COVID-19 RCTs: Treatment of symptomatic outpatients at high risk for progression to severe COVID-19

M LeBras, L Regier, A Crawley © www.RxFiles.ca Oct 2022

COVID-19 Trials	Intervention & Comparator	Trial Criteria	Risk Factors for Severe COVID-19	Results (intervention vs placebo)* Superior / No difference	
				Hospitalization**	Death, any cause
EPIC-HR 2022 Enrollment: **July 2021 to Dec 2021** Delta variant n=2246 Follow up: 24 weeks	**Nirmatrelvir 300mg + Ritonavir 100mg** **PAXLOVID** **po q12h x 5 days** **vs** **Placebo**	Inclusion: - ≥18yrs - COVID-19 (PCR or antigen) - Symptomatic **≤5 days** - Unvaccinated outpatients - ≥1 risk factor for progression Exclusion: - eGFR <45mL/min - Active liver disease - HIV, viral load >400copies/mL - CYP3A4 substrates/inducers	Age: 45yrs (≥65yrs 12%) BMI>25: 80% Smoking: 39% HTN: 33% Diabetes: 12% CKD: <1% Immunocompromised: <1% HIV: <1% Neurodevelopmental disorder: <1% ≥2 risk factors: 61%	Hospitalization, COVID-19 8 (0.8%) vs 65 (6.2%) RRR 88% (95% CI, 74 to 94) **NNT=19/28 days**	0 (0%) vs 12 (1.2%) **NNT=87/28 days**
PINETREE 2022 Enrollment: **Sept 2020 to Apr 2021** Early variants n=562 Follow up: 28 days (stopped early)	**Remdesivir** **VEKLURY** **IV x 3 days** (200mg Day 1, 100mg Day 2, 100mg Day 3) **vs** **Placebo**	Inclusion: - ≥12yrs - COVID-19 (PCR or antigen) - Symptomatic **≤7 days** - Unvaccinated outpatients - ≥1 risk factor for progression or ≥60 years old Exclusion: - CrCl <30mL/min - ALT or AST ≥ 5x ULN - Strong pgp inducer - hydroxychloroquine / chloroquine use ≤ 7 days	Age: 50yrs (≥60yrs 30%) BMI, mean: 31 Diabetes: 62% HTN: 48% Chronic lung disease: 24% Cardiovascular/ cerebrovascular disease: ~8% Cancer: 5% Immunocompromised: 4% CKD: 3%	Hospitalization, COVID-19 2 (0.7%) vs 15 (5.3%) RRR 87% (95% CI, 41 to 97) **NNT=22/28 days**	Day 28: 0 (0%) vs 0 (0%) 1 death reported in placebo group at Day 59
TACKLE 2022 Enrollment: **Jan 2021 to July 2021** Alpha 60%, Gamma 20%, Delta 15% n=910 Follow up: ~84 days, median	**Tixagevimab 300mg + Cilgavimab 300mg‡** **EVUSHELD** **IM x 1 dose** **vs** **Placebo**	Inclusion: - ≥18yrs - COVID-19 (PCR or antigen) - Symptomatic **≤7 days** - Unvaccinated outpatients - WHO Clinical Progression Scale score of >1 to <4 Exclusion: - Previous reaction to monoclonal antibody - No exclusion based on eGFR	Age: 46yrs (≥65yrs 13%) BMI>30: 43% Smoking: 40% HTN: 28% Diabetes: 12% Chronic lung or asthma: 12% CVD: 9% Immunocompromised: 5% Cancer: 4% CKD: 2% Chronic liver: 2% Risk for progression to severe COVID-19 (≥1 risk factor for progression or ≥65 years old): 89%	*Hospitalization, COVID-19* **exploratory interim result** *17 (4.1%) vs 40 (9.5%)*	Death, any cause Day 84: 6 (1.5%) vs 6 (1.4%)
COMET-ICE 2021 Enrollment: **Aug 2020 to Mar 2021** Early variants n=583 Follow up: 24 weeks, ongoing (stopped early for benefit)	**Sotrovimab** **XEVUDY** **500mg IV x 1 dose** **vs** **Placebo**	Inclusion: - ≥18yrs - COVID-19 (PCR or antigen) - Symptomatic **≤5 days** - Unvaccinated outpatients - ≥1 risk factor for progression Exclusion: - Severe immunocompromise e.g. cancer receiving active treatment, solid organ transplant, or stem cell treatment ≤ 3mos - No exclusion based on eGFR	Age: 53yrs (≥55yrs 47%) BMI>30: 63% Diabetes: 23% Asthma, mod-severe: 16% COPD: 4% CKD, <60mL/min: <1% HF, class II-IV: <1% 58% of patients had 1 risk factor (30% had 2, 11% had ≥3)	Hospitalization, any cause: 3 (1%) vs 21 (7%) RRR 85% (97.24%% CI, 44 to 96) **NNT=17/29 days**	Day 29: 0 (0%) vs 1 (<1%)

Summary

COMET-ICE, PINETREE, TACKLE, EPIC-HR

All trials were randomized, blinded, with concealed allocation; industry sponsored and were involved in data management.

Efficacy:
Trials found a reduction in the composite primary outcome e.g. hospitalization & death.

- Only **EPIC-HR** found a mortality reduction.
- Benefit related to study population risk level for progression to severe COVID-19. For example, **EPIC-HR** enrolled a higher-risk population than others e.g. ≥2 risk factors: 61% **EPIC-HR** vs 41% **COMET-ICE**.

Serious Adverse Effects: (favours treatment)
Greater incidence in placebo group likely related to untreated COVID-19 symptoms e.g. pneumonia, cough, etc rather than placebo causing harm.

COVID-19 Trial	Intervention vs Comparator
COMET-ICE	1.6% vs 5.9%; **NNT=24**
PINETREE	1.8% vs 6.7%; **NNT=20**
TACKLE	7.3% vs 11.9%; **NNT=22**
EPIC-HR	1.6% vs 6.6%; **NNT=20**

Adverse Effects:

- **PAXLOVID**: more dysguesia **NNH=18** and diarrhea **NNH=66**.
- **EVUSHELD**: 2 CV-related deaths (out of 6 deaths total), CV harm also seen in prevention study **PROVENT**.

RCT Limitations and Uncertainties: extrapolation is difficult due to current Omicron strain circulation and highly vaccinated population.

- *Many populations of interest were underrepresented*: immunocompromised (1-5%); cancer (4-5%); adults ≥65yrs ~12%).
- All results represent effect in an *unvaccinated population*. Expected benefit likely diminished in a vaccinated population e.g. 70-95% vaccine efficacy for COVID-19 hospitalizations and mortality outcomes.
- Some trials are ongoing, and more complete results will be available over the next 6-18 months. Thus caution warranted given the preliminary and incomplete nature of data.

Observational Trials: some real-world insight that provide reassuring results for applicability concerns related to Omicron, vaccinated, and immunosuppressed individuals.[6,7]

*Primary outcome in most trials was composite of hospitalization and all-cause death. **Hospitalization definition often qualified e.g. COMET-ICE: >24 hours for acute management of illness. ‡ Double dose compared to on-label prophylaxis dosing.
COVID-19 Treatment, Health Canada Approved: **PAXLOVID, VEKLURY, EVUSHELD, XEVUDY** (utilization on hold in SK due to uncertain efficacy vs Omicron BA.2).
Abbreviations, select: **CI**=confidence interval **NNT**=number needed to treat **RCT**=randomized controlled trial **RRR**=relative risk reduction **SAE**=serious adverse events

COVID-19 RCTs: Treatment of symptomatic, outpatients at high-risk for progression to severe COVID-19

Acknowledgements: Written by Marlys LeBras, Loren Regier, Alex Crawley. Thanks to our reviewers: M Legge, S Takaya, S Lee, S Duggal, C DeLonghi, T Rawn, S Black.

References:

1) Gupta A, Gonzalez-Rojas Y, Juarez E, et al. **Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab (COMET-ICE)**. N Engl J Med. 2021;385(21):1941-1950.
2) Gottlieb RL, Vaca CE, Paredes R, et al. GS-US-540-9012 Investigators. **Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients (PINETREE)**. N Engl J Med. 2022 Jan 27;386(4):305-315.
3) Montgomery H, Hobbs FDR, Padilla F, et al. **Efficacy and safety of intramuscular administration of tixagevimab–cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised double-blind, placebo-controlled trial.** *Lancet Respir Med.* 2022; (published online June 7.) Accessed 10 Jun 2022 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9173721
4) Hammond J, Leister-Tebbe H, Gardner A, et al. **Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with COVID-19 (EPIC-HR)**. N Engl J Med. 2022;386(15):1397-1408
5) Levin, M.J., et al., Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of Covid-19 **(PROVENT)**. New England Journal of Medicine, 2022. Supplementary Appendix available online.
6) Young-Xu Y, Epstein L, Marconi VC, Davey V, Zwain G, Smith G, et al. **Tixagevimab/Cilgavimab for Prevention of COVID-19 during the Omicron Surge: Retrospective Analysis of National VA Electronic Data** medRxiv 2022.05.28.22275716; doi: https://doi.org/10.1101/2022.05.28.22275716
7) Najjar-Debbiny R, Gronich N, Weber G, Khoury J, Amar M, Stein N, Goldstein LH, Saliba W. **Effectiveness of Paxlovid in Reducing Severe COVID-19 and Mortality in High Risk Patients**. Clinical Infectious Diseases. 2022.