Safety and Efficacy of Tixagevimab/Cilgavimab Administered Intramuscularly or Intravenously in Non-Hospitalized Patients with COVID-19: Two Randomized Phase 2 ACTIV-2 Trials

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BACKGROUND

- The ACTIV-2/A5401 platform (NCT04518410) was established to rapidly test anti-SARS-CoV-2 monoclonal antibodies (mAbs) and other therapies for early COVID-19 against shared placebo
- Safe and accessible therapies for outpatients with COVID-19 are lacking; intramuscularly (IM) administered mAbs could increase access
- Tixagevimab/cilgavimab (T/C) is a long-lasting mAb administered either IM or intravenously (IV)

METHODS

Design

- Non-hospitalized adults were eligible for ACTIV-2 within 10 days of positive SARS-CoV-2 test and symptom onset
- All were eligible for IM T/C 600mg (300mg each) administered to the lateral thigh or placebo
- Only participants at higher risk of disease progression were eligible for IV T/C 300mg (150mg each component) or placebo
- Target sample size n=220 each phase 2; IV stopped enrollment early by administrative decision, unrelated to safety

Outcomes

- The 3 primary outcomes were:
  1) time to symptom improvement through 28 days
  2) SARS-CoV-2 RNA < lower limit of quantification (LLoQ; 2.0 $\log_{10}$ copies/mL) on NP at days 3, 7, or 14, and
  3) new grade 3 or higher treatment-emergent adverse events through day 28.
- Time to symptom improvement: days from entry to the first of two consecutive days when all 13 targeted symptoms scored moderate or severe at study entry were scored mild or absent, and all symptoms scored mild or absent at entry were absent.

Analysis, mITT population: Randomized participants who initiated study intervention

- Time to symptom improvement and to return to usual health through day 28; Gehan-Wilcoxon test
- Nasopharyngeal (NP) SARS-CoV-2 RNA below lower limit of quantification (LLoQ) on days 3, 7 or 14
  - Modified Poisson regression with robust variance, adjusted for Day 0, RR, 95% CI; joint Wald test
- Quantitative RNA levels post-entry visits; Wilcoxon Rank-Sum
- Treatment emergent Grade ≥ 3 adverse events
  - Log-binomial regression, RR, 95% CI, Wald test
- Hospitalization through 28 days; Fisher's exact test

CONCLUSIONS

- T/C administered IM and IV was safe.
- Modest antiviral effect of T/C observed, but no difference in symptom improvement compared to placebo.
- There were numerically fewer hospitalizations in those receiving T/C vs placebo.
- Currently circulating SARS-CoV-2 variants have impacted utility of this and other previously authorized mAbs.
- These studies support the development of future anti-SARS-CoV-2 mAbs, as well as IM administration of mAbs to the thigh.

RESULTS

- Median time (days) to symptom improvement:
  - IM group: 8 T/C (95%CI 7, 12) vs 10 placebo (8, 13) (p=0.35, **Figure 1**)
  - IV group: 11 T/C (9, 15) vs 10 placebo (7, 15) (p=0.51)
- Hospitalization:
  - IM group: 4 T/C vs 7 placebo (p=0.54)
  - IV group: 0 T/C vs 4 placebo (p=0.06)
- There were no deaths during study follow-up
- At day 7, 80% in the IM T/C arm (80%) and 65% in placebo arm had SARS-CoV-2 RNA < LLoQ at day 7, aRR 1.33 (95%CI 1.12, 1.57, **Figure 2**).
- No differences in proportions with quantifiable NP SARS-CoV-2 RNA in IV study
- Treatment-emergent grade ≥ 3 AEs:
  - 9 (9%) IM T/C and 7 (6%) placebo, RR (95%CI) =1.42 (0.55, 3.68), p=0.47 and 5%)
  - 3 IV T/C (5%) vs 7 (13%) placebo participants, RR (95%CI) =0.41 (0.11, 1.52), p=0.18
  - None of 11 SAEs were attributed to study drug; most were progression of COVID-19

Table 1: Baseline characteristics of participants receiving tixagevimab/cilgavimab intramuscularly (IM) or intravenously (IV), or their respective pooled placebo arms

Characteristics	Tixagevimab/Cilgavimab IM			Tixagevimab/Cilgavimab IV		
	T/C IM (N=106)	Placebo (N=117)	Total (N=223)	T/C IV (N=58)	Placebo (N=56)	Total (N=114)
Age (years), median (Q1, Q3)	40 (32, 48)	38 (29, 48)	39 (30, 48)	43 (33, 51)	46 (35, 58)	44 (35, 54)
Sex, n (%)						
Female	52 (49)	58 (50)	110 (49)	34 (59)	33 (59)	67 (59)
Male	54 (51)	59 (50)	113 (51)	24 (41)	23 (41)	47 (41)
Race, n (%)						
Asian	2 (2)	1 (1)	3 (1)	1 (2)	0 (0)	1 (1)
Black	8 (8)	18 (15)	26 (12)	10 (17)	12 (21)	22 (19)
White	88 (83)	93 (79)	181 (81)	47 (81)	42 (75)	89 (78)
Other or Multiracial[A]	7 (7)	5 (4)	12 (5)	0 (0)	2 (4)	2 (2)
Ethnicity, n (%)						
Hispanic/Latino	52 (49)	47 (40)	99 (44)	27 (47)	27 (48)	54 (47)
Not Hispanic/Latino	54 (51)	70 (60)	124 (56)	31 (53)	29 (52)	60 (53)
Body mass index (kg/m^2), median (Q1, Q3)	28 (25, 33)	28 (25, 32)	28 (25, 32)	34 (26, 37)	31 (27, 36)	31 (27, 37)
Symptoms prior to entry, median days (Q1, Q3)	6 (4, 7)	6 (4, 7)	6 (4, 7)	6 (3, 7)	6 (4, 7)	6 (4, 7)
COVID-19 progression risk, n (%)						
Higher	33 (31)	33 (28)	66 (30)	58 (100)	56 (100)	114 (100)
Lower	73 (69)	84 (72)	157 (70)	0 (0)	0 (0)	0 (0)
History of SARS-CoV-2 Vaccination, n (%)	9 (8)	4 (3)	13 (6)	1 (2)	0 (0)	1 (1)

Figure 1: Time to symptom improvement and time to return to usual health amongst those treated with tixagevimab/cilgavimab 600mg IM or placebo (**1A and 1B**) or 300mg IV or placebo (**1C and 1D**).

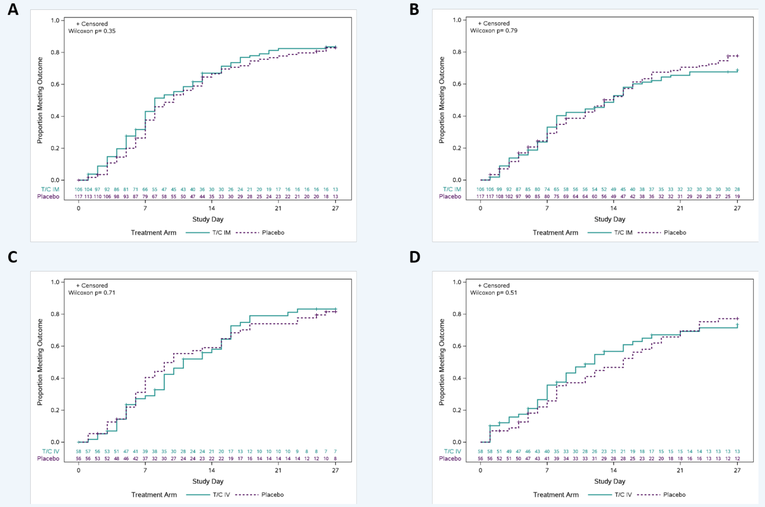
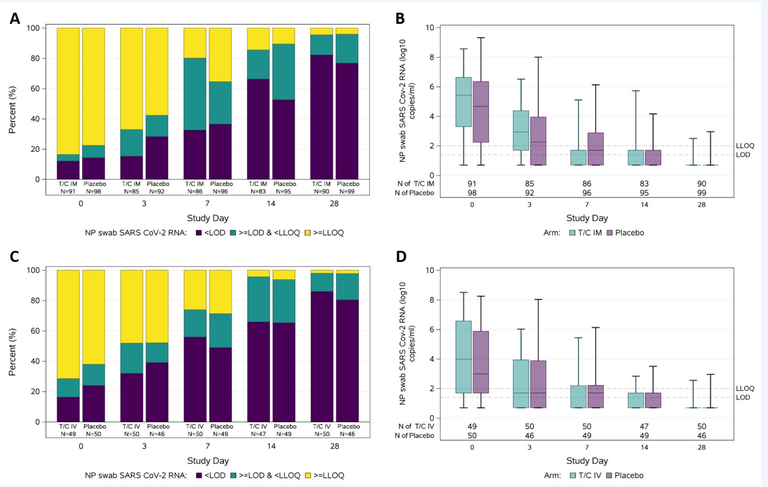


Figure 2: Virologic Outcomes of Tixagevimab/Cilgavimab 600mg IM or 300mg IV vs placebo

Panels A and C demonstrate proportion of participants with SARS-CoV-2 RNA on NP swabs below the limit of detection (LOD) in purple, above the limit of detection but below limit of quantitation (≥ LOD & < LLOQ) in green, or with quantifiable SARS-CoV-2 RNA (≥ LLOQ) in yellow on days 0, 3, 7, 14, and 28 by nasopharyngeal (NP) swab for IM and IV groups, respectively. Panels B and D display SARS-CoV-2 $\log_{10}$ copies/mL levels in NP swabs for T/C and placebo arms by study day in the IM and IV groups, respectively.



OTHER KEY INFORMATION

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Acknowledgements and Funding

National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number UM1AI068636, UM1AI068634, and UM1AI106701
Study drug was donated by AstraZeneca

We thank the study participants, site staff and investigators, and the entire ACTIV-2/A5401 study team; the AIDS Clinical Trials Group; the the Foundation for the National Institutes of Health and the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership; and our Community Advisory Board