Antivirals for pre- or post-exposure prophylaxis

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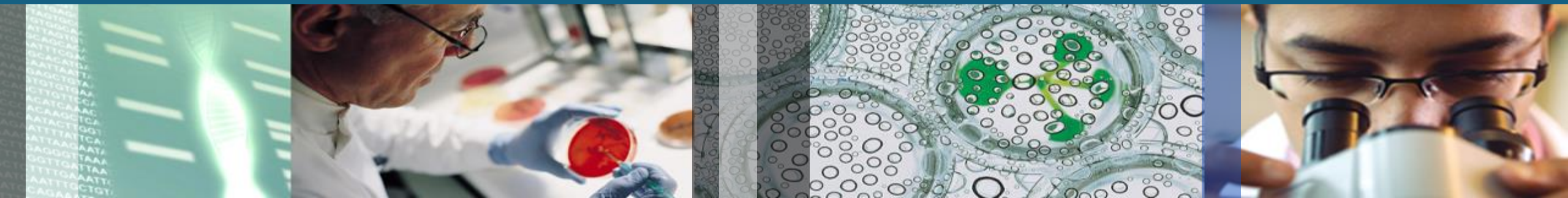

Topics to discuss:

COVID 19 Pre-exposure Prophylaxis (PrEP)

- pemivibart (CANOPY trial)
- sipavibart (SUPERNOVA)

(tixagevimab / cilgavimab (PROVENT))

COVID 19 Post-exposure Prophylaxis (PEP)

- ensitrilvir (SCORPIO-PEP)
- nirmatrelvir-R
- molnupiravir (MOVe-AHEAD)

(bamlanivimab / etesevimab (BLAZE2))
(casirivimab / imdevimab)

Disclosures – 12 months:

- Drug Safety Monitoring Board
  - CSL, Biogen, J&J – immunomodulators
  - Atea – HCV antivirals
  - Cidara – influenza antibodies
  - BrioVAD –cardiac assist devices
- Speaker's Bureau
  - Merck – CMV antivirals
- Manuscript writing support
  - Invivyd – Covid19 antibodies

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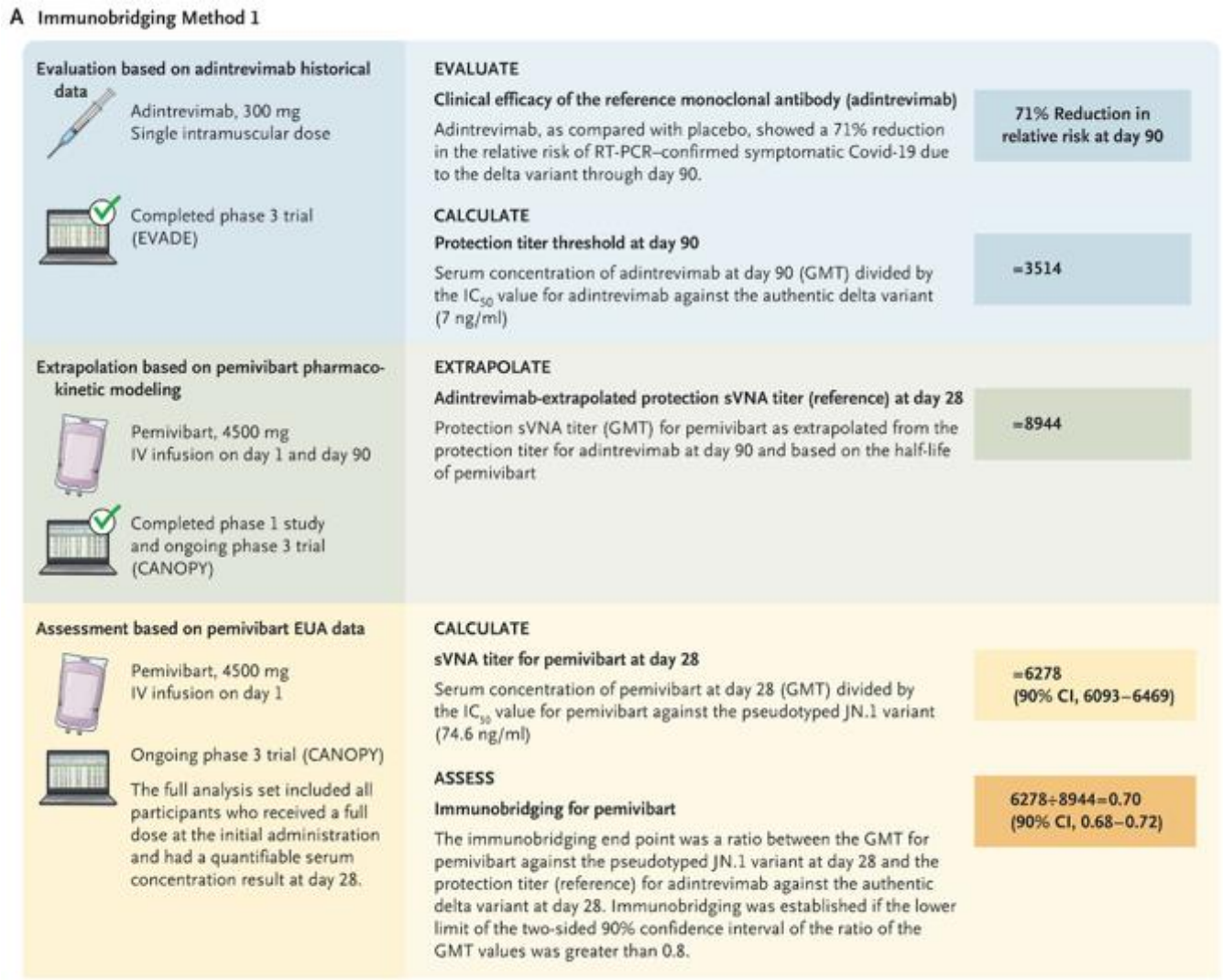
COVID 19 Pre-exposure Prophylaxis (PrEP)

Pemivibart

- Long half-life anti-spike g1 mAb
- Based on adintrevimab (delta var)

- Given FDA EUA for safety data + immunobridging analysis.

- CANOPY trial:
  - 4500mg IV, rpt in 90days
  - Cohort A – open label for I/C
  - Cohort B – RCT for 'at-risk'



Clin Infect Dis,2025, https://doi.org/10.1093/cid/ciaf265

Schmidt et al, *NEJM* 2024,

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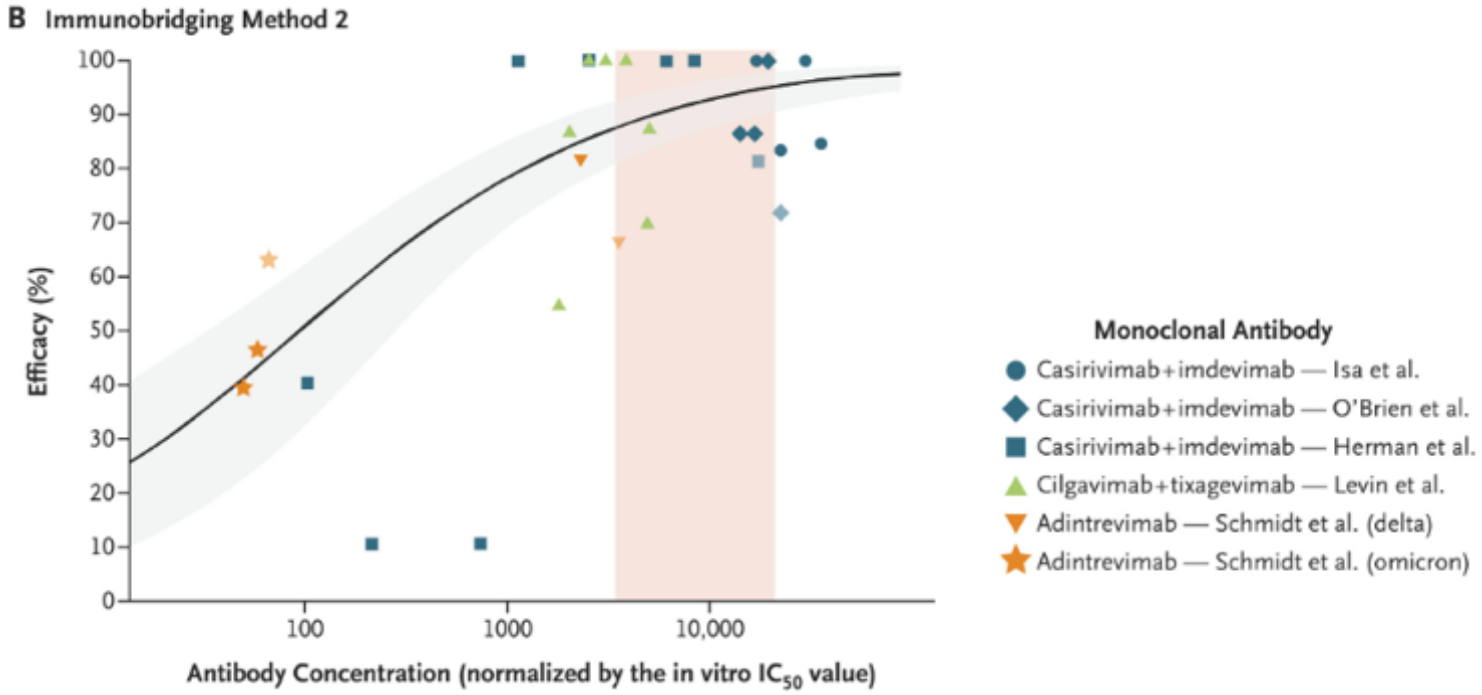

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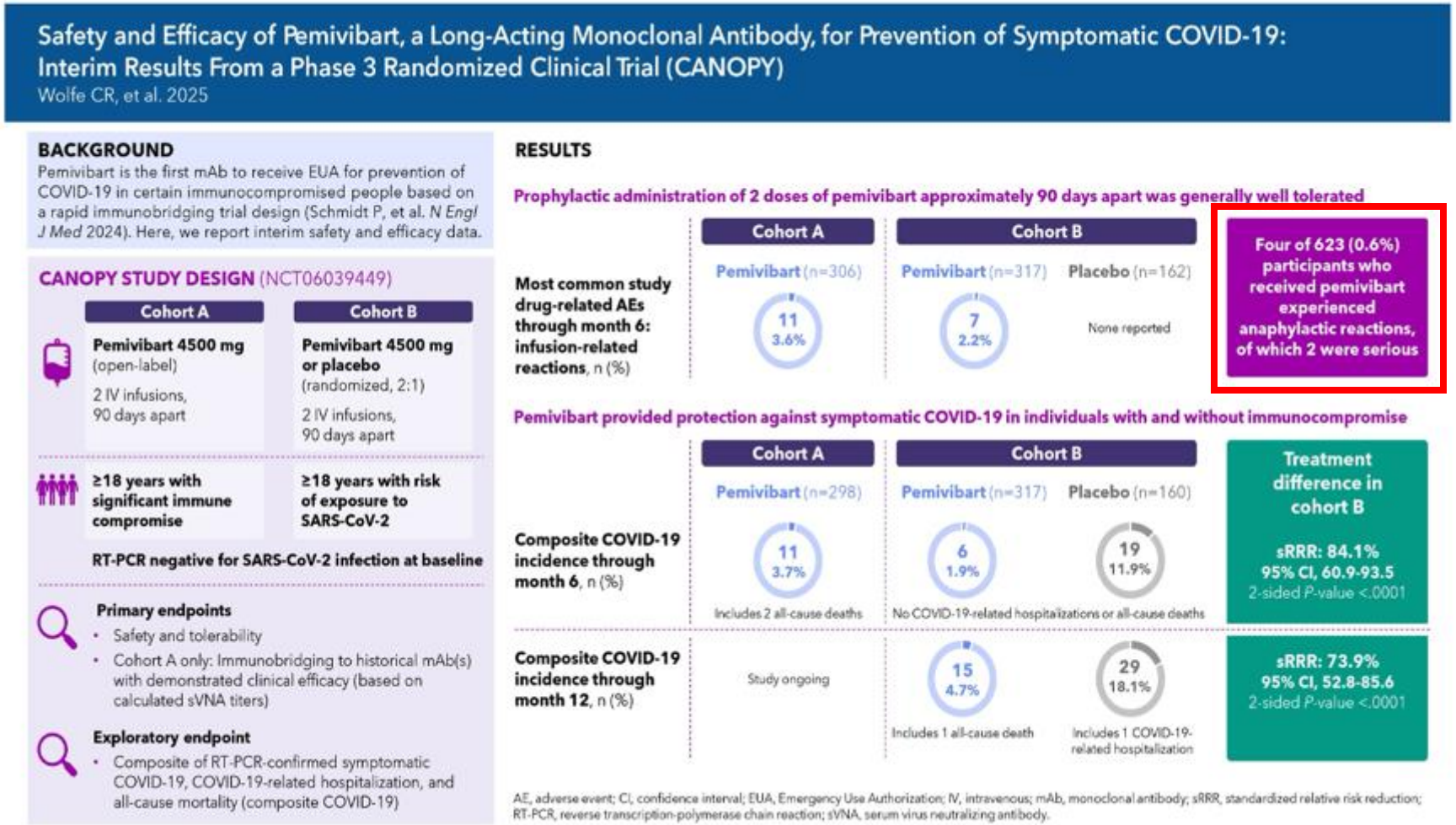

Safety and Efficacy of Pemivibart, a Long-Acting Monoclonal Antibody, for Prevention of Symptomatic COVID-19: Interim Results From a Phase 3 Randomized Clinical Trial (CANOPY)

Wolfe CR, et al. 2025

BACKGROUND

Pemivibart is the first mAb to receive EUA for prevention of COVID-19 in certain immunocompromised people based on a rapid immunobridging trial design (Schmidt P, et al. *N Engl J Med* 2024). Here, we report interim safety and efficacy data.

CANOPY STUDY DESIGN (NCT06039449)

	Cohort A	Cohort B
	Pemivibart 4500 mg (open-label) 2 IV infusions, 90 days apart	**Pemivibart 4500 mg or placebo** (randomized, 2:1) 2 IV infusions, 90 days apart
	≥18 years with significant immune compromise	**≥18 years with risk of exposure to SARS-CoV-2**

RT-PCR negative for SARS-CoV-2 infection at baseline

Primary endpoints
- Safety and tolerability
- Cohort A only: Immunobridging to historical mAb(s) with demonstrated clinical efficacy (based on calculated sVNA titers)

Exploratory endpoint
- Composite of RT-PCR-confirmed symptomatic COVID-19, COVID-19-related hospitalization, and all-cause mortality (composite COVID-19)

RESULTS

Prophylactic administration of 2 doses of pemivibart approximately 90 days apart was generally well tolerated

Most common study drug-related AEs through month 6: infusion-related reactions, n (%)	Cohort A: Pemivibart (n=306)	Cohort B: Pemivibart (n=317)	Cohort B: Placebo (n=162)
	11 (3.6%)	7 (2.2%)	None reported

Four of 623 (0.6%) participants who received pemivibart experienced anaphylactic reactions, of which 2 were serious

Pemivibart provided protection against symptomatic COVID-19 in individuals with and without immunocompromise

	Cohort A: Pemivibart (n=298)	Cohort B: Pemivibart (n=317)	Cohort B: Placebo (n=160)	Treatment difference in cohort B
Composite COVID-19 incidence through month 6, n (%)	11 (3.7%) Includes 2 all-cause deaths	6 (1.9%) No COVID-19-related hospitalizations or all-cause deaths	19 (11.9%)	sRRR: 84.1% 95% CI, 60.9-93.5 2-sided *P*-value <.0001
Composite COVID-19 incidence through month 12, n (%)	Study ongoing	15 (4.7%) Includes 1 all-cause death	29 (18.1%) Includes 1 COVID-19-related hospitalization	sRRR: 73.9% 95% CI, 52.8-85.6 2-sided *P*-value <.0001

AE, adverse event; CI, confidence interval; EUA, Emergency Use Authorization; IV, intravenous; mAb, monoclonal antibody; sRRR, standardized relative risk reduction; RT-PCR, reverse transcription-polymerase chain reaction; sVNA, serum virus neutralizing antibody.

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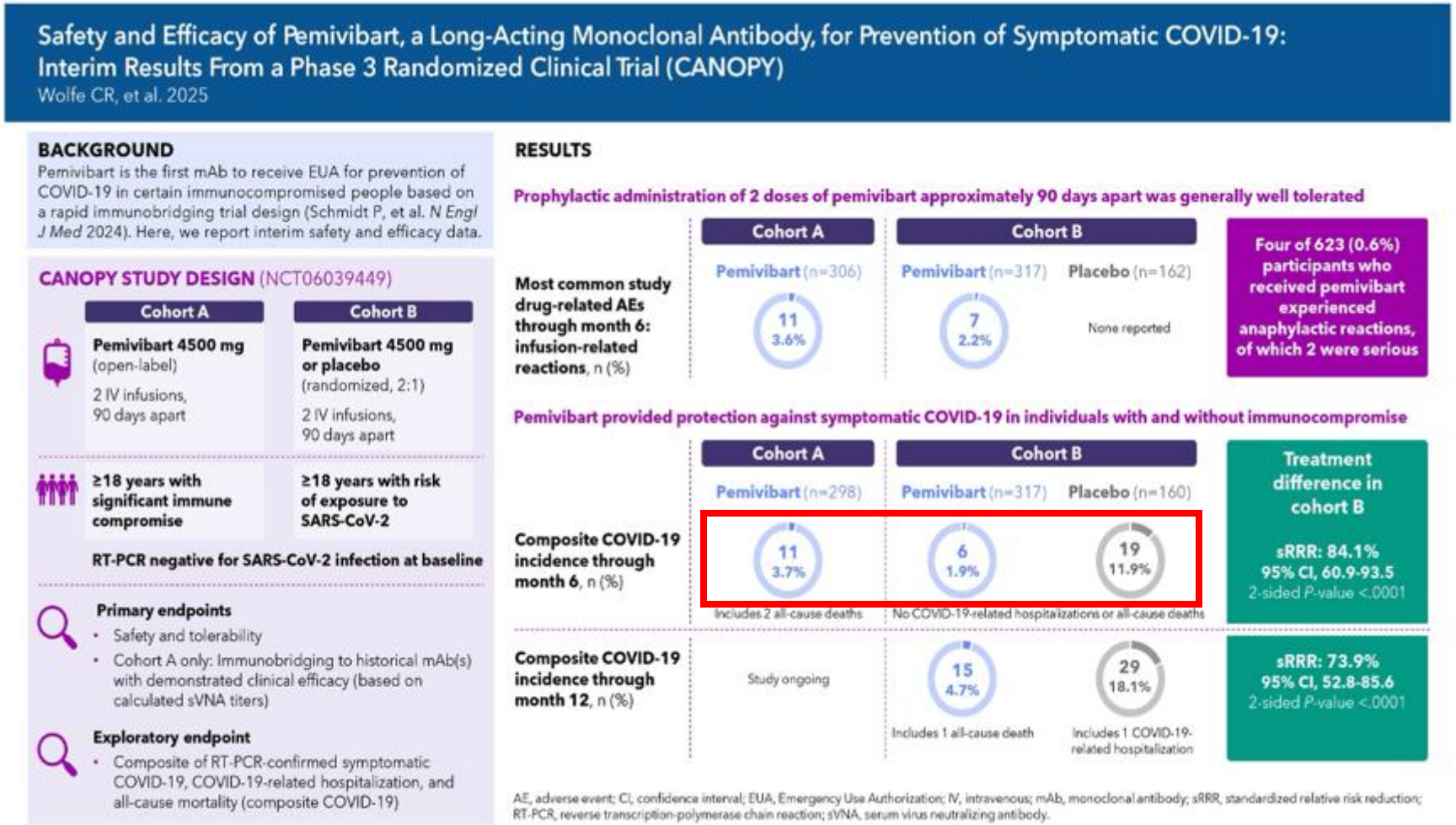

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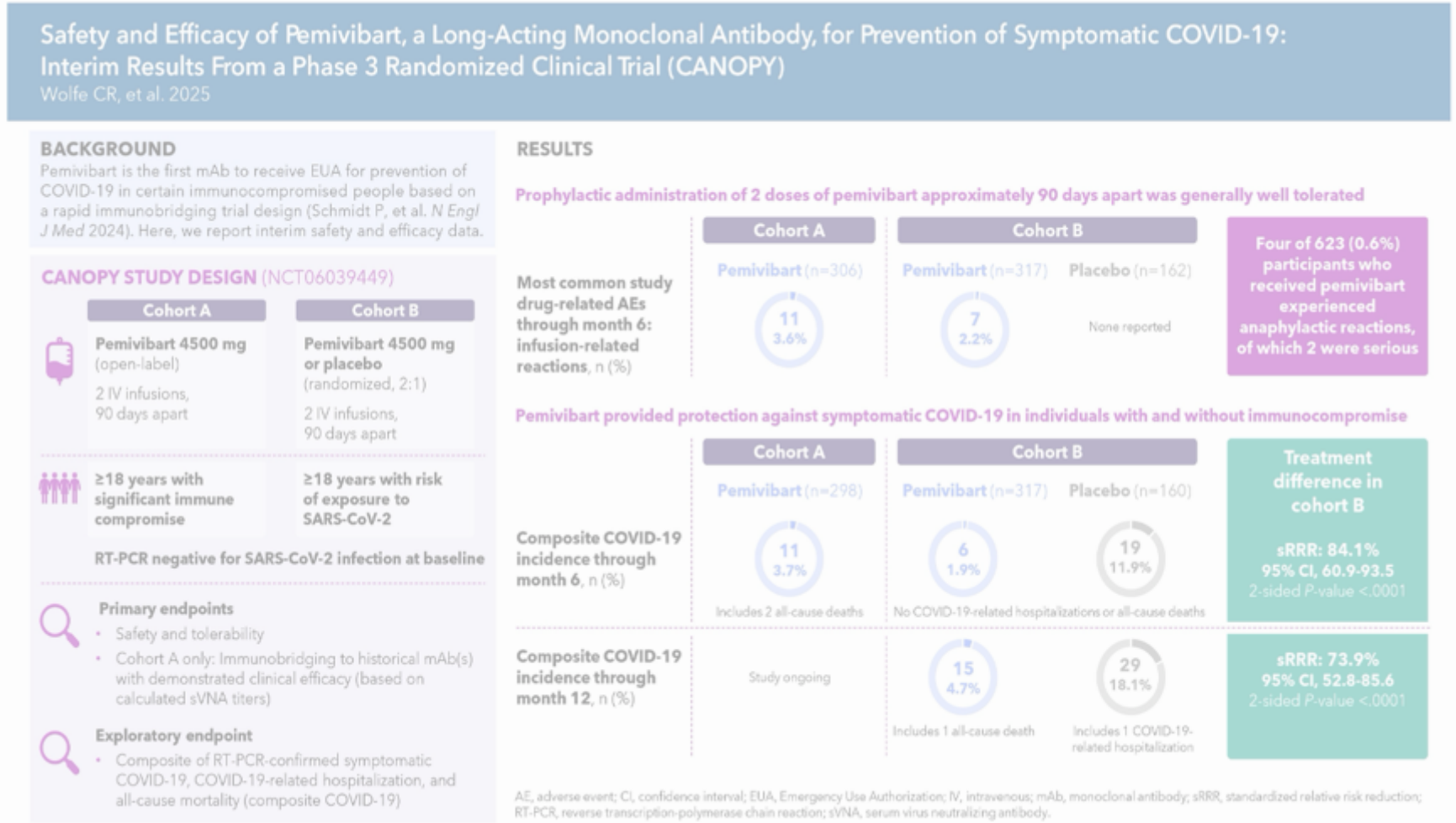
COVID 19 Pre-exposure Prophylaxis (PrEP)

Pemivibart – Practical issues

- Long half-life, and trial re-dosed after 90 days, but ? necessary
- No COVID19 hospitalizations in Cohort B, so ? practical benefit
- Logistics of IV infusion
- Anaphylactic signal (0.6%)
- Expense



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Schmidt et al, *NEJM* 2024,

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COVID 19 Pre-exposure Prophylaxis (PrEP)

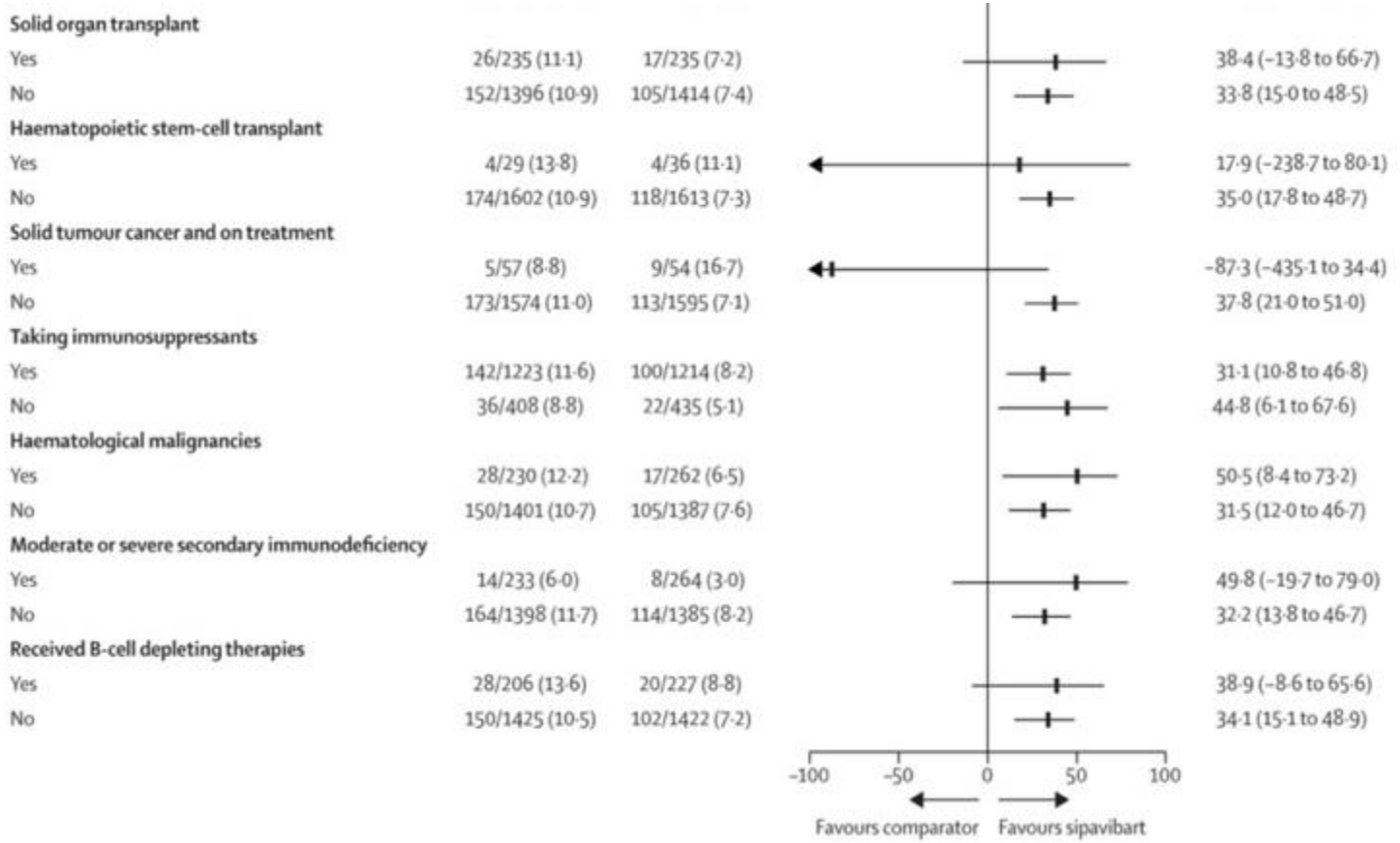
Sipavibart

- 1:1 randomized trial, immunocompromised
- 300mg sipavibart Vs Tixa/Cilga or placebo on day 1
- 300mg additional sipavibart Vs placebo at 6m

- Primary outcome – rates of symptomatic covid with *non-Phe456Leu-containing* variants within 6m
  - *Lost activity against KP2,3 variants mid trial, 2024*

- 1669 active Vs 1675 placebo

- SAE's rare = 0.1% vs 0.4%



Haider et al, *Lancet Infectious Disease*, 2025

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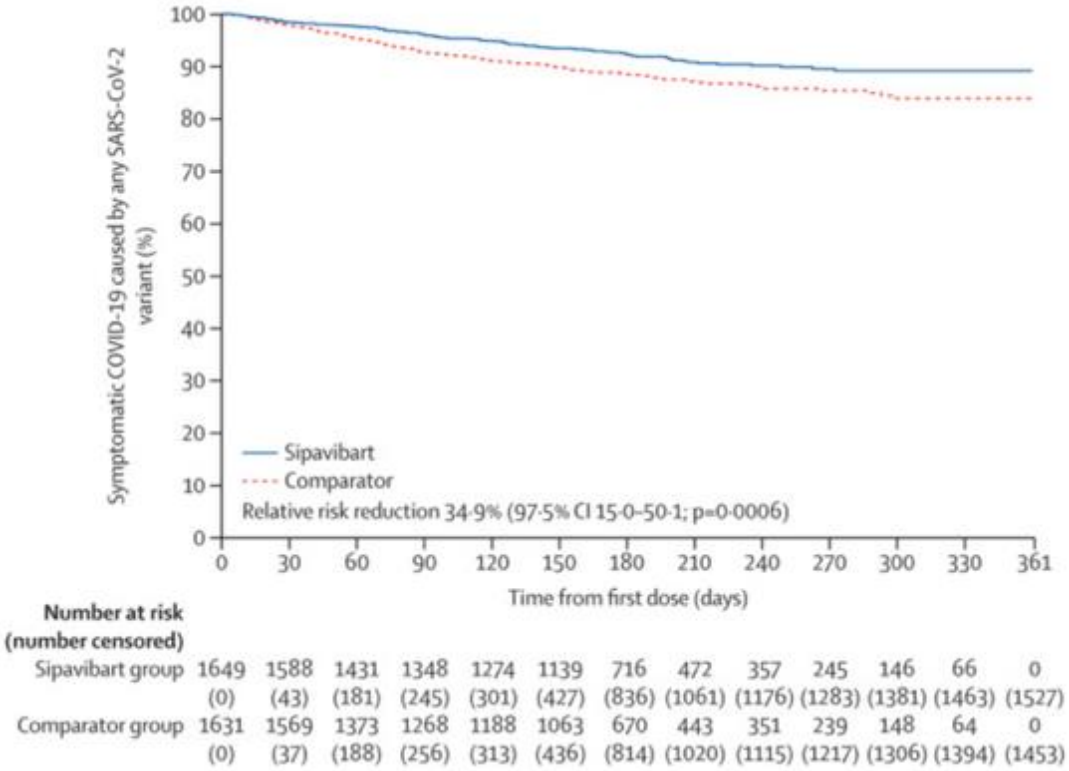

Results:

122 (7·4%) sipavibart Vs 178 (10·9%) "placebo" had symptomatic COVID-19 due to *any* variant [RRR] 34·9% , p=0·0006)

Significantly different looking only at earlier non-Phe456Leu variants

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COVID 19 Pre-exposure Prophylaxis (PrEP)

Historically speaking:

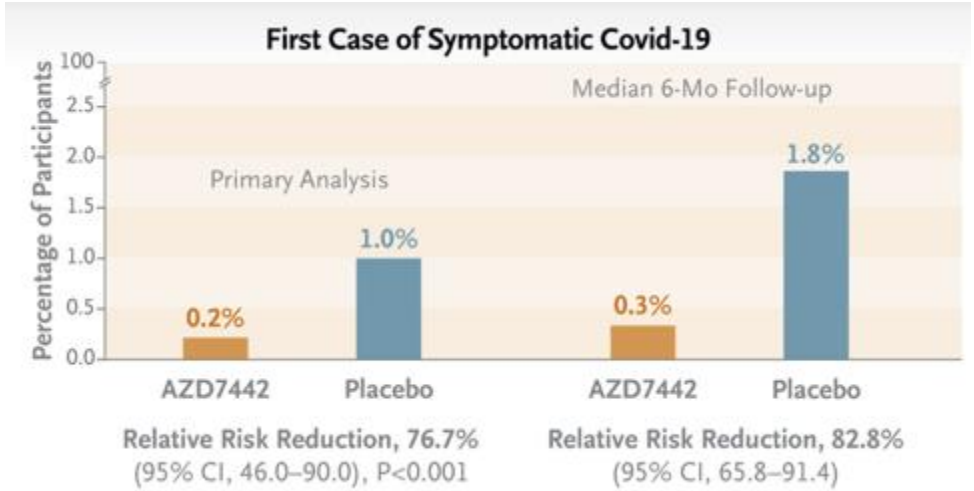
Tixagevimab / cilgavimab (PROVENT

Risk factors for an inadequate response to Covid-19 vaccination

- Age ≥60 years
- Obesity
- Immunocompromised status
- Inability to receive vaccines without adverse effects
- Congestive heart failure
- Chronic obstructive pulmonary disease
- Chronic kidney disease
- Chronic liver disease

Persons at increased risk for SARS-CoV-2 exposure

- Health care workers (including staff working in long-term care facilities)
- Workers in industrial settings shown to increase risk of SARS-CoV-2 transmission
- Military personnel
- Students living in dormitories
- Others living together in close or high-density proximity



Difficulties in 2025:

- no longer protective against current var's
- study done with vaccine naïve population
- COVID mitigation efforts very different
- risk factors for severity now different

Ongoing Promise:

- similar to Sipavibart, 6m activity, efficacy

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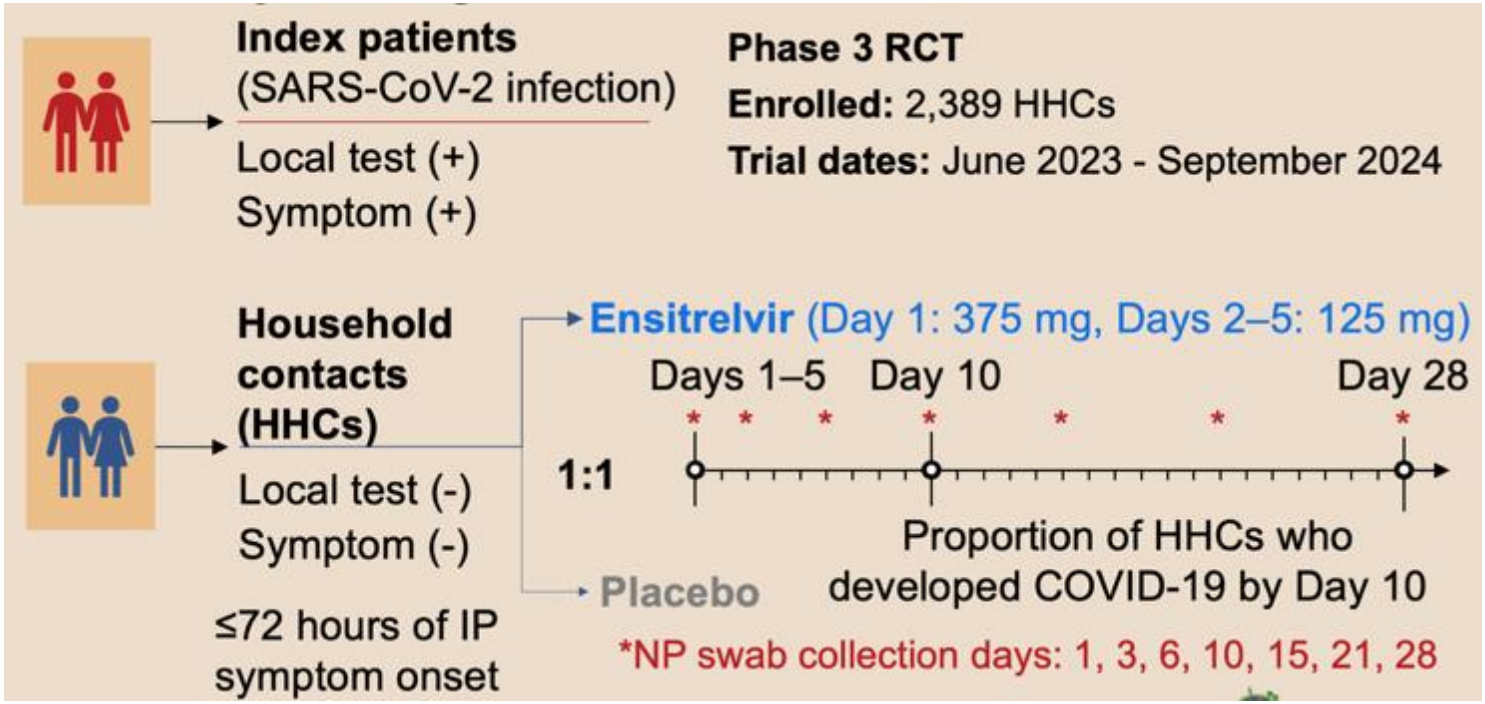
COVID 19 Post-exposure Prophylaxis (PEP)

Ensitrelvir (SCORPIO-PEP)

- Oral SARS-CoV-2 3C-like protease inhibitor

- Approved in Japan for Rx of mild-to-mod COVID-19

- Phase III - post exposure prophylaxis efficacy in household contacts of index patients, confirmed COVID-19



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Hayden et al, CROI 2025

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Characteristic	Ensitrelvir (N=1,030)	Placebo (N=1,011)
Hours from symptom onset in the IP to enrollment of HHC, n (%)		
<48	732 (71.1)	720 (71.2)
Geographic region, n (%)		
US	692 (67.2)	683 (67.6)
Japan	266 (25.8)	270 (26.7)
Vietnam	59 (5.7)	49 (4.8)
Argentina	7 (0.7)	4 (0.4)
South Africa	6 (0.6)	5 (0.5)
Risk status, n (%)		
High risk*	382 (37.1)	374 (37.0)
Positive baseline serology, n (%)[a]**		
S-antibody	1018 (99.4)	1004 (99.7)

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Hayden et al, CROI 2025

COVID 19 Post-exposure Prophylaxis (PEP)

Ensitrelvir (SCORPIO-PEP)

	Ensitrelvir (N=1,030)	Placebo (N=1,011)
COVID-19 development, n (%)	30 (2.9)	91 (9.0)
[95% CI]*	[1.97, 4.13]	[7.31, 10.94]
Risk ratio**	0.33	
[95% CI]***	[0.22, 0.49]	
P-value****	<0.0001	

In participants with central negative tests at baseline, ensitrelvir demonstrated a statistically significant reduction in the risk of COVID-19 vs placebo (2.9% vs 9.0%)

Drug position:

SCORPIO-SR
- early illness, OP
- reduced time to sustained symptom recovery

SCORPIO-HR
- high(ish) risk, early, OP
- antiviral activity, but no reduced sustained symptom resolution

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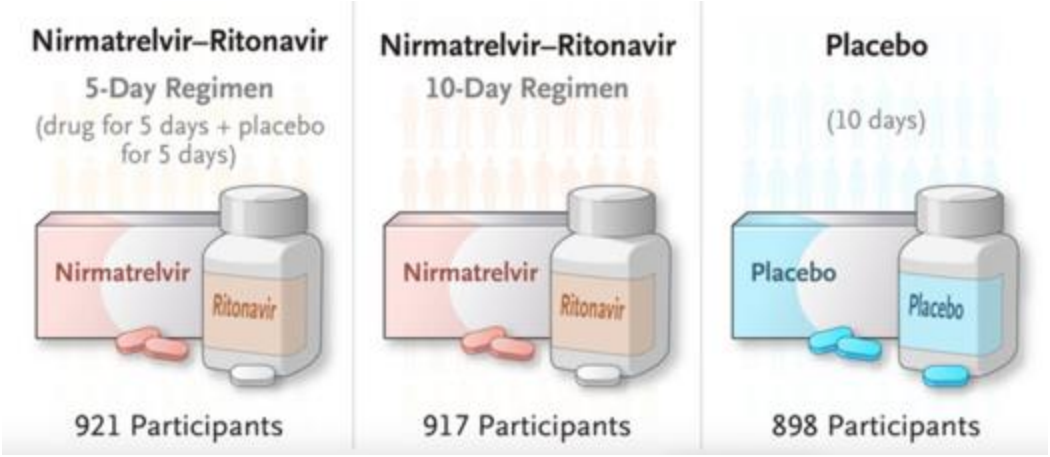
Hayden et al, CROI 2025

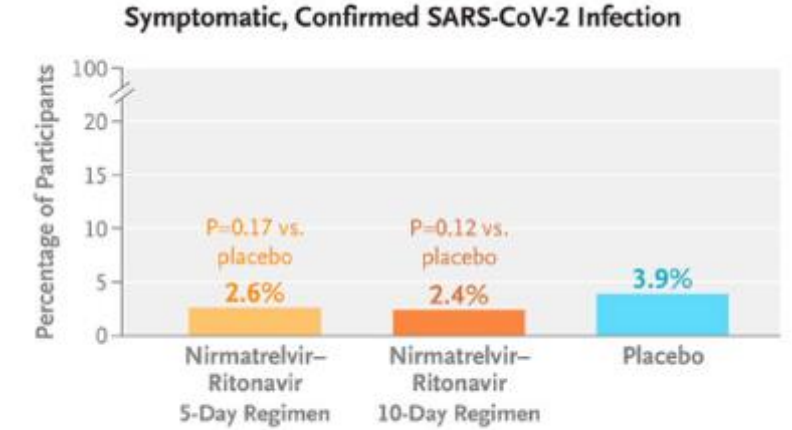
COVID 19 Post-exposure Prophylaxis (PEP)

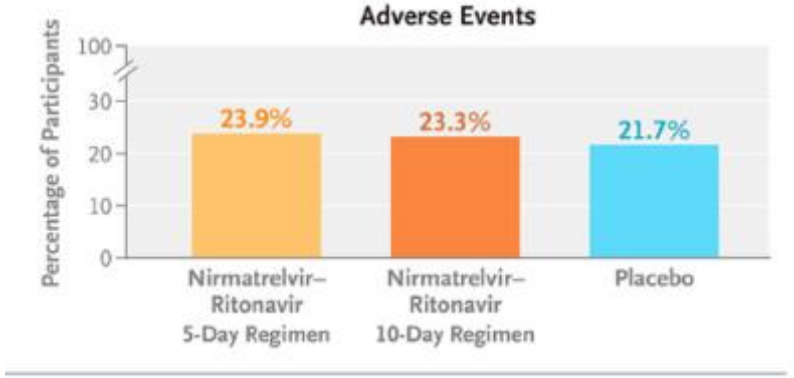
Nirmatrelvir/ritonavir

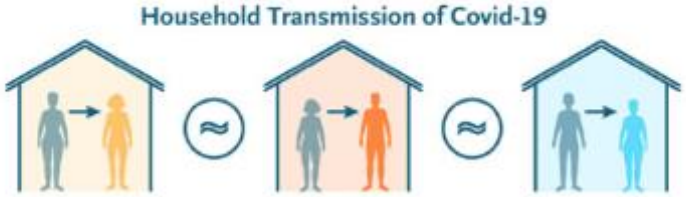
-2736 adults, exposed to COVID in house < 72hrs earlier

- Sept 21 – April 22
- neg rapid Ag, no prior positive, no vaccine within 6m
- outcome symptomatic positive covid by d14
- “blinded” but often taste difference









Hammond et al, NEJM 2024

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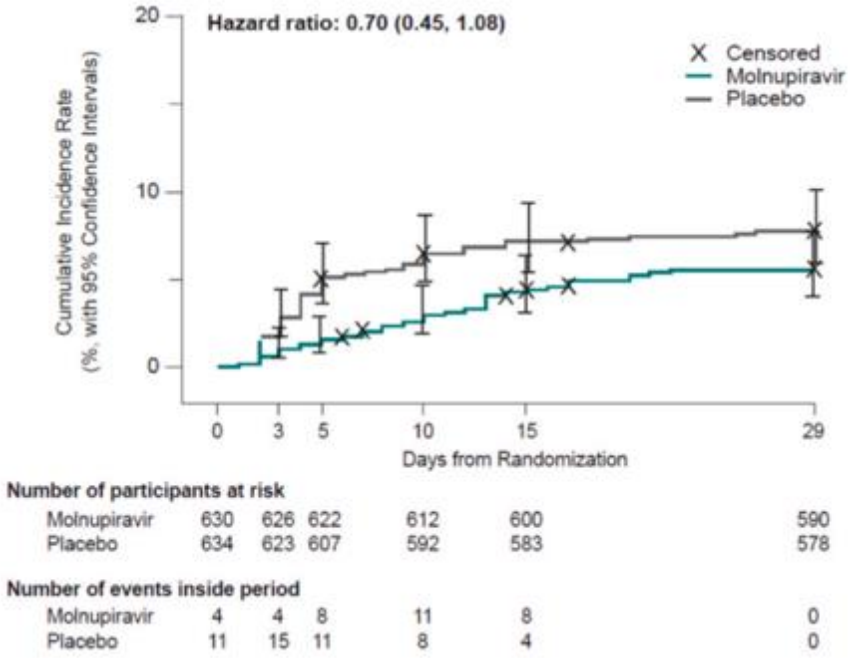
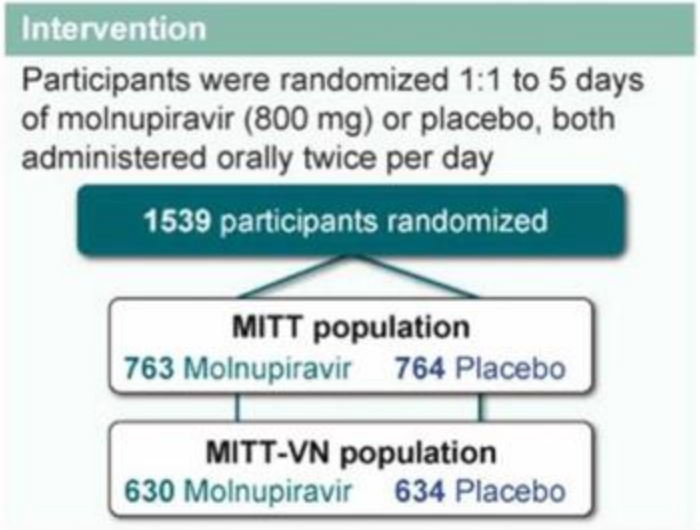
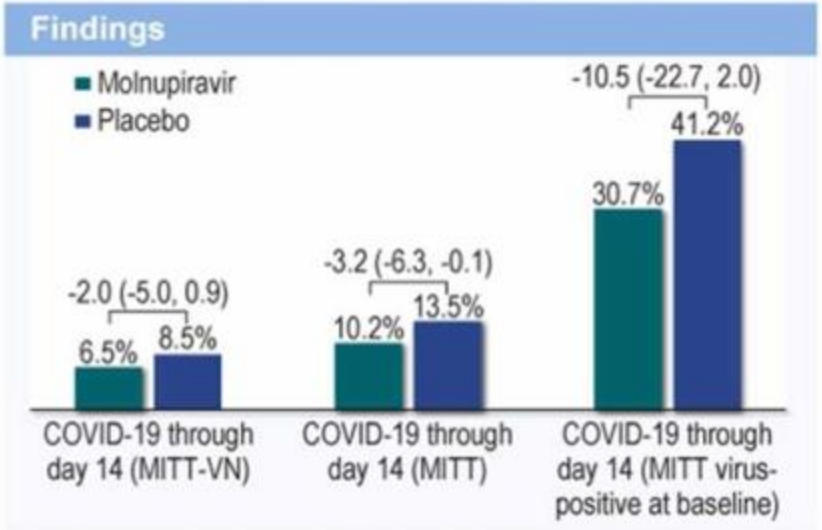
Molnupiravir (MOVe-AHEAD)







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Alpziar et al, *J Infection* 2023

COVID 19 Post-exposure Prophylaxis (PEP)

PEP drugs that came & went:

bamlanivimab / etesevimab (BLAZE2)

- 8.5% (active) vs 15.2% (placebo) incidence of infection, BLAZE-2
- nursing home staff, residents

casirivimab / imdevimab

- 1.5% (active) vs 7.8% (placebo) incidence of infection, s/c dosing trial
- appeared to have shorter illness, lower viral loads

Ultimately both used rarely, in unvaccinated groups, and with variants that emerged

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Cohen, et al, JAMA 2021
O'Brien, et al, NEJM 2021

Conclusions for 2025:

- Multiple examples of antiviral or mAb protecting against symptomatic SARs-CoV2 infection

- Currently for PrEP - only Pemivibart (mAb) available
- Currently for PEP – nothing available, ensitrilvir pending

- Clinically impactful to have options for *immunosuppressed patients*, in addition to vaccines
- Lays a good platform for study rollout in future pandemic viral countermeasure development

- Challenges ahead
  - Pemivibart activity against variant drift
  - Availability of ensitrilvir and other antivirals
  - Further trials struggle with changing endpoints, fluctuating definitions of high-risk, prior immunity (native or vaccine)
  - Public / government interest in drugs, vaccines, mAbs

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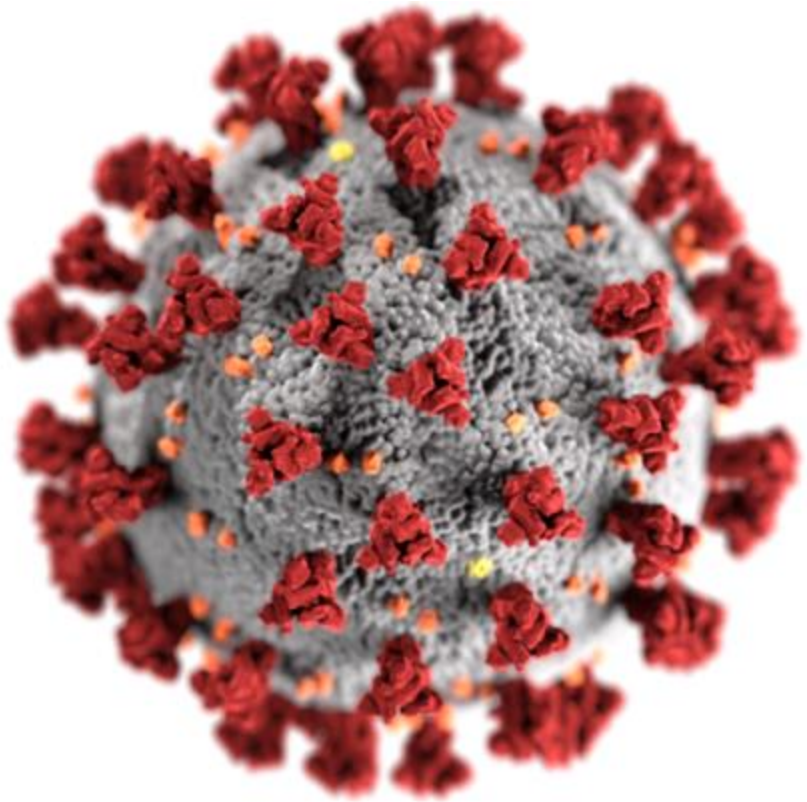
Questions?



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