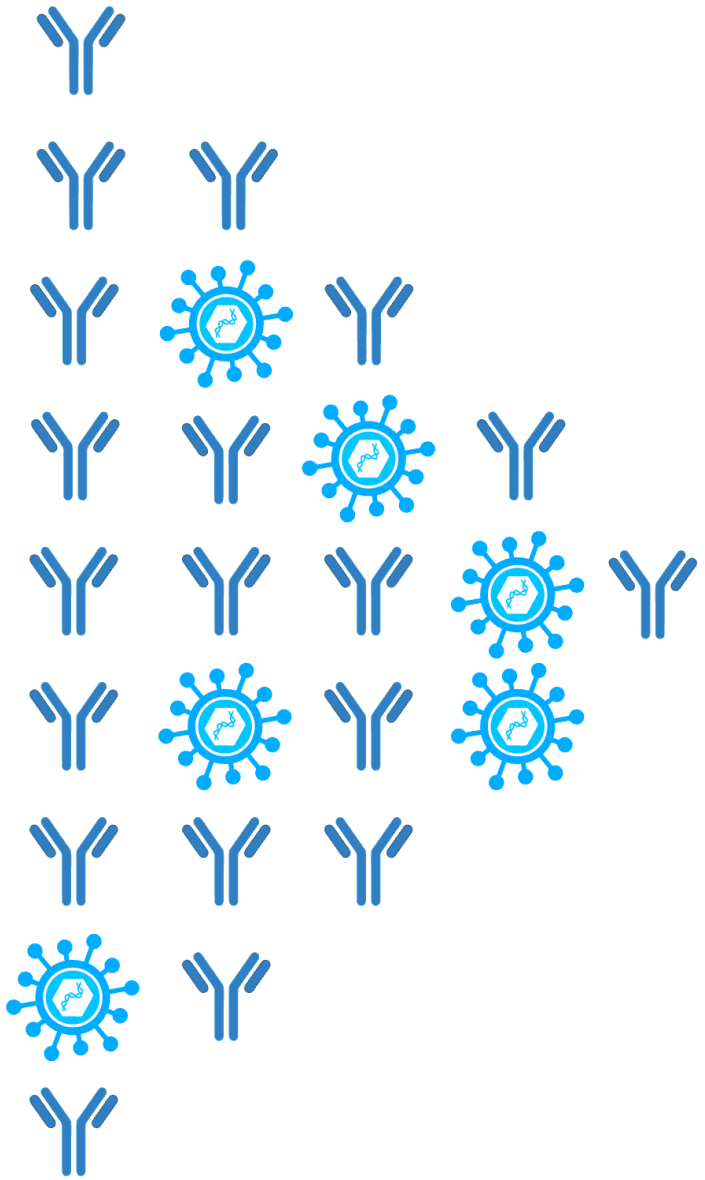

Challenges in Evidence Generation for Influenza mAbs: Industry Perspective

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A challenge for industry in mAb development: The Phase 2 dilemma

What are efficient ways to generate proof of efficacy to inform decision to advance or halt development?

Lessons learned from mAb trials

Why did some fail?

What are some new approaches to overcome failure?

Early- to Late-Stage: Phase 2 Considerations for mAb Development

PHASE 1
Is it safe?

PHASE 2
Is it likely to work?

PHASE 3
Is it safe & efficacious?

Vaccines	**Immunogenicity**: HAI titers as surrogate to predict clinical efficacy in preventing illness
Antivirals	**PK**: Drug concentration/EC relationship support development in treatment and prevention settings **Outcomes**: Viral load reduction and symptomatic recovery
Monoclonal Antibodies	**PK**: No accepted standard for a surrogate of protection, especially for non-systemic routes of administration **Outcomes:** **Human Challenge**: may not accurately predict human efficacy in setting of natural infection; phase 2 field efficacy still required **Field Efficacy**: large undertaking and risk of false negative outcomes (e.g., low flu activity)

Frequently Used Influenza Case Definitions for Influenza Prevention Trials

Efficacy Endpoints with
Positive RT PCR for Influenza

					Relative efficacy (95% CI)		
Endpoint	**Source**	**Fever Threshold**	**Fever Required?**	**Symptoms Required**	**Phase 2** **VIR2482 (1200mg) vs Placebo[1]** 18-64 years; N=1,975	**Phase 3** **Fluzone HD vs SD[2]** ≥65 years; N=31,989	**Phase 3** **Flublok vs Fluarix[3]** ≥50 years; N=9,003
Primary	**Protocol**	Varies	No	New onset or worsening of at least 1 systemic symptom and at least 1 respiratory symptom*	**Not met** **15.9%** (-49.3, 52.6) Fever definition T > 37.8º C	**Met superiority** **24.2%** (9.7, 36.5) Fever definition T > 37.2º C	**Met superiority** **30%** (10, 47) Fever definition T > 37.2º C
Secondary	**WHO**	≥ 38.0º C	Yes	Cough	**44.13%** (-50.5, 79.3)	N/A	N/A
Secondary	**CDC**	≥ 37.8º C	Yes	Cough and/or sore throat	**57.2%** (-2.5, 82.1)	N/A	**35%** (8, 54)

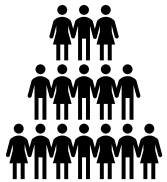
*New onset or worsening of at least 1 systemic symptom: chills, tiredness, headaches, myalgia or joint pain, or fever. New onset or worsening of at least 1 respiratory symptom: sore throat, cough, sputum production, wheezing, or difficulty breathing. N/A: not available.

1. Tan SK, et al. *Clin Infect Dis.* 2024;79(40:1054-1061. 2. DiazGranados CA, et al. *NEJM.* 2014; 371:635-645. 3. Dunkle LM, et al. *NEJM.* 2017;376:2427-2436.

New influenza study expected to read out this month

Phase 2 NCT06609460

CD388: long-acting zanamivir-Fc conjugate



18-64 years
N = 5,041

3 dose levels vs placebo
Subcutaneous injection

Primary efficacy endpoint definition(s)	**PCR-confirmed** influenza *and* **Temp** ≥ 38.0º C *and* **≥2 Symptoms** • ≥2 Respiratory symptoms, or • 1 Respiratory symptom and 1 Systemic symptom

Considerations for Trial Designs for a Phase 2 Proof-of-Concept Study

Purpose of Phase 2 is to understand potential for efficacy to inform decision to advance development

- **Sample size assumptions: What is considered a clinically meaningful efficacy signal?**
  - VIR2482: ≥ 70%
  - CD388: ≥ 50%

- **Onset of efficacy endpoint collection**
  - Vaccine trials — From Day 14 following administration
  - CD388 — From Day 8 after administration
  - VIR2482 — From Day 1 (day of administration)

Relative Risk Reductions

VIR 2482 at 1200mg vs. placebo[1]	Cases from Day 1 onwards	Cases from Day 8 onwards
Protocol-defined cases	15.9% (-49.3, 52.6) n = 23 in pbo, 21 in VIR	34.0% (-25.7, 65.3) n = 23 in pbo, 15 in VIR
CDC-defined cases	57.2% (-2.5, 82.1) n = 17 in pbo, 7 in VIR	64.9% (-3.9. 87.2) n = 15 in pbo, 5 in VIR
WHO-defined cases	44.13 (-50.5, 79.3) n = 11 in pbo, 6 in VIR	42.9% (-69.7, 81) n = 19 in pbo, 5 in VIR

1. Tan SK, et al. *Clin Infect Dis.* 2024;79(40):1054-1061.

Influenza mAb Human Challenge and Phase 2 Field Trials

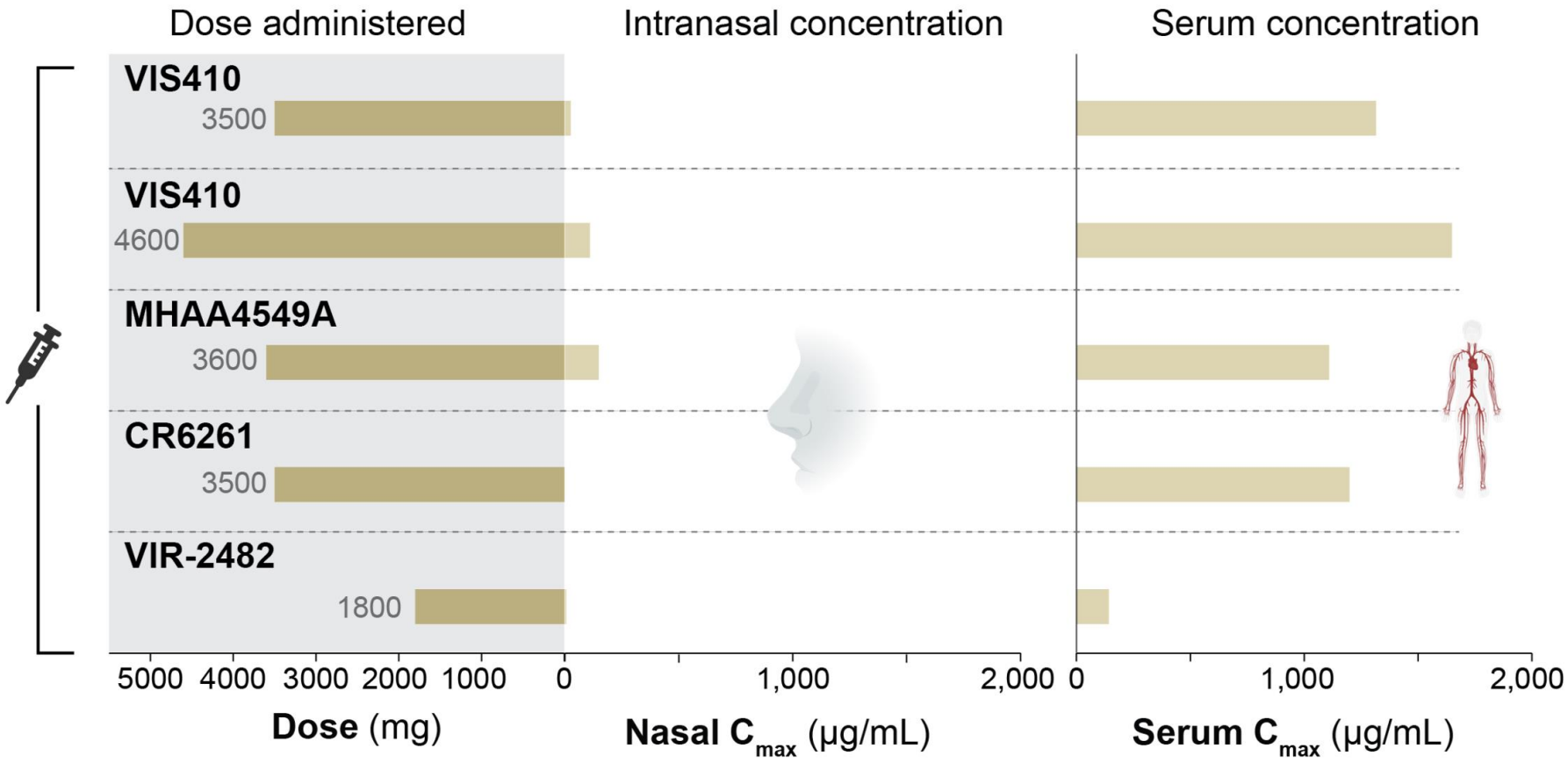
All are systemically administered and most did not meet efficacy endpoint

Human Challenge Trials				
Antibody	**MHAA 4549A (1)**	**CR8020 (2)**	**CR6261 (3)**	**VIS410 (4)**
Activity	**Flu A**	**Flu A2**	**Flu A1**	**Flu A**
Route	IV, -24hr or -36hr	IV, -2days	IV, +24hr	IV, +24hr
Design	H3N2	H3N2	H1N1	H1N1
Dose	1 x 400mg, 1200mg, 3600mg	1 x 15mg/kg	1 x 50mg/kg	1 x 2300mg, 4600mg
Efficacy endpoint	Viral load	Viral load	Viral load	Viral load
Outcome	**Only met at the highest dose of 3600mg**	**Not met**	**Not met**	**Primary endpoint met**

Phase 2 Field Trials				
Antibody	**VIR-2482 (5)**	**VIS410 (6)**	**MEDI8852 (7)**	**MHAA4549A (8)**
Activity	**Flu A**	**Flu A**	**Flu A**	**Flu A**
Route	IM	IV	IV	IV
Design	Prevention	Treatment outpatient	Treatment outpatient	Treatment hospitalized
Dose	1 x 450mg or 1200mg	1 x 2000mg, 4000mg	1 x 750mg, 3000mg w/wo oseltamivir	1 x 3600mg, 8400mg AND oseltamivir
Efficacy endpoint	Protocol defined ILI	Flu symptoms, viral load	Flu symptoms	Removal of oxygen supp in hosp with severe flu
Outcome	**Not met**	**Primary endpoint met**	**Not met (similar to oseltamivir alone)**	**Not met (similar to oseltamivir alone)**

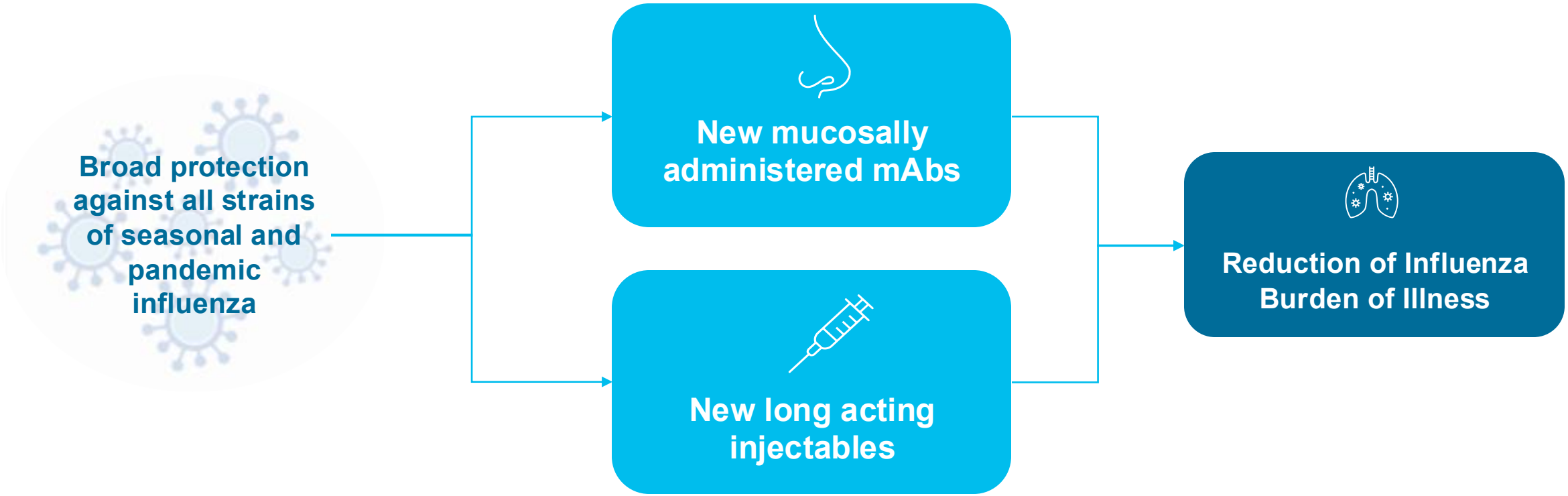
1. McBride JM, et al. *Antimicrob Agents Chemother.* 2017 ;61(11) :e01154-17. 2. Beigel JH, Hayden FG. *Cold Spring Harb Perspect Med.* 2021;11(4):a038463. 3. Han MJ, et al. *Clin Infect Dis.* 2020 ;70(5) :748-753. 4. Sloan SE, et al. *Antivir Res.* 2020 ;184 :104763. 5. Tan SK, et al. *Clin Infect Dis.* 2024;79(40):1054-1061. 6. Hershberger E, et al. *EBioMedicine.* 2019;40:574-582. 7. Omar Ali S, et al. *Antimicrob Agents Chemother.* 2018;62(11):e00694-18. 8. Lim JJ, et al. *Antimicrob Agents Chemother.* 2020;64(7):e00352-20.

Systemically-administered mAbs have low mucosal levels even at high doses



Submitted manuscript

Challenges and Opportunities for Development of mAb against Influenza



Novel insights from development of new modalities:

- Develop new surrogates of protection
- Create differentiated models for preclinical and clinical testing
- Identify ways to complement vaccine-induced immunity