FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Translational PK-PD Modeling During COVID-19

Evusheld & Points to Consider

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Disclaimer

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Roadmap

- Tale of Evusheld: first Omicron wave & revision to EUA
- PK-PD to inform decision making
  - Objective & Approach
  - Modeling Limitations & Strengths
- Conclusions

Initial Evusheld EUA

- Initial Emergency Use Authorization (EUA) - Dec 8, 2021
  - Evusheld is tixagevimab co-packaged with cilgavimab
    - Combination of Anti-SARS-CoV-2 spike mAbs
    - Amino Acid substitutions extend half-life & reduce Fc-mediated effector functions
  - 300 mg Evusheld IM every 6 months for Pre-exposure prophylaxis (PrEP)
    - Only product available for PrEP
- Phase 3 PROVENT trial (through Aug 29, 2021)
  - 77% relative risk ↓ of SARS-CoV-2 RT-PCR-positive symptomatic illness vs. placebo
  - Predominant SARS-CoV-2 variants were Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), and Epsilon (B.1.429)

Source: https://www.fda.gov/media/155107/download

IM = Intramuscular | SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

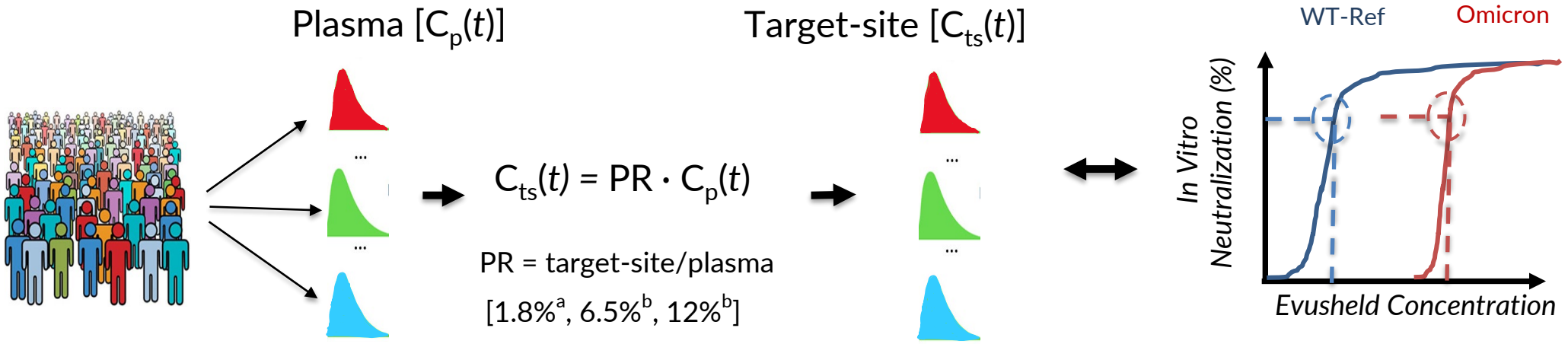
First Omicron Wave & Revision to EUA

- Emergence of Omicron variant BA.1.1.529
  - December 2021 | Evusheld neutralization activity unknown at time of initial EUA
- Predominance of Omicron variants circulating in US
  - January 2022 | ↓ in vitro activity against BA.1.1.529 and BA.1.1 (12 to 424-fold)
    - Near full activity retained against BA.2 (3 to 9-fold)
- Revision to Evusheld IM dosing regimen
  - Considerations: PK-PD | Clinical safety | Variant forecasting | No alternatives
    - From 300 mg to 600 mg

Sources: https://www.fda.gov/media/155107/download | https://www.fda.gov/media/156674/download | https://www.fda.gov/media/154701/download

PK-PD to Inform Decision Making

- Approach
  - Perform Population PK simulations
  - Compare predicted target-site concentration to target Minimum Protective Conc.



  - Compute probability of target attainment (PTA) using clinical doses

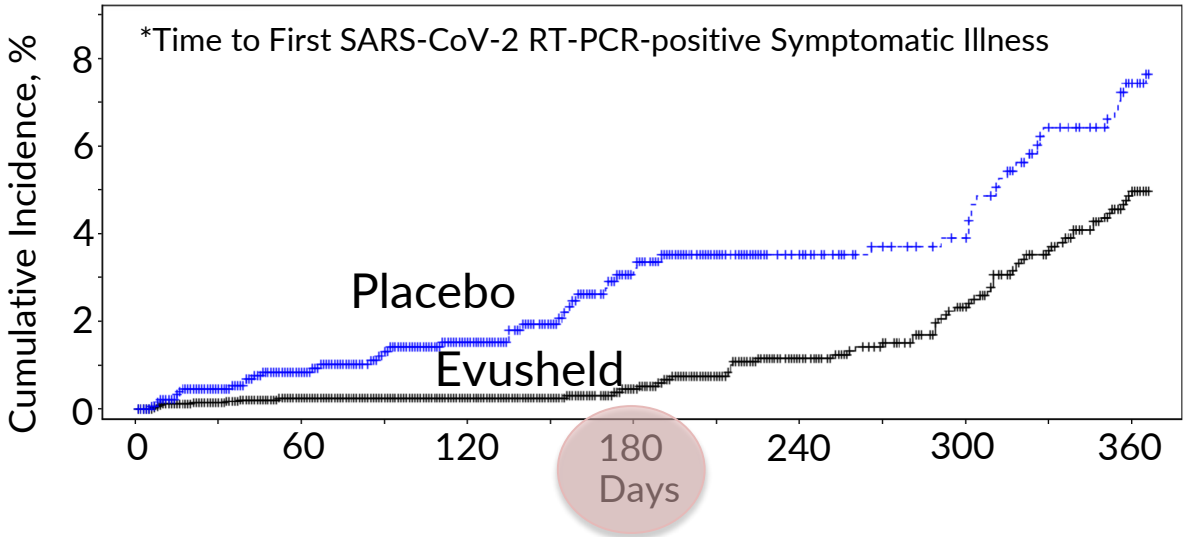
$$PTA = \frac{\#\ simulated\ individuals\ \geq target\ MPC}{\#\ of\ individuals\ in\ simulated\ population}$$

Sources: https://www.fda.gov/media/156674/download

[a]Upper respiratory penetration ratio (PR) value: Nasal Swab, experimentally determined | [b]Lower respiratory PR values: Epithelial lung lining fluid, other mAb literature

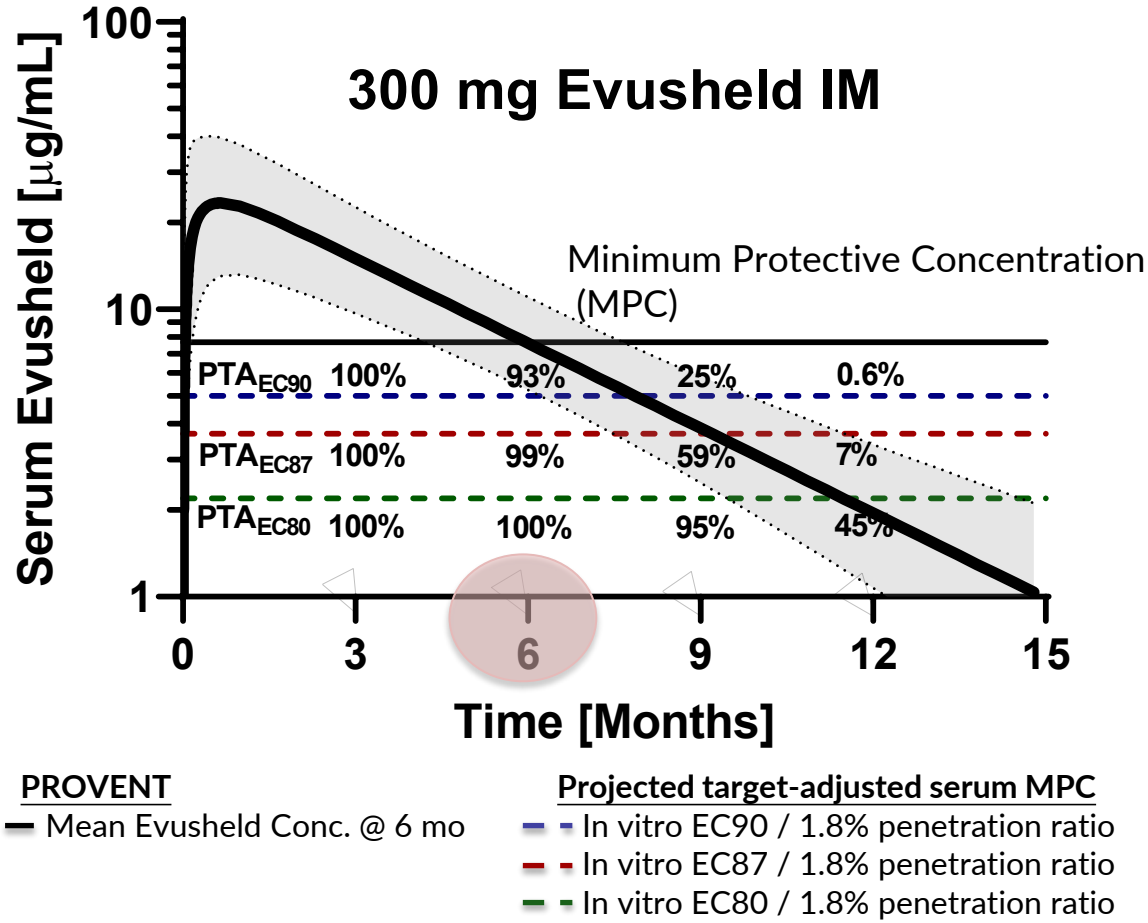
Translational PK-PD Are Consistent w/ PROVENT

PROVENT: No Protective Efficacy* after 6 months



Similar % of first SARS-CoV-2 RT-PCR-positive Symptomatic Illness between Day 184 to Day 366

- 1.4% Evusheld | 1.3% Placebo



Combination of 1.8% penetration ratio + In vitro EC90 describe PROVENT data, reasonably well

Parameter identifiability issue –quotient with two unknowns

PTA- in vivo Target remains unknown

Source: https://www.fda.gov/media/163209/download

Predicted % of participants with EVUSHELD concentrations ≥ a minimum protective concentration against BA.1.1.529

Evusheld dose adaption based on safety cap, range of possible system parameters, & unmet need population

	Time (Months)	% of participants					
		EC80		EC87		EC90	
300 mg EVUSHELD IM		Penetration of 6.5%	Penetration of 12%	Penetration of 6.5%	Penetration of 12%	Penetration of 6.5%	Penetration of 12%
	1	91	99	60	93	30	82
	2	86	99	40	90	11	73
	3	71	98	13	80	2	47
	6	6	65	0	11	0	1
	9	0	9	0	0	0	0

PK-PD predicted 300 mg suboptimal

	Time (Months)	% of participants					
		EC80		EC87		EC90	
600 mg EVUSHELD IM		Penetration of 6.5%	Penetration of 12%	Penetration of 6.5%	Penetration of 12%	Penetration of 6.5%	Penetration of 12%
	1	99	100	95	99	86	98
	2	99	100	93	99	80	98
	3	99	100	85	99	57	96
	6	73	98	16	82	3	51
	9	13	65	0	19	0	5

600 mg may provide 3 months duration of protection

IM = intramuscular; EC80 = drug concentration that gives 80% of maximum effect; EC87 = drug concentration that gives 87% of maximum effect; EC90 = drug concentration that gives 90% of maximum effect; 300 mg EVUSHELD IM = 150 mg tixagevimab and 150 mg cilgavimab; 600 mg EVUSHELD IM = 300 mg tixagevimab and 300 mg cilgavimab)

*PTA results with 1.8% penetration suggest no in vivo drug activity against BA.1.529

Sources: https://www.fda.gov/media/156674/download

Modeling Limitations

- PTA findings sensitive to assumed model input values
  - Target-site penetration coefficient
    - What is the relevant respiratory tract site(s) of drug action?
    - Can we specifically & accurately measure drug at principal sites of drug action?
  - Minimum protective concentration
    - Uncertainty in in vivo validity of using in vitro EC80 or EC90 values from a microneutralization assay, for which results are likely dependent on specific conditions and platform, as the PD metric associated with clinical protection
    - What EC50 fold change is clinically meaningful (inter-assay variability, etc.) ?
- Additional Considerations
  - No clinical PK-PD relationships or thresholds of protection have been identified
  - Predictive accuracy is not established for this translational PK-PD approach

Sources: https://www.fda.gov/media/156674/download

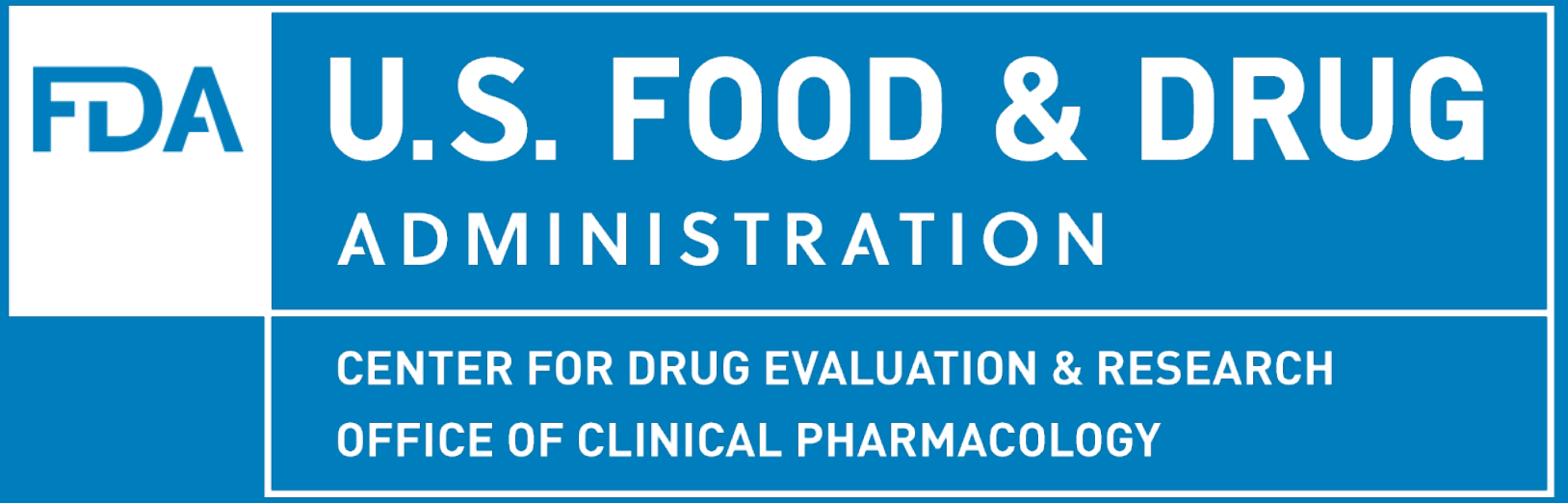
Modeling Strengths

- Dose selection approach in majority of Anti-SARS-Cov-2 spike mAbs clinical trial programs
- Some biologic/mechanistic plausibility
  - Evusheld directly neutralizes virus | No host cell-based killing[1]
    - in vitro system provide value into direct pathogen-drug interaction
  - MPC may block early replication | reduce risk of viral acquisition
- Helps identify uncertainty and can help explore impact of uncertainty
- Provides evidence to inform decision making
  - Integrates different sources of data | makes assumptions clear

Sources: [1] PMID: 35076282 [2] PMID: 35727916

Conclusions

- First revision to Evusheld EUA based on totality of scientific evidence available and favorable Benefit-Risk
- Translational PK-PD modeling played a part in supporting evidence available for regulatory decision
  - Suggested 300 mg Evusheld IM unlikely adequate against Omicron variants BA.1.1.529 & BA.1.1 (not shown)
  - Suggested 600 mg Evusheld IM may provide 3 months protection against Omicron variants BA.1.1.529
  - Logic: Increase probability of effectiveness through dose increase
- Translational PK-PD modeling has limitations and strengths that need to be considered when making decisions
  - Value of PTA as tool for relative comparisons between variants?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Emergency Use Authorization (EUA)

- EUA authority allows FDA to help strengthen the nation's public health protections against CBRN (chemical, biological, radiological, and nuclear) threats by facilitating the availability and use of medical countermeasures during public health emergencies.

Criteria for Issuance of an EUA

- ✓ Serious or life-threatening disease or condition
- ✓ Evidence of effectiveness ("may be effective" in treating the disease or condition; case-by-case basis)
- ✓ Risk-benefit analysis (based on the totality of scientific evidence available)
- ✓ No adequate, approved, and available alternatives

https://www.fda.gov/media/97321/download