1 IM
Randomized Master Protocol for Immune Modulators for Treating COVID-19

Abatacept: Day 60 Safety assessment

There is no statistically significant difference in serious adverse events, or grade 3 & 4 adverse events.

Slightly higher bacterial infections reported, although similar rates of confirmed (culture positive) infections were found.

Secondary Infections	Abatacept n=509	Placebo n=510
Any secondary infection/Superinfection	16.1%	14.3%
Confirmed	5.9%	5.3%
Probable	10.2%	9.0%
Any bacterial	13.4%	10.8%
Bacterial pneumonia	8.3%	7.1%
Bloodstream infections	2.8%	3.1%
Any fungal	3.3%	4.7%
Invasive candidiasis	0.6%	1.0%
Mold infection (Aspergillus species, mucormycosis or other)	0.2%	0.4%

Conclusions

- **We found substantial benefit of 28-day all cause mortality for both infliximab and abatacept.**
- **Our findings show similar results compared to other immunomodulators. Baricitinib (COV-BARRIER) and tocilizumab (RECOVERY) each demonstrated a ~4% absolute reduction in 28-day mortality when added to standard of care.**
- **Subgroup analysis demonstrated benefit for participants on low-flow oxygen (moderate disease).**
- **Enrichment of the mortality benefit was found for participants with elevated CRP (>75mg/L).**

Greatest Appreciation

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Acknowledgements:

Infliximab writing team:

https://www.medrxiv.org/content/10.1101/2022.09.22.22280245v2

Jane A. O'Halloran, Eyal Kedar, Kevin J. Anstrom, Matthew W. McCarthy, Emily R. Ko, Patricia Segura Nunez, Cynthia Boucher, P. Brian Smith, Reynold A. Panettieri Jr, Sabina Mendivil Tuchia de Tai, Martin Maillo, Akram Khan, Alfredo J. Mena Lora, Matthias Salathe, Gerardo Capo, Daniel Rodríguez Gonzalez, Thomas F Patterson, Christopher Palma, Horacio Ariza, Maria Patelli Lima, Anne M. Lachiewicz, John Blamoun, Esteban C. Nannini, Eduardo Sprinz, Analia Mykietiuk, Radica Alicic, Adriana M. Rauseo, Cameron R. Wolfe, Britta Witting, Daniel K. Benjamin Jr, Steven E. McNulty, Pearl Zakroysky, Susan Halabi, Sandra Butler, Jane Atkinson, Stacey J. Adam, Richard Melsheimer, Soju Chang, Lisa LaVange, Michael Proschan, Samuel A. Bozzette, William G. Powderly, ACTIV-1 IM study group members

Abatacept writing team:

https://www.medrxiv.org/content/10.1101/2022.09.22.22280247v1

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Funder	Biomedical Advanced Research and Development Authority (BARDA)	Holli Hamilton, MD; Derek Eisnor, MD
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Role	Organization	Key Members
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	Bristol Myers-Squibb	Brian Gavin, PhD Jonathan Sadeh, MD MSc Sheila Kelly, MD Michael Maldonado, MD
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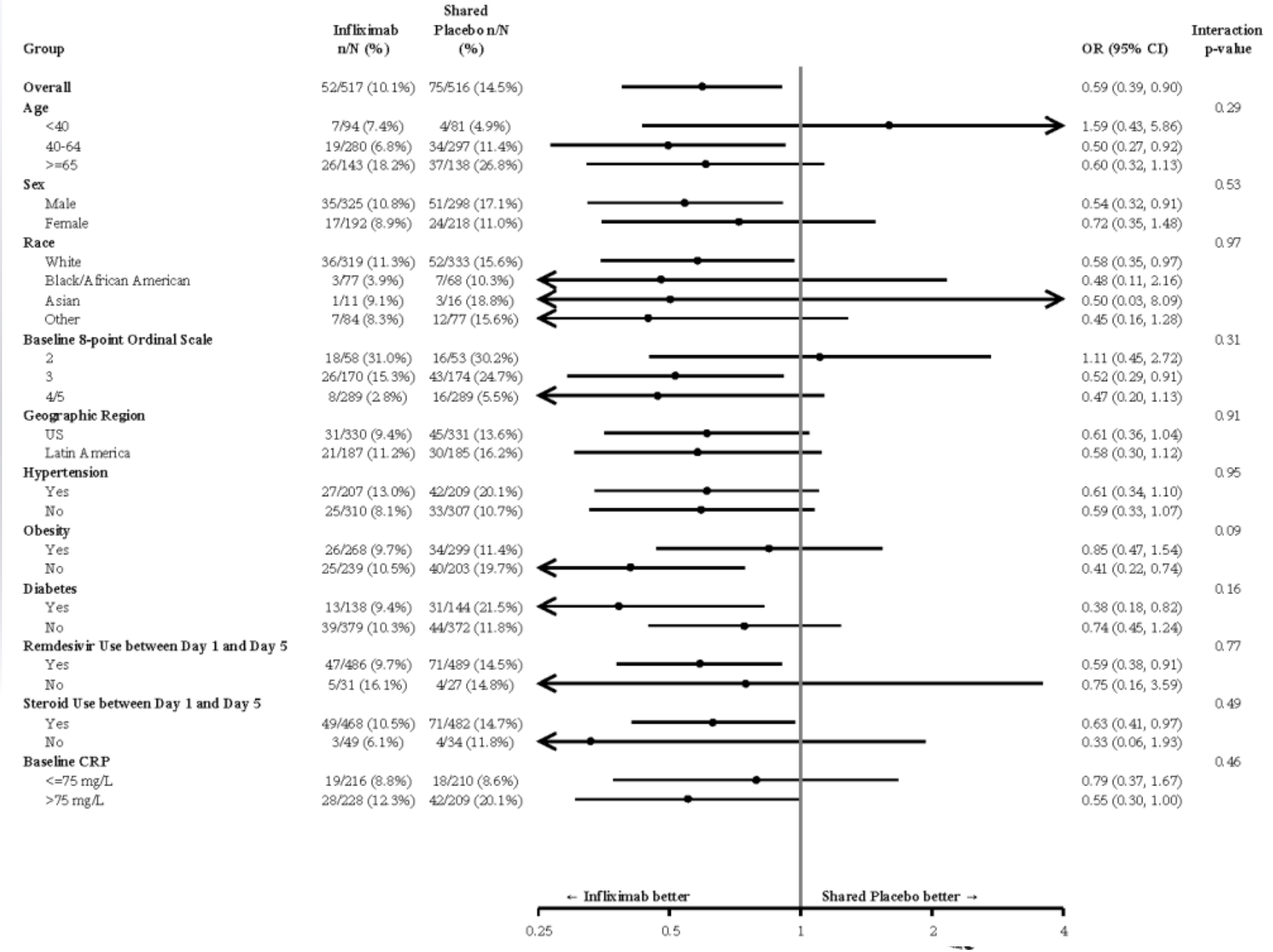
Forest plot for 28-day mortality for infliximab vs placebo



Group	Infliximab n/N (%)	Shared Placebo n/N (%)	OR (95% CI)	Interaction p-value
Overall	52/517 (10.1%)	75/516 (14.5%)	0.59 (0.39, 0.90)	
Age				0.29
<40	7/94 (7.4%)	4/81 (4.9%)	1.59 (0.43, 5.86)	
40-64	19/280 (6.8%)	34/297 (11.4%)	0.50 (0.27, 0.92)	
>=65	26/143 (18.2%)	37/138 (26.8%)	0.60 (0.32, 1.13)	
Sex				0.53
Male	35/325 (10.8%)	51/298 (17.1%)	0.54 (0.32, 0.91)	
Female	17/192 (8.9%)	24/218 (11.0%)	0.72 (0.35, 1.48)	
Race				0.97
White	36/319 (11.3%)	52/333 (15.6%)	0.58 (0.35, 0.97)	
Black/African American	3/77 (3.9%)	7/68 (10.3%)	0.48 (0.11, 2.16)	
Asian	1/11 (9.1%)	3/16 (18.8%)	0.50 (0.03, 8.09)	
Other	7/84 (8.3%)	12/77 (15.6%)	0.45 (0.16, 1.28)	
Baseline 8-point Ordinal Scale				0.31
2	18/58 (31.0%)	16/53 (30.2%)	1.11 (0.45, 2.72)	
3	26/170 (15.3%)	43/174 (24.7%)	0.52 (0.29, 0.91)	
4/5	8/289 (2.8%)	16/289 (5.5%)	0.47 (0.20, 1.13)	
Geographic Region				0.91
US	31/330 (9.4%)	45/331 (13.6%)	0.61 (0.36, 1.04)	
Latin America	21/187 (11.2%)	30/185 (16.2%)	0.58 (0.30, 1.12)	
Hypertension				0.95
Yes	27/207 (13.0%)	42/209 (20.1%)	0.61 (0.34, 1.10)	
No	25/310 (8.1%)	33/307 (10.7%)	0.59 (0.33, 1.07)	
Obesity				0.09
Yes	26/268 (9.7%)	34/299 (11.4%)	0.85 (0.47, 1.54)	
No	25/239 (10.5%)	40/203 (19.7%)	0.41 (0.22, 0.74)	
Diabetes				0.16
Yes	13/138 (9.4%)	31/144 (21.5%)	0.38 (0.18, 0.82)	
No	39/379 (10.3%)	44/372 (11.8%)	0.74 (0.45, 1.24)	
Remdesivir Use between Day 1 and Day 5				0.77
Yes	47/486 (9.7%)	71/489 (14.5%)	0.59 (0.38, 0.91)	
No	5/31 (16.1%)	4/27 (14.8%)	0.75 (0.16, 3.59)	
Steroid Use between Day 1 and Day 5				0.49
Yes	49/468 (10.5%)	71/482 (14.7%)	0.63 (0.41, 0.97)	
No	3/49 (6.1%)	4/34 (11.8%)	0.33 (0.06, 1.93)	
Baseline CRP				0.46
<=75 mg/L	19/216 (8.8%)	18/210 (8.6%)	0.79 (0.37, 1.67)	
>75 mg/L	28/228 (12.3%)	42/209 (20.1%)	0.55 (0.30, 1.00)	

ACTIV-1 IM
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Summary of primary and secondary outcomes