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Lessons on Correlates of Protection from COVID-19 Vaccines and HIV-1 Monoclonal Antibodies

EMA/FDA workshop "*Efficacy of monoclonal antibodies in the context of rapidly evolving SARS-CoV-2 variants*"

December 15, 2022

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Outline

1. COVID-19 vaccine CoPs from efficacy trials
2. HIV-1 monoclonal antibody CoPs from efficacy trials

How to apply learnings to help define CoPs for SARS-CoV-2 monoclonal antibody prevention?

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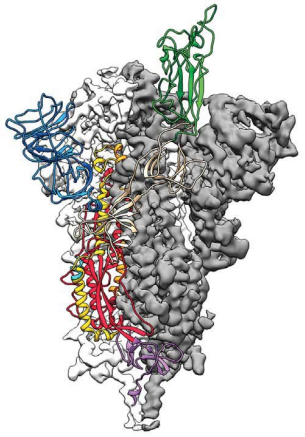
Five U.S. Government-Supported Public-Private Partnership Phase 3 COVID-19 Vaccine Efficacy Trials

- Protein vaccine



NOVAVAX
Creating Tomorrow's Vaccines Today

SANOFI

- Viral vector vaccines

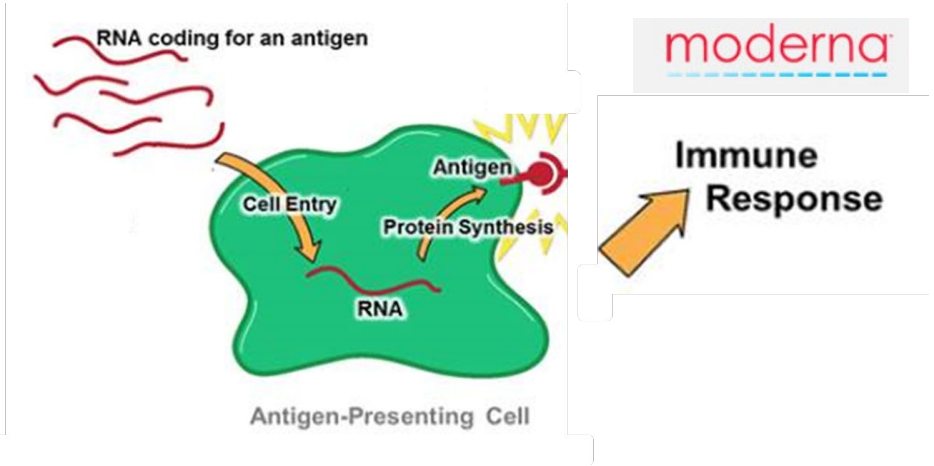
  - Ad26 vector

janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

  - ChAdOx1

AstraZeneca

- mRNA technology



moderna

Manufacturer	Trial	Location
Moderna	COVE	U.S.
Janssen	ENSEMBLE	Latin America, South Africa, U.S
Astra-Zeneca	AZD-1222	Latin America, U.S.
Novavax	PREVENT-19	Mexico, U.S.
Sanofi-Pasteur	VAT08	Africa, Asia, Latin America, U.S.

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COVID-19 VE Trial CoP Results Published/Posted

Phase 3 Trial	CoP Articles*
Moderna COVE	• Gilbert et al. (Aug. 2021 *medRxiv*, 2022 *Science*); • Benkeser et al. (*under revision*)
Janssen ENSEMBLE	• Fong et al. (April 2022 *medRxiv*; 2022 *Nat Microbiology*) EUA data set
Novavax PREVENT-19	• Fong et al (June 2022 *medRxiv*; 2022 *Nat Communications, in press*)
Astra-Zeneca AZD1222	• Benkeser et al. (*under revision*)
Meta	• Earle et al. (2021, *Vaccine*) • Koup et al. (2021, *Nat Medicine*) • Gilbert et al. (2022, *NEJM*)

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Scope of Published CoP Studies to Date

Attribute	Description
Timing of measuring antibody markers	2-4 weeks post primary vaccination series - Post dose 2 except post dose 1 for Janssen/ENSEMBLE
Study outcome	Virologically-confirmed symptomatic COVID-19 through to 2.5-7 months post primary vaccination series*
Lineages of outcomes	Ancestral and pre-omicron variants
Study cohort	SARS-CoV-2 naïve per-protocol

*Moderna COVE: 35-126 days post dose 2
Janssen ENSEMBLE: 35-209 days post dose 1
Novavax PREVENT-19: 21-73 days post dose 2
AZD1222: 35-120 days post dose 2

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Univariable CoRs in COVE, ENSEMBLE, PREVENT-19, AZD1222

Vaccine/ Trial	Ab marker 4 weeks post-Vx	Follow-up post vaccination	Estimated HR per 10-fold Incr (95% CI)*	P-value	Q-value	FWER-Adjusted P
COVE mRNA	Spike IgG	126 days	0.66 (0.50, 0.88)	0.005	0.014	0.010
ENSEMBLE Ad26*	Spike IgG	209 days	0.67 (0.45, 1.00)	0.048	0.10	0.13
PREVENT-19 Prot	Spike IgG	73 days	0.36 (0.20, 0.64)	< 0.001	0.005	0.005
AZD1222 ChAdOx	Spike IgG	120 days	0.32 (0.14, 0.76)	0.009	0.016	0.014
COVE mRNA	RBD IgG	126 days	0.57 (0.40, 0.82)	0.002	0.009	0.010
ENSEMBLE Ad26*	RBD IgG	209 days	0.60 (0.38, 0.95)	0.028	0.082	0.084
PREVENT-19 Prot	RBD IgG	73 days	0.35 (0.18, 0.69)	0.002	0.012	0.013
COVE mRNA	PsV nAb ID50	126 days	0.42 (0.27, 0.65)	< 0.001	0.002	0.003
ENSEMBLE Ad26*	PsV nAb ID50	209 days	0.51 (0.32, 0.79)	0.002	0.029	0.017
PREVENT-19 Prot	PsV nAb ID50	73 days	0.39 (0.19, 0.82)	0.013	0.032	0.030
AZD1222 ChAdOx	PsV nAb ID50	120 days	0.28 (0.10, 0.77)	0.013	0.019	0.016
ENSEMBLE Ad26	ADCP	209 days	0.84 (0.53, 1.32)	0.44	0.45	0.45

*BLA data (data cut July 9, 2021 as in Sadoff et al., 2022, *NEJM*)

- Spike, RBD IgG; nAb ID50 markers are consistently inverse CoRs, generally passing FWER-correction

Multivariable Correlates of Risk (CoRs): PsV nAb ID50 titer is the Independent Inverse Correlate of COVID-19

Vaccine/ Trial	Ab marker 4 weeks post-Vx	Estimated HR per SD Incr (95% CI)*	P-value
COVE mRNA	RBD IgG	0.94 (0.64, 1.37)	0.75
	PsV nAb ID50	**0.59 (0.36, 0.95)**	**0.029**
	LV nAb MN50	1.31 (0.76, 2.27)	0.34
		Overall test for CoR	0.001
ENSEMBLE Ad26*	Spike IgG	0.83 (0.53, 1.31)	0.43
	RBD IgG	0.82 (0.55, 1.21)	0.32
	PsV nAb ID50	**0.67 (0.52, 0.87)**	**0.002**
	ADCP	1.54 (1.10, 2.15)	0.011
		Overall test for CoR	0.002
AZD1222 ChAdOx1	Spike IgG	1.60 (0.47, 5.42)	0.45
	PsV nAb ID50	**0.35 (0.12, 1.03)**	**0.056**
		Overall test for CoR	0.040

*BLA data

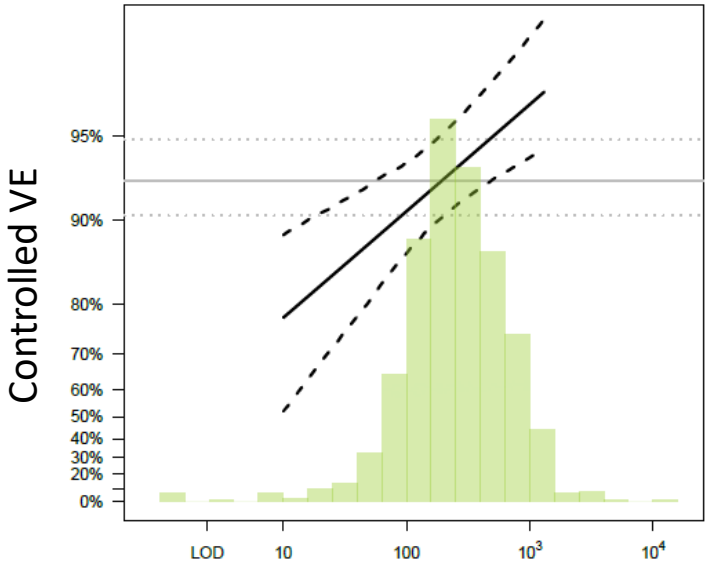
Multivariable analysis not done for PREVENT-19 because < 20 vaccine arm COVID-19 endpoints

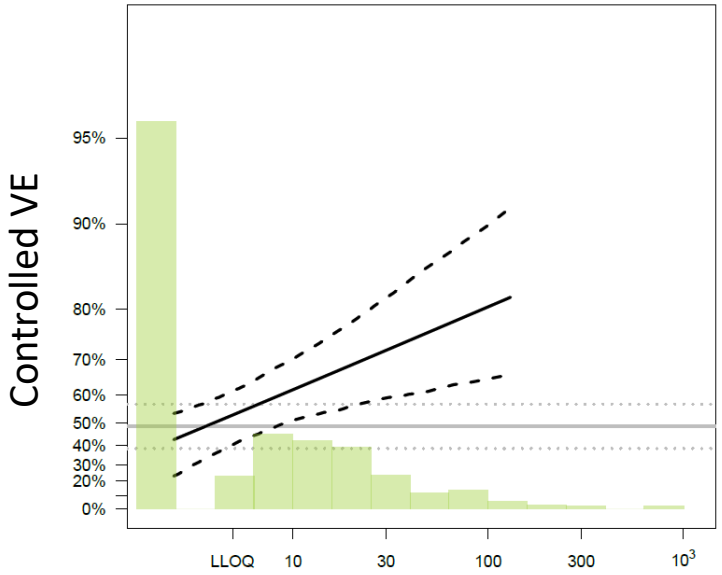
- All 3 trials: PsV nAb ID50 is the significant independent inverse CoR; other markers are not significant independent inverse CoRs

VE Against COVID-19 Increases with PsV nAb ID50 Titer (4 of 4 Phase 3 Trials)

Moderna COVE

Gilbert et al. (2022)





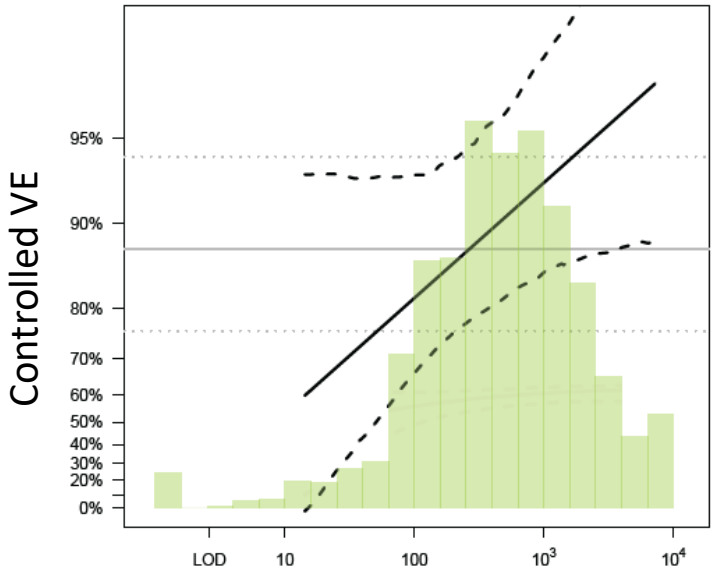
Janssen ENSEMBLE

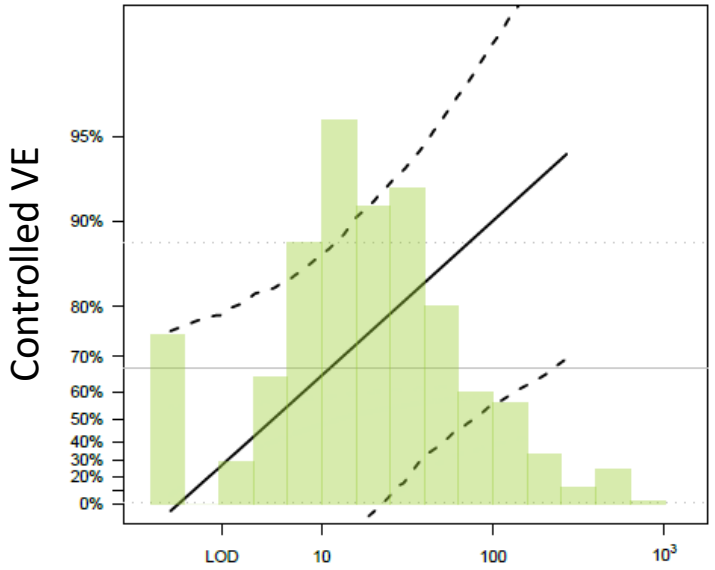
BLA data

Solid lines = point estimates
Dashed lines = 95% CIs

Novavax PREVENT-19

Fong et al. (2022)





Astra-Zeneca AZD1222

Benkeser et al. (2022)

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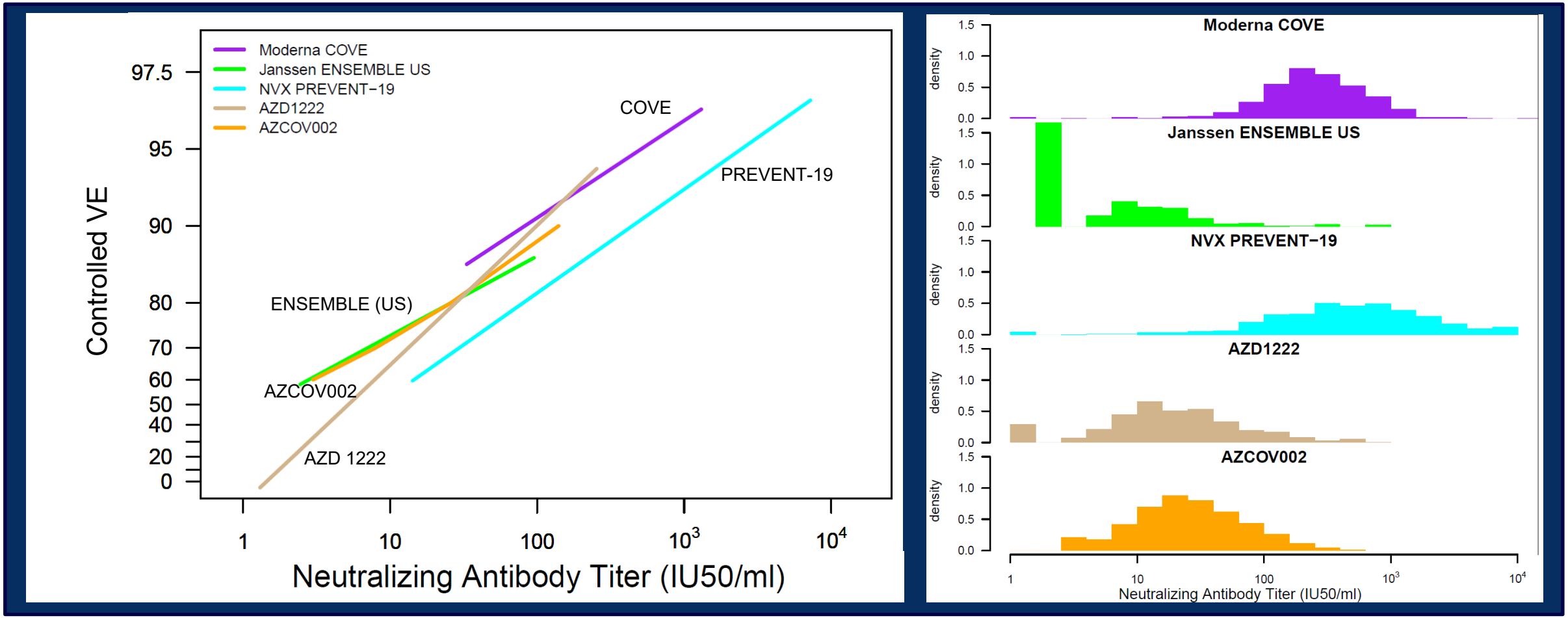
Similar VE-by-nAb ID50 Titer Curves Across 5 Phase 3 Trials (Adding the AZ COV002 UK Study)



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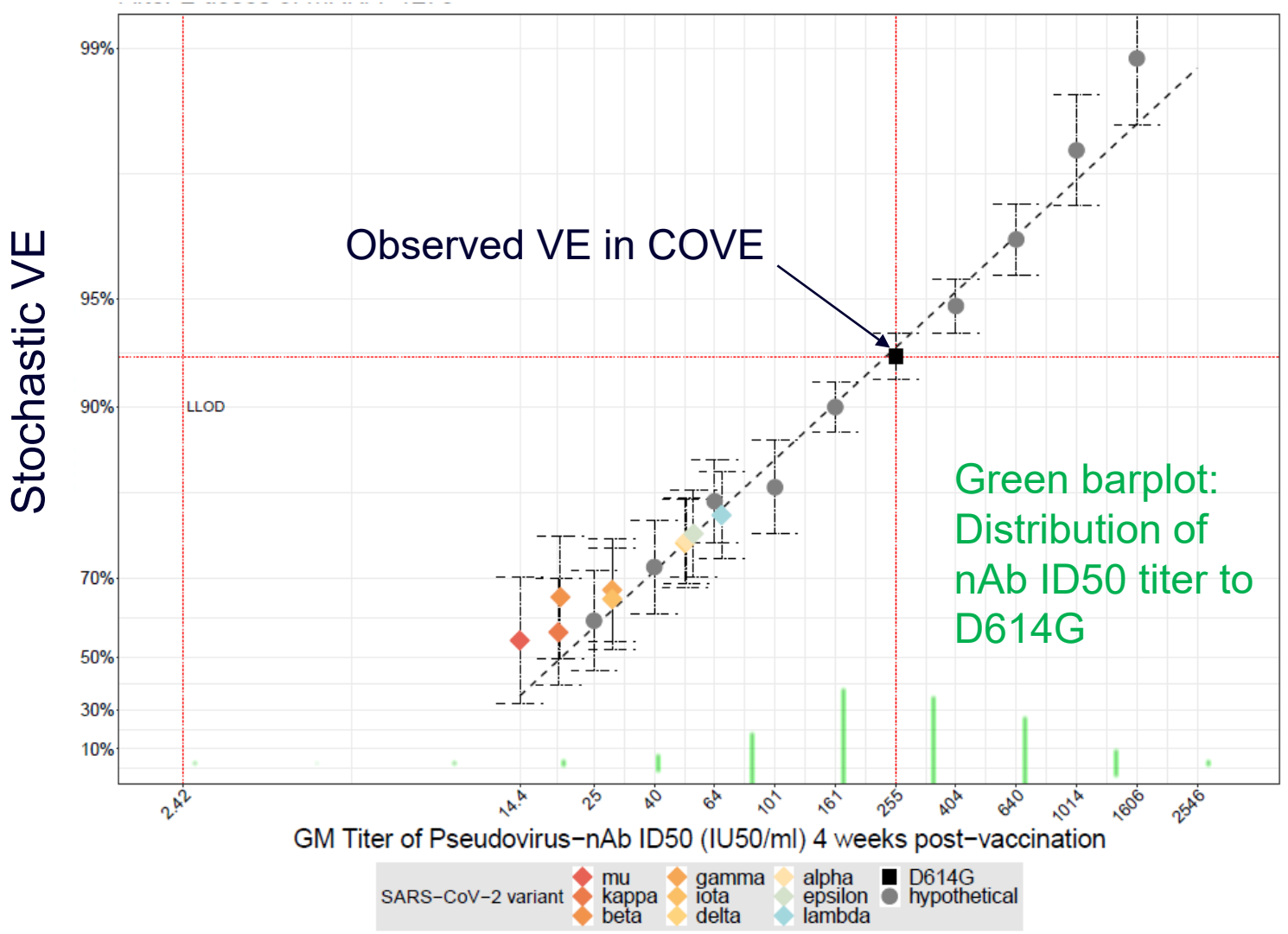
- Gilbert, Donis, Koup, Fong, Plotkin, Follmann (2022, *NEJM*). "A COVID-19 milestone attained – a correlate of protection for vaccines."

- ENSEMBLE (US) results updated to BLA data set with all blinded follow-up (Sadoff et al., 2022, *NEJM*). Increases number of vaccine breakthrough cases from 22 to 67.

Vaccine Efficacy Monotone with nAb ID50 Distribution Shifts Upwards or Downwards: COVE Trial

- Estimated VE under different stochastic interventions defined by constant shifts of log10 titer
- Hejazi et al. (2021, *Biometrics*) nonparametric method
  - Shifts annotated by estimated GMT values of 2-dose mRNA-1273 recipients against a panel of variants (Montefiori lab)



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Impact of Phase 3 Immune Correlates Results

- Undergird decisions to use nAb titer surrogate endpoint for:
  - Emergency Use Authorization of mRNA vaccines for children
  - Strain and dose changes of vaccines (e.g., June 28, 2022, FDA Vaccines and Related Biological Products Advisory Committee)
  - Modeling of vaccination schedules/when to boost
  - De novo authorization/approval of vaccine boosters
    - EMA's acceptance of clinical immunobridging with PsV nAb titer surrogate endpoint for Sanofi's monovalent Beta vaccine as a booster (BNT162b2 comparator vaccine)

Additional Stage 1 Correlates Analyses of the Phase 3 Trials Addressing New Questions (Blinded Periods)

Phase 3 Trial	Correlates Project
Sanofi VAT08 Rec. Protein - Monovalent vaccine (Ancestral) vs. placebo - Bivalent vaccine (Ancestral, Beta) vs. placebo	• Assess PD2 Ab against (Ancestral, Beta, Omicron BA.1, BA.4/BA.5) as CoR and CoP against Omicron COVID-19 • Assess for SARS-CoV-2 naïve and non-naïve individuals*
Janssen ENSEMBLE	• Test the variant-invariant CoP model by assessing Ab against (Ancestral, Gamma, Lambda, Mu, Epsilon) as CoP for lineage-matched COVID-19 in Latin America**
Meta/All phase 3 trials	• Meta-analysis surrogate endpoint evaluation of Ab 2-4-weeks post-vaccination; pursuing incorporation of T-cell responses (McElrath lab)

*~80% of participants SAR-CoV-2 non-naïve

**Will provide individual-level breakthrough analyses, complementing investigation of CoP for variants by the Davenport group via population-level analyses (e.g., Cromer et al., 2022, *medRxiv*)

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New Correlates Study Including T cell Markers

- COVAIL trial of U.S. recipients of a primary series + one homologous/heterologous booster enrolled starting in March 2022*
  - Randomize 1250 participants to 17 vaccine Ancestral and Variant booster arms:
    - 6 Moderna mRNA, 6 Pfizer mRNA, 3 Sanofi Rec. Prot., 2 Pfizer bivalent
  - Assess PsV ID50 titers to (D614G, Delta, Beta, BA.1, BA.2.12.1, BA.4/BA.5) as CoR/CoP for COVID-19 accounting for lineage and sequence
  - Also assess T cells, Fc effector function markers as correlates

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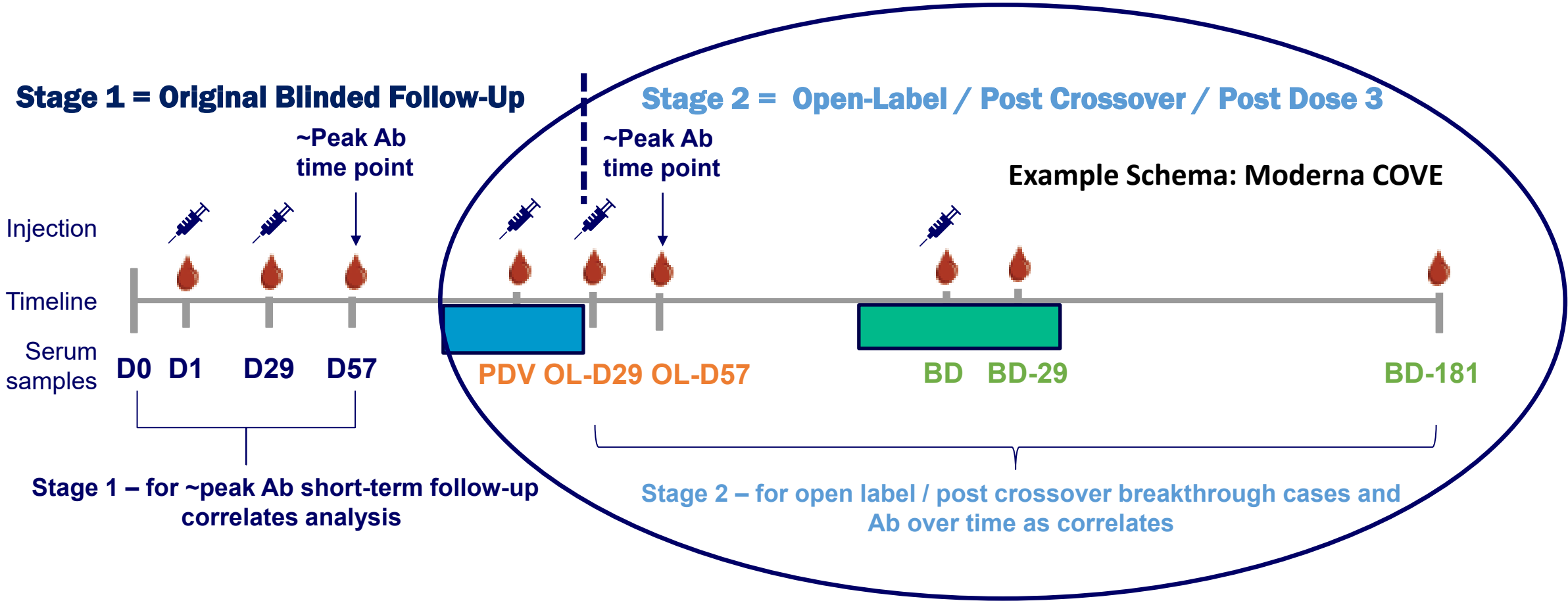
*Branche et al. (2022, *medRxiv*) preliminary analysis results

Stage 2 CoPs: Variants, Durability, Boosters (Post Blinded Period)



PDV = Participant decision visit (unblinding)

BD = Booster dose

OL = Open-label period

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Ongoing Stage 2 CoP Studies in the Phase 3 Trials

Question	Trial	Ongoing Stage 2 CoP Studies
CoP for Ab over time at exposures?	COVE	PD3 BA.1 Ab over time as CoP for BA.1 COVID-19
	PREVENT-19	PD2 Delta Ab over time as CoP for Delta COVID-19
CoP for variants?	COVE	PD3 BA.1 Ab as CoP for BA.1 COVID-19
	PREVENT-19	PD2 Delta Ab as CoP for Delta COVID-19
	ENSEMBLE	PD2 or PD3 Omicron BA.1 and BA.4/BA.5 Ab as CoP for Omicron COVID-19 (after Ad26.CoV2S, Ad26.CoV2S or mRNA, mRNA, Ad26.CoV2S)
CoP for severe COVID-19?	All studies	All studies measure Ab from all vaccinees with severe COVID-19
CoP for key subpopulations?	All Studies	All studies can assess CoP in age >= 65
	Ubuntu/P3008	Omicron Ab correlates in persons living with HIV; Moderna (Ancestral, BA.4/BA.5) bivalent vs. Ancestral
CoP for hybrid- vs. pure-vaccine-immunity	COVE	PD3 BA.1 Ab as CoP for BA.1 COVID-19 in SAR-CoV-2 naïve and non-naïve (acquired COVID-19 before dose 3)
	ENSEMBLE	PD2 or PD3 Omicron BA.1 and BA.4/BA.5 Ab as CoP for Omicron COVID-19 (after Ad26.CoV2S, Ad26.CoV2S or mRNA, mRNA, Ad26.CoV2S)

Outline

1. COVID-19 vaccine CoPs from efficacy trials
2. **HIV-1 monoclonal antibody CoPs from efficacy trials**

How to apply learnings to help define CoPs for SARS-CoV-2 monoclonal antibody prevention?

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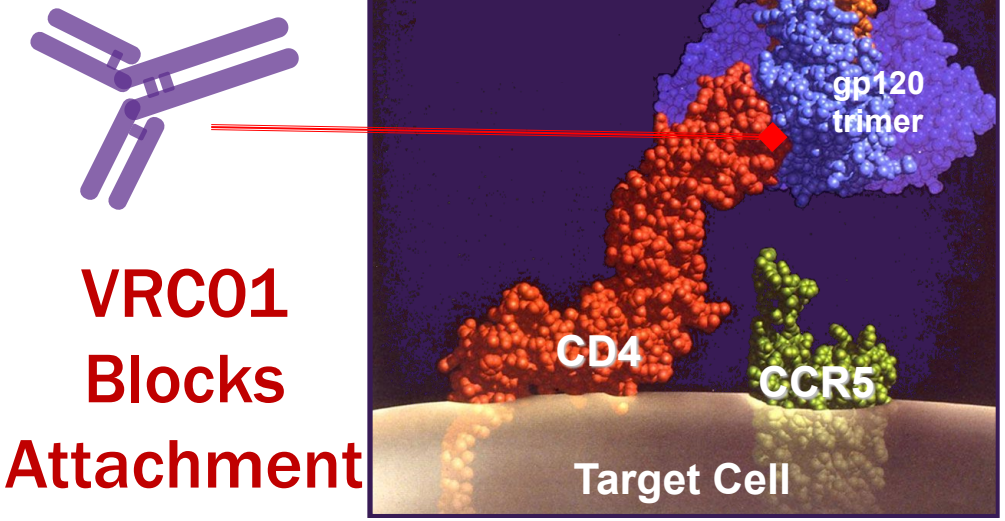
STUDY



VRC01 Blocks Attachment to CD4

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two Randomized Trials of Neutralizing Antibodies to Prevent HIV-1 Acquisition

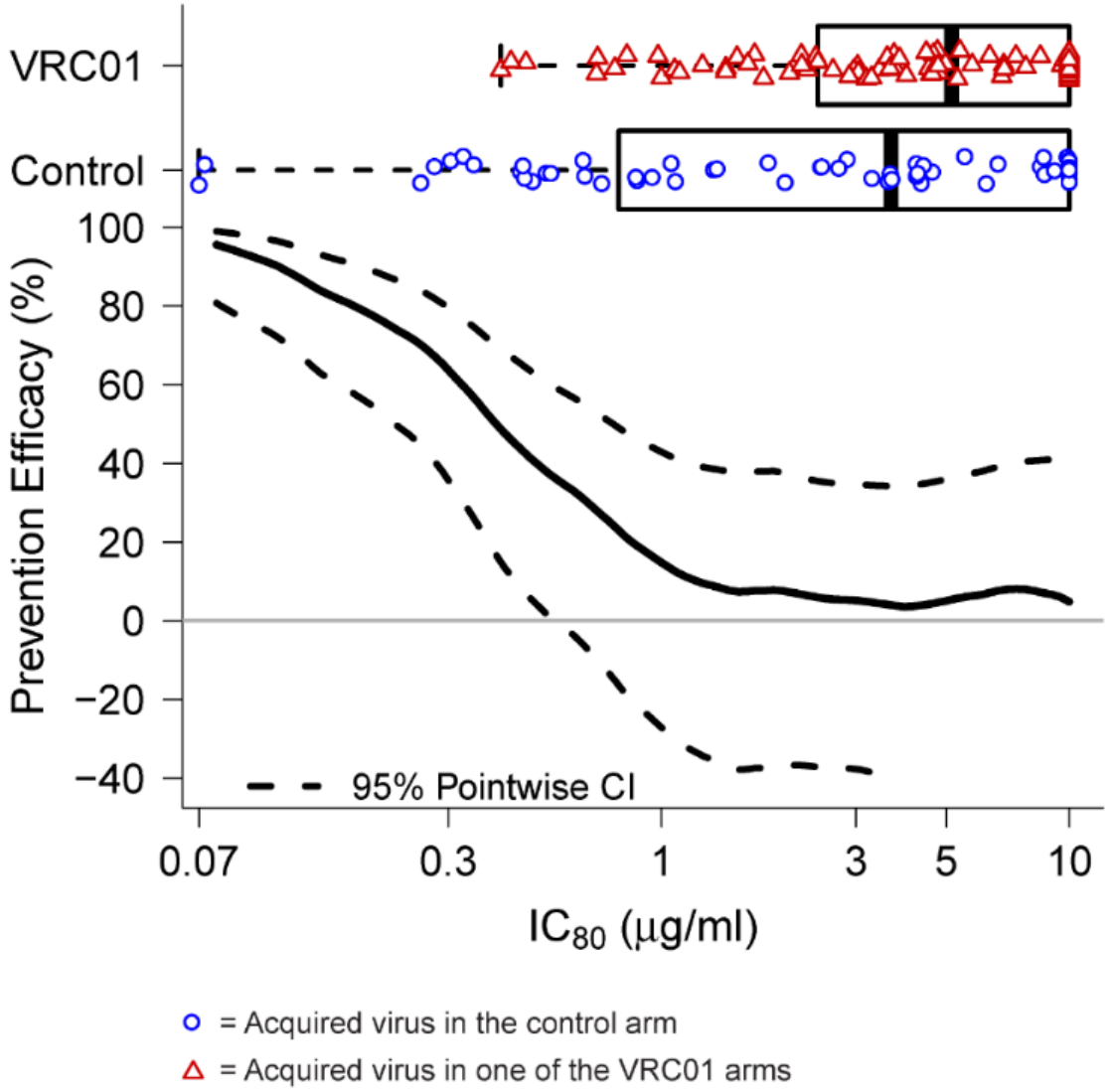
L. Corey, P.B. Gilbert, M. Juraska, D.C. Montefiori, L. Morris, S.T. Karuna, S. Edupuganti, N.M. Mgodi, A.C. deCamp, E. Rudnicki, Y. Huang, P. Gonzales, R. Cabello, C. Orrell, J.R. Lama, F. Laher, E.M. Lazarus, J. Sanchez, I. Frank, J. Hinojosa, M.E. Sobieszczyk, K.E. Marshall, P.G. Mukwekwerere, J. Makhema, L.R. Baden, J.I. Mullins, C. Williamson, J. Hural, M.J. McElrath, C. Bentley, S. Takuva, M.M. Gomez Lorenzo, D.N. Burns, N. Espy, A.K. Randhawa, N. Kochar, E. Piwowar-Manning, D.J. Donnell, N. Sista, P. Andrew, J.G. Kublin, G. Gray, J.E. Ledgerwood, J.R. Mascola, and M.S. Cohen, for the HVTN 704/HPTN 085 and HVTN 703/HPTN 081 Study Teams*

March 18, 2021
N Engl J Med 2021; 384:1003-1014
DOI: 10.1056/NEJMoa2031738

AMP: Neutralization Sieve Analysis was Critical For Progress Toward a Neutralization Surrogate Endpoint

- **Identified that IC80 of VRC01 against the majority acquired virus measured by the TZM-bl target-cell assay was a predictive biomarker for the level of VRC01 prevention efficacy (PE)***

PE = % reduction in risk of HIV-1 acquisition (VRC01 vs. placebo)



*Corey et al. (2021, *NEJM*)

Build on the Neutralization Sieve Results to Define a PT80 Biomarker that is Promising as a Surrogate Endpoint for bnAb Prevention of HIV-1 Acquisition

- PT80 biomarker defined for a serum sample of a bnAb recipient at a given time point against a given virus

PT80 = Predicted ID80 titer against the virus
= Estimated serum concentration/IC80

- Can predict prevention efficacy of a bnAb regimen by calculating the PT80 distribution over time (PK modeling) and against a population of circulating viruses (IC80 measurements)

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-022-01953-6

Check for updates

OPEN

Neutralization titer biomarker for antibody-mediated prevention of HIV-1 acquisition

Peter B. Gilbert[1,2,26]✉, Yunda Huang[1,3,26], Allan C. deCamp[1], Shelly Karuna[1], Yuanyuan Zhang[1], Craig A. Magaret[1], Elena E. Giorgi[4,24], Bette Korber[4], Paul T. Edlefsen[1], Raabya Rossenkhan[1], Michal Juraska[1], Erika Rudnicki[1], Nidhi Kochar[1], Ying Huang[1], Lindsay N. Carpp[1], Dan H. Barouch[5,6], Nonhlanhla N. Mkhize[7,8], Tandile Hermanus[7,8], Prudence Kgagudi[7,8], Valerie Bekker[7,8,25], Haajira Kaldine[7,8], Rutendo E. Mapengo[7,8], Amanda Eaton[9], Elize Domin[9], Carley West[9], Wenhong Feng[9], Haili Tang[9], Kelly E. Seaton[10], Jack Heptinstall[10], Caroline Brackett[10], Kelvin Chiong[10], Georgia D. Tomaras[10], Philip Andrew[11], Bryan T. Mayer[1], Daniel B. Reeves[1], Magdalena E. Sobieszczyk[12], Nigel Garrett[13,14], Jorge Sanchez[15], Cynthia Gay[16], Joseph Makhema[17,18], Carolyn Williamson[19], James I. Mullins[3,20,21], John Hural[1], Myron S. Cohen[22], Lawrence Corey[1,21,23], David C. Montefiori[9] and Lynn Morris[7,8,13]

Copying the Roadmap for Defining a Neutralization Surrogate Endpoint for an HIV-1 bnAb Regimen to a SARS-CoV-2 bnAb Regimen

1. Phase 2b/3 efficacy trials
   - ✓ Neutralization sieve analysis to characterize the relationship of prevention efficacy (PE) with virus IC80
2. NHP challenge studies
   - ✓ Characterize day-of-challenge PT80 against the challenge virus as a correlate of protection against SARS-CoV-2 acquisition
3. Prediction of PE for a given bnAb regimen, based on:
   - ✓ Time-concentration curves estimated by PK modeling
   - ✓ IC80 distribution of bnAb clinical lots against a SARS-CoV-2 virus population of interest
   - ✓ Model for distribution of exposures to SARS-CoV-2 viruses in a hypothetical phase 3 trial
   - ➡ Integrate the 3 sources of information to calculate the distribution of PT80 at exposures to yield an estimate of PE in the hypothetical phase 3 trial

Surrogate endpoint of bnAb regimen: PT80 distribution over time and the SARS-CoV-2 virus population (or the predicted PE itself)

Acknowledgments: COVID-19 Vaccine Correlates

- COVE, ENSEMBLE, AZD1222, PREVENT-19 study participants and study teams
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