Got anything for this cough?

Finding treatments for early COVID-19

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Protocol Co-Chair ACTIV-2

Professor of Medicine, UC San Diego

TikTok & Twitter @DaveySmithMD

August 13, 2021

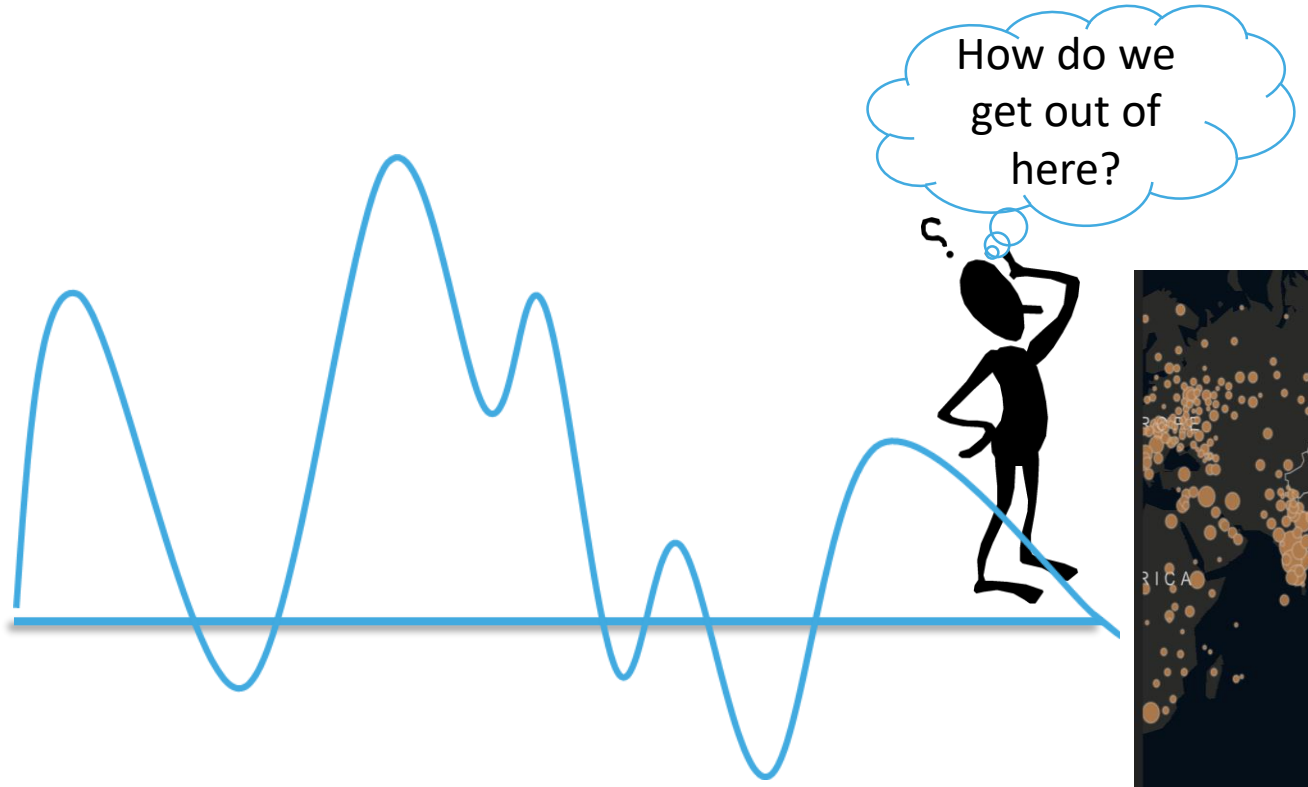
RISE ABOVE COVID

Smith Disclosures

- Consultant for
  - Bayer, Arena and Kiadis Pharmaceuticals
  - Matrix Biomed

- Scientific Advisory Board
  - FluxErgy
  - Linear Therapies

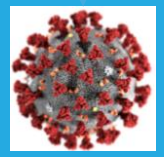
RISE ABOVE COVID



https://coronavirus.jhu.edu/map.html

Natural history

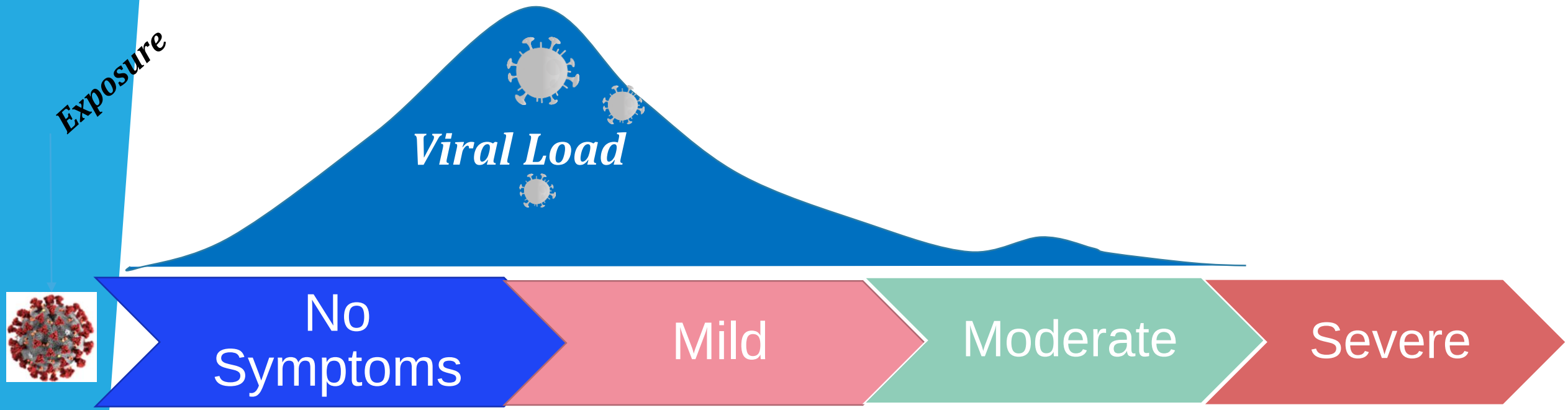
Exposure



No Symptoms → Mild → Moderate → Severe

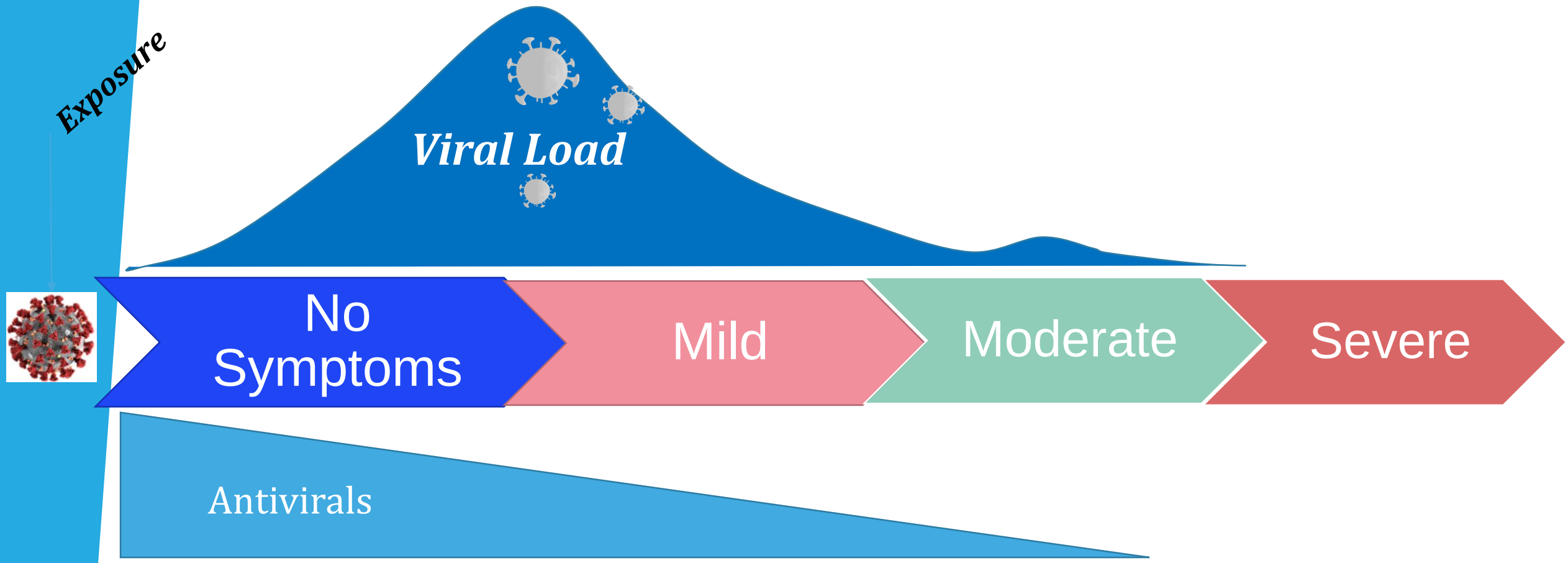
Courtesy of A. Chaillon

Viral Stage



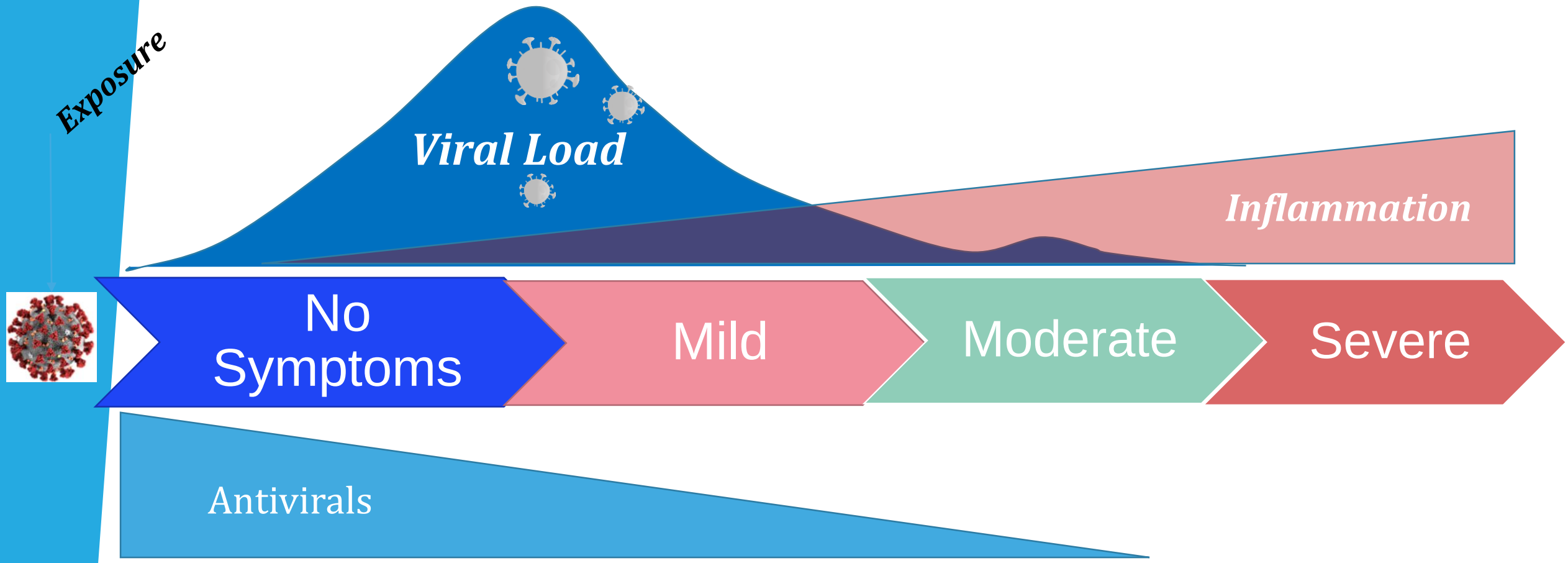
Courtesy of A. Chaillon

Use Antivirals



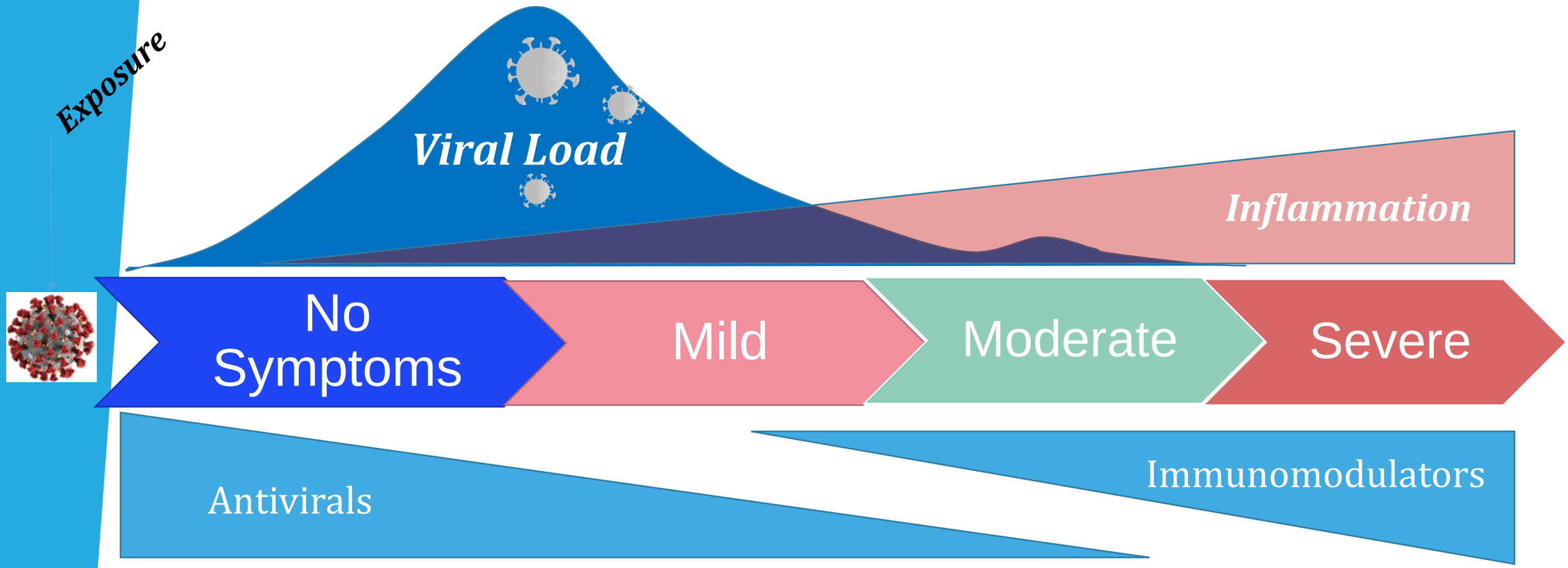
Courtesy of A. Chaillon

Inflammatory Stage



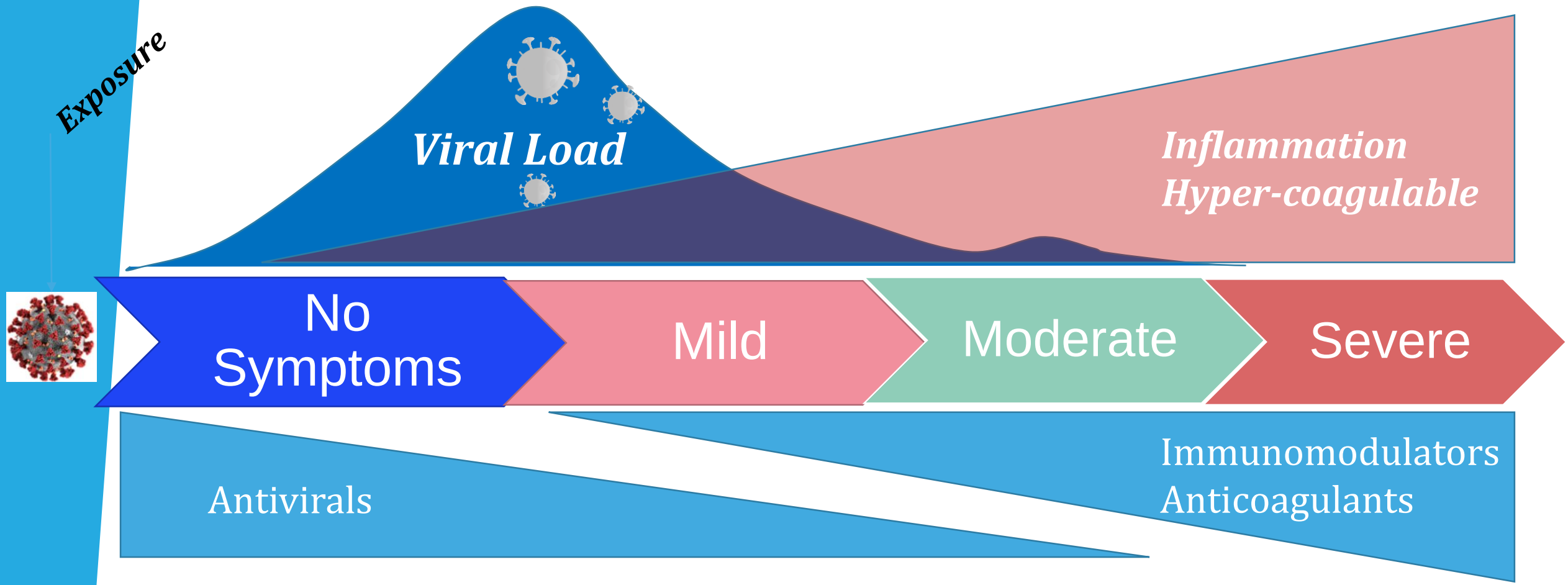
Courtesy of A. Chaillon

Immune Modulatory Drugs



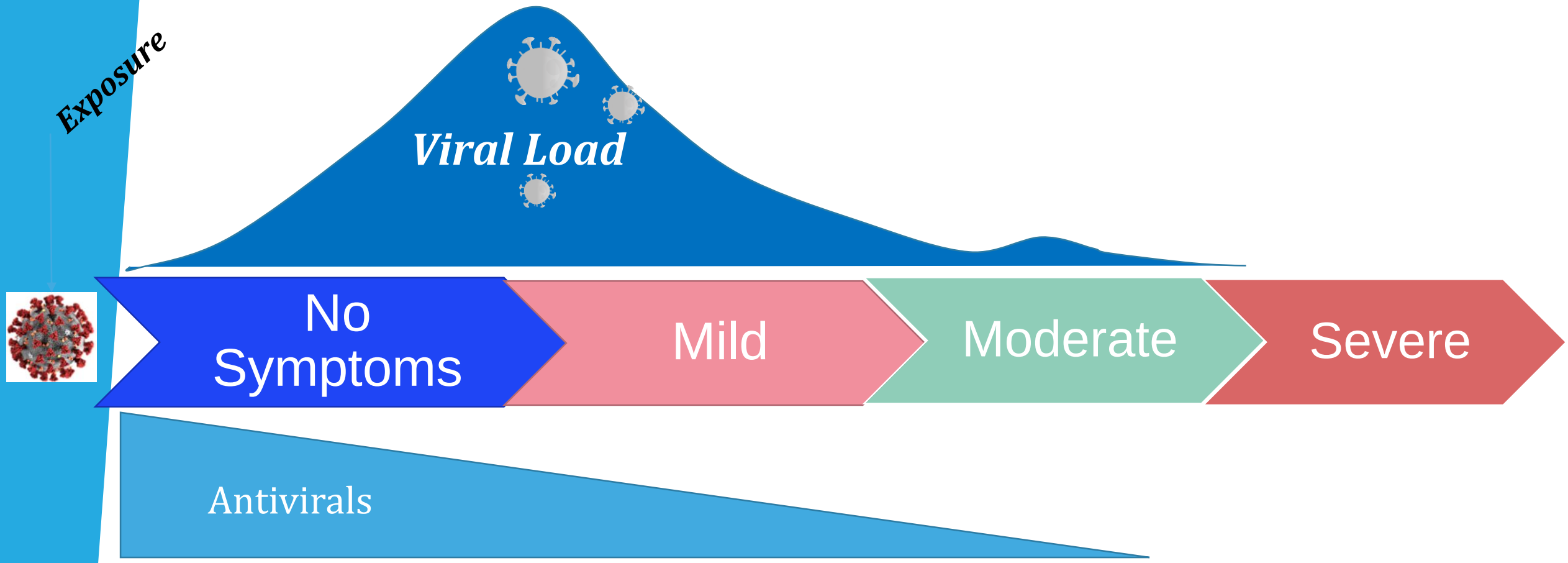
Courtesy of A. Chaillon

Coagulopathy



Courtesy of A. Chaillon

EARLY COVID= Antivirals



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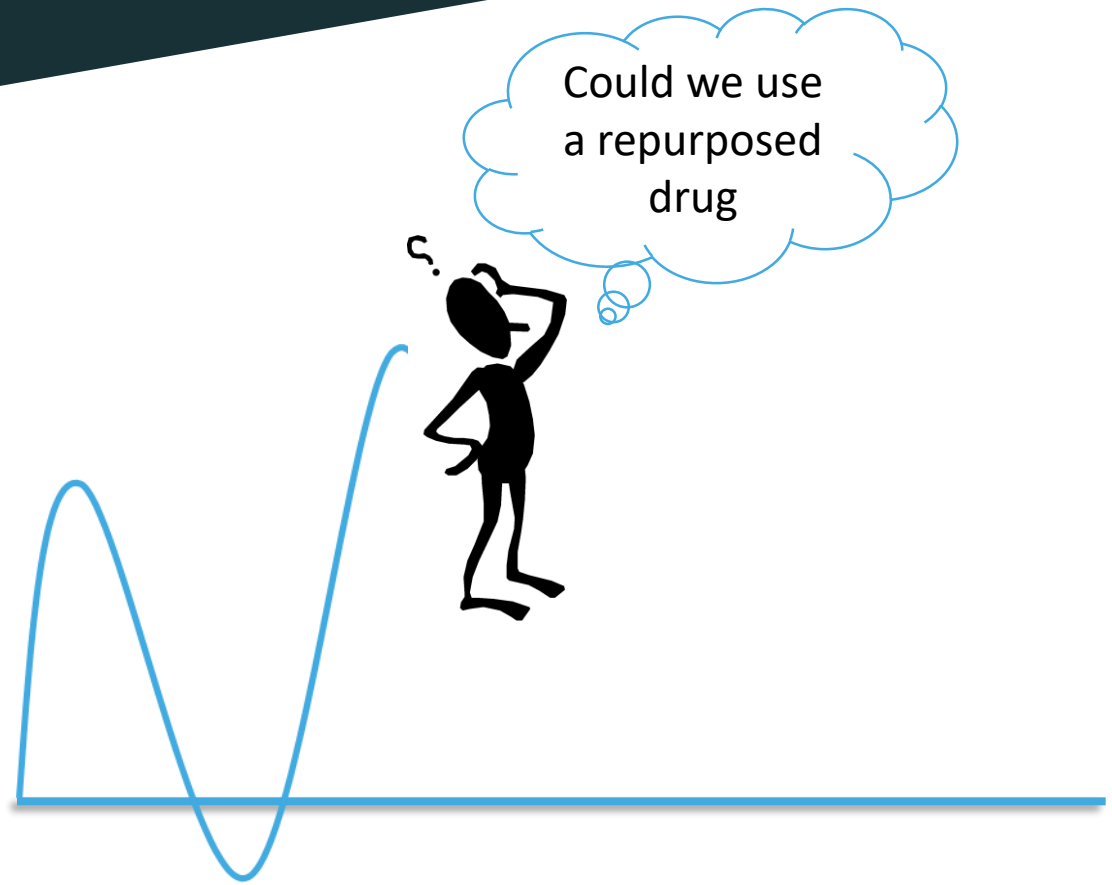
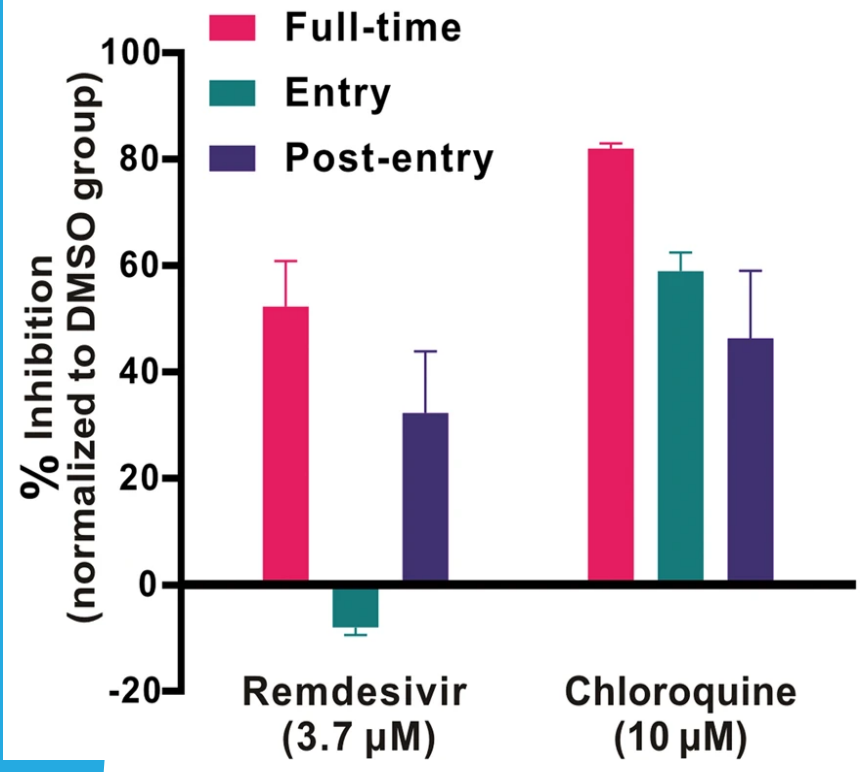
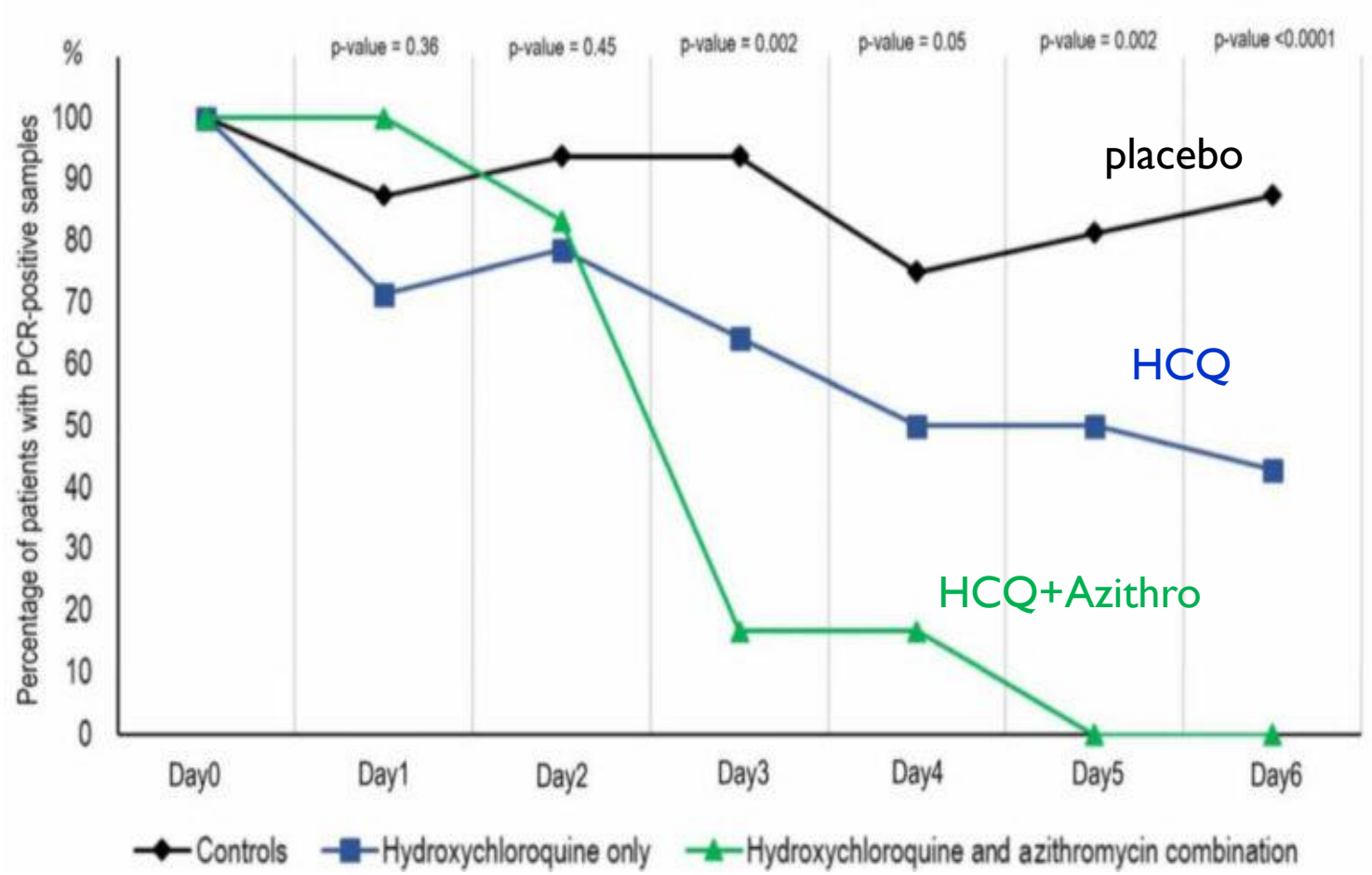

Could we use
a repurposed
drug

Hydroxychloroquine: in vitro and in vivo



Wang et al. Cell Research 2020



Gautret P, et al. Int J Antimicrob Agents 2020

Tragedy of HCQ

March 21st Trump Tweet

Donald J. Trump
@realDonaldTrump

HYDROXYCHLOROQUINE & AZITHROMYCIN, taken together, have a real chance to be one of the biggest game changers in the history of medicine. The FDA has moved mountains - Thank You! Hopefully they will BOTH (H works better with A, International Journal of Antimicrobial Agents).....

10:13 AM · Mar 21, 2020 · Twitter for iPhone

Tragedy of HCQ

- March 21st Trump Tweet
- March 28th FDA EUA

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Tragedy of HCQ

- March 21st Trump Tweet
- March 28th FDA EUA
- HAz COVID Trial for early COVID launched in 6 weeks after call
- Multiple observational studies of HCQ in late COVID
- June 15th EUA Revoked
- Haz COVID Trial Stopped

New Opportunity

ACTIV2 / Adapt Out COVID

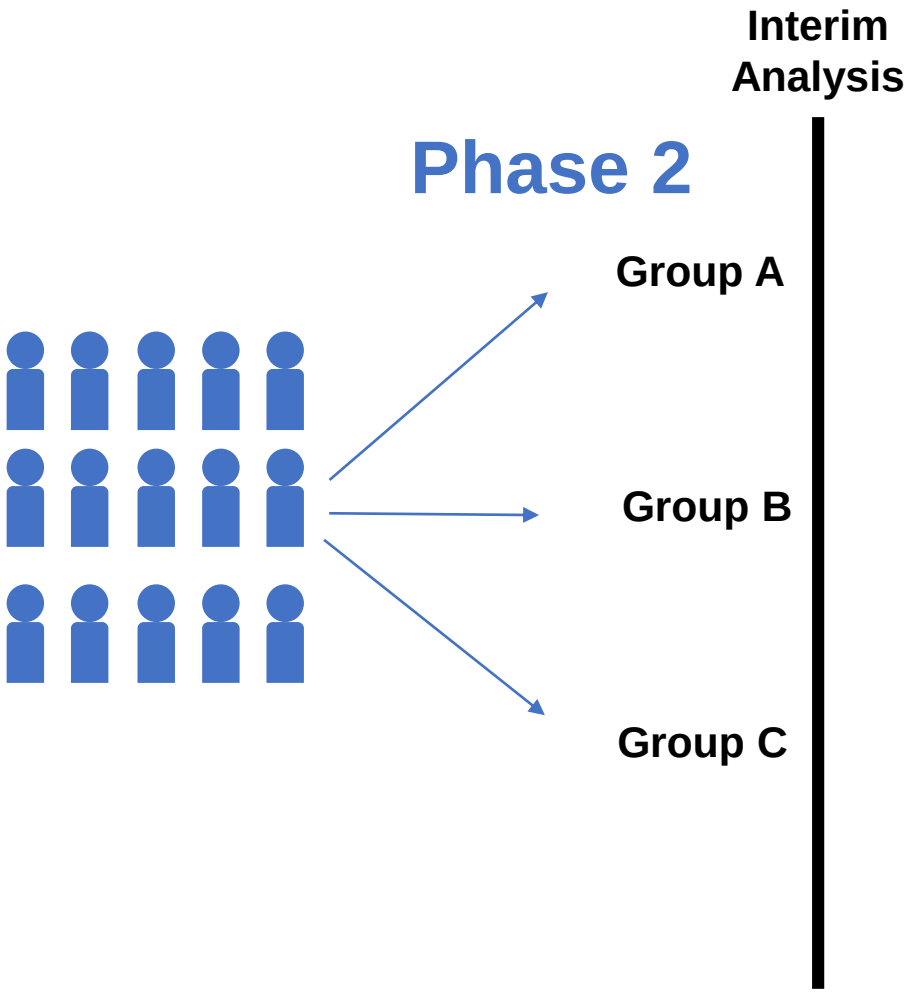
We need science

- Clinical Trials
- Keywords
  - Adapt
  - Platform
  - Seamless
  - Bayesian

https://musicchartsarchive.com/singles/huey-lewis/i-want-a-new-drug

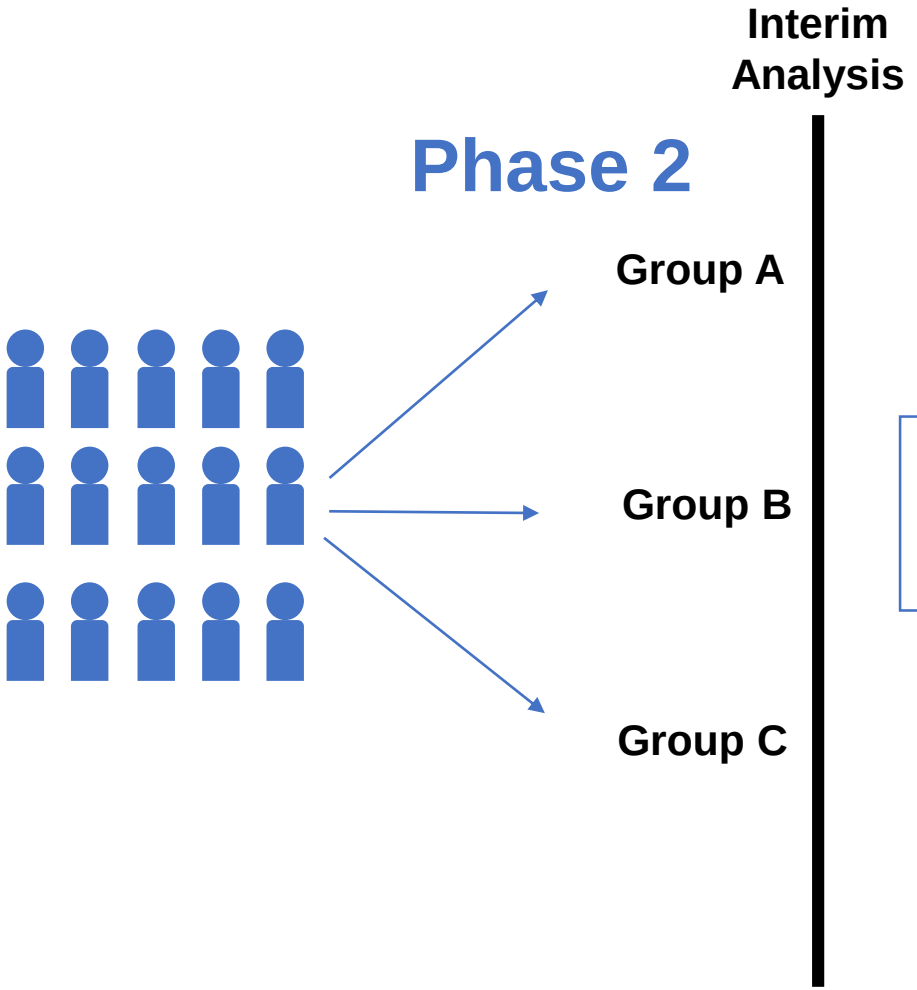
What is an Adaptive Platform Trial?

Phase 2/3 Platform



Woodcock, J. & LaVange, L. M. *N. Engl. J. Med.* **377**, 62–70 (2017).

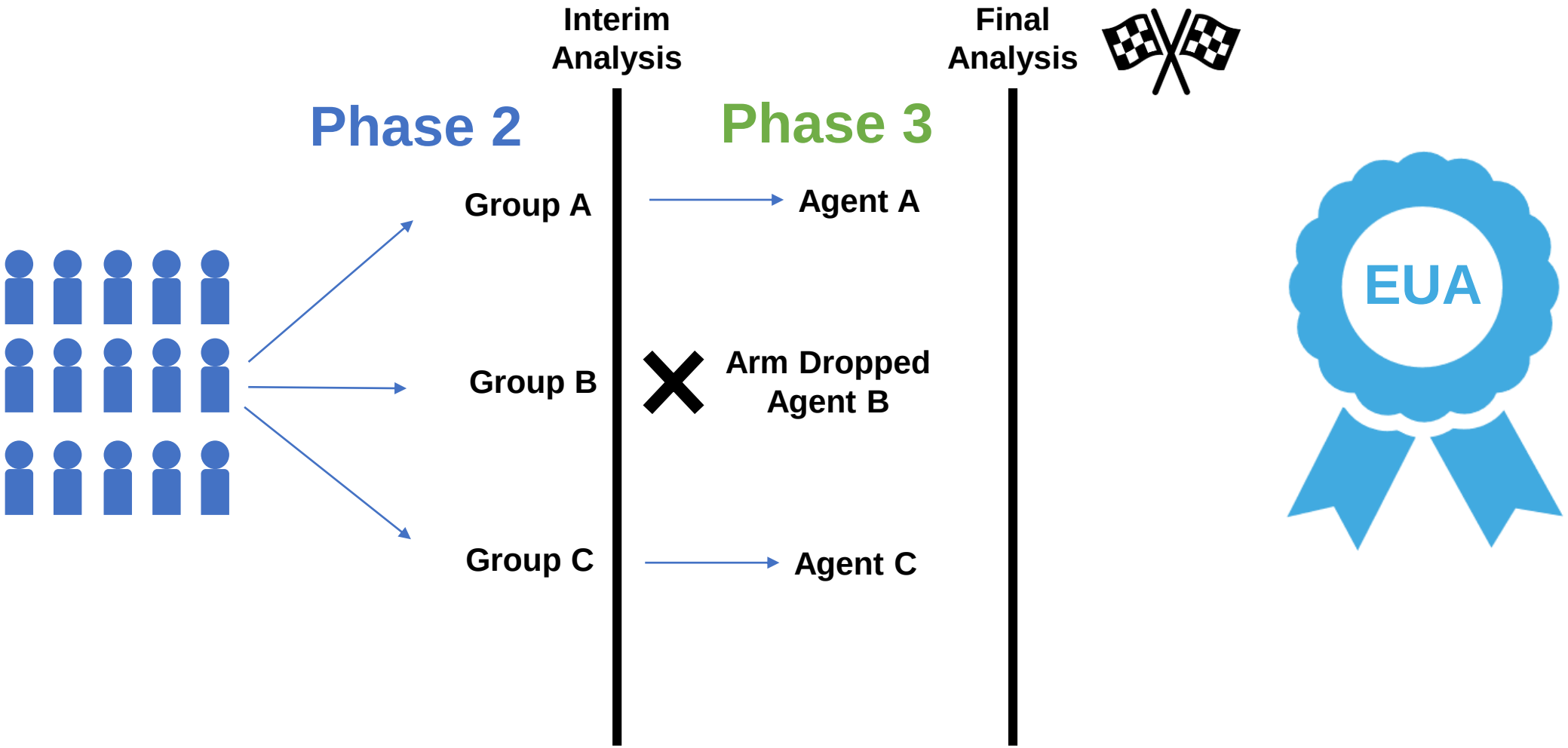
Phase 2/3 Platform



Interim Analysis
Does the agent show some measure of efficacy?
(Like symptoms or viral loads or hospitalizations)

Woodcock, J. & LaVange, L. M. *N. Engl. J. Med.* **377**, 62–70 (2017).

Phase 2/3 Platform



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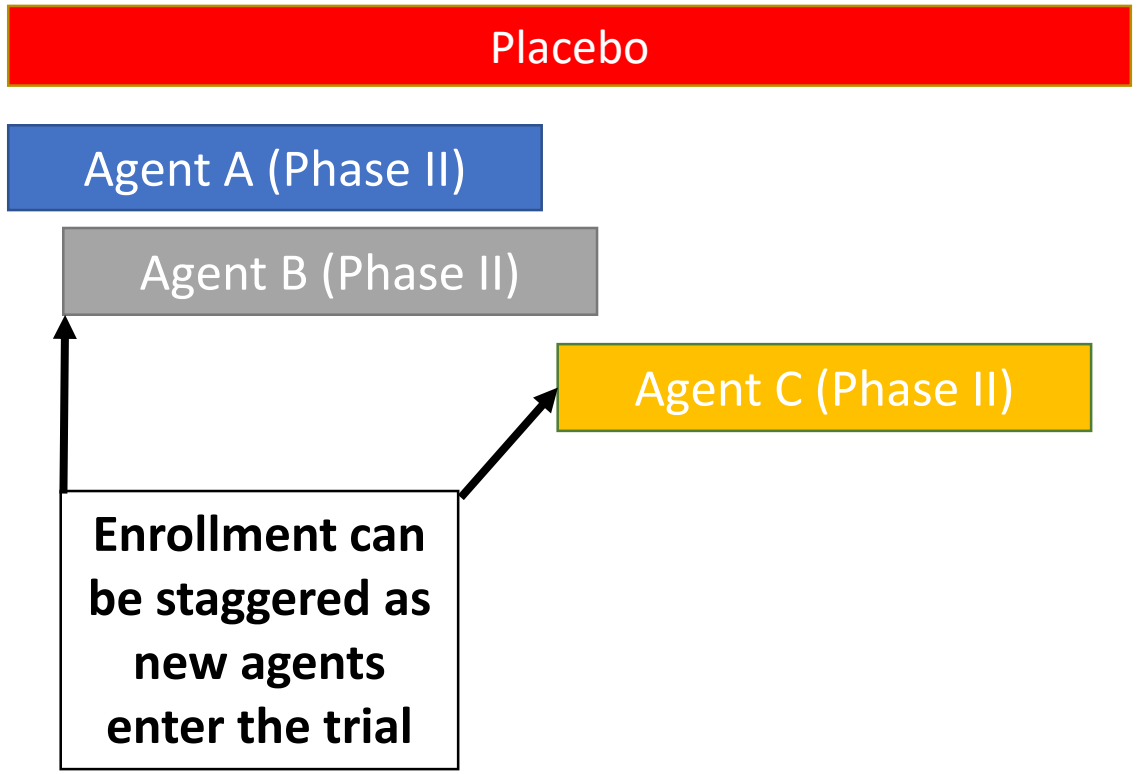

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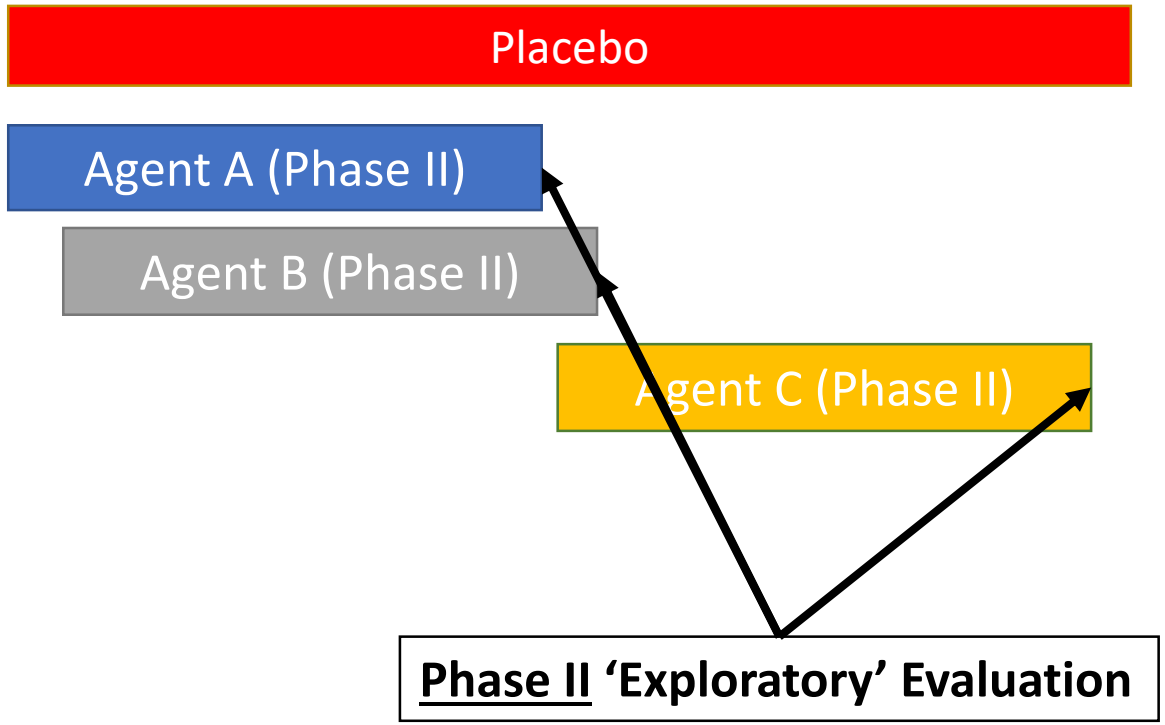

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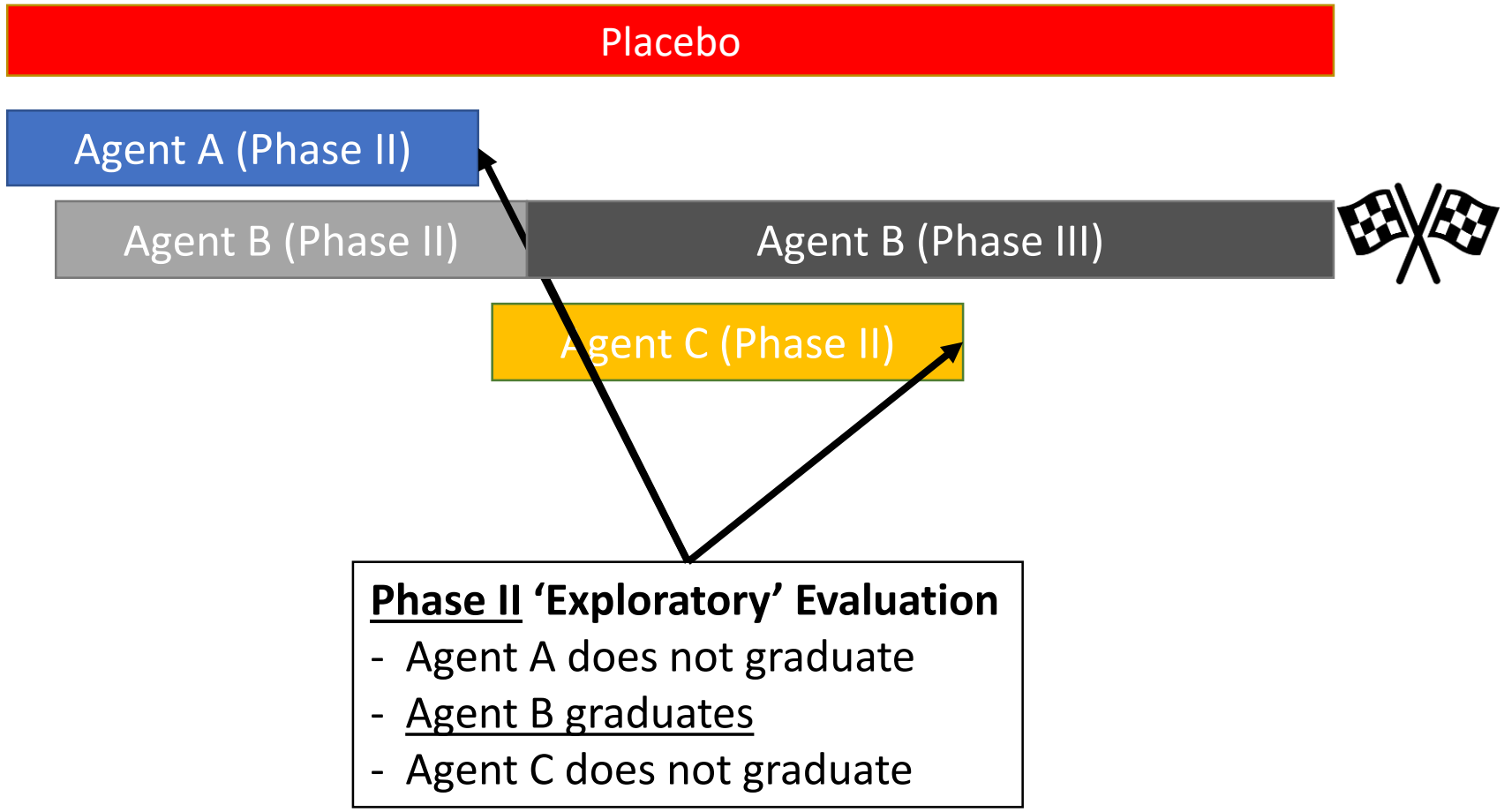
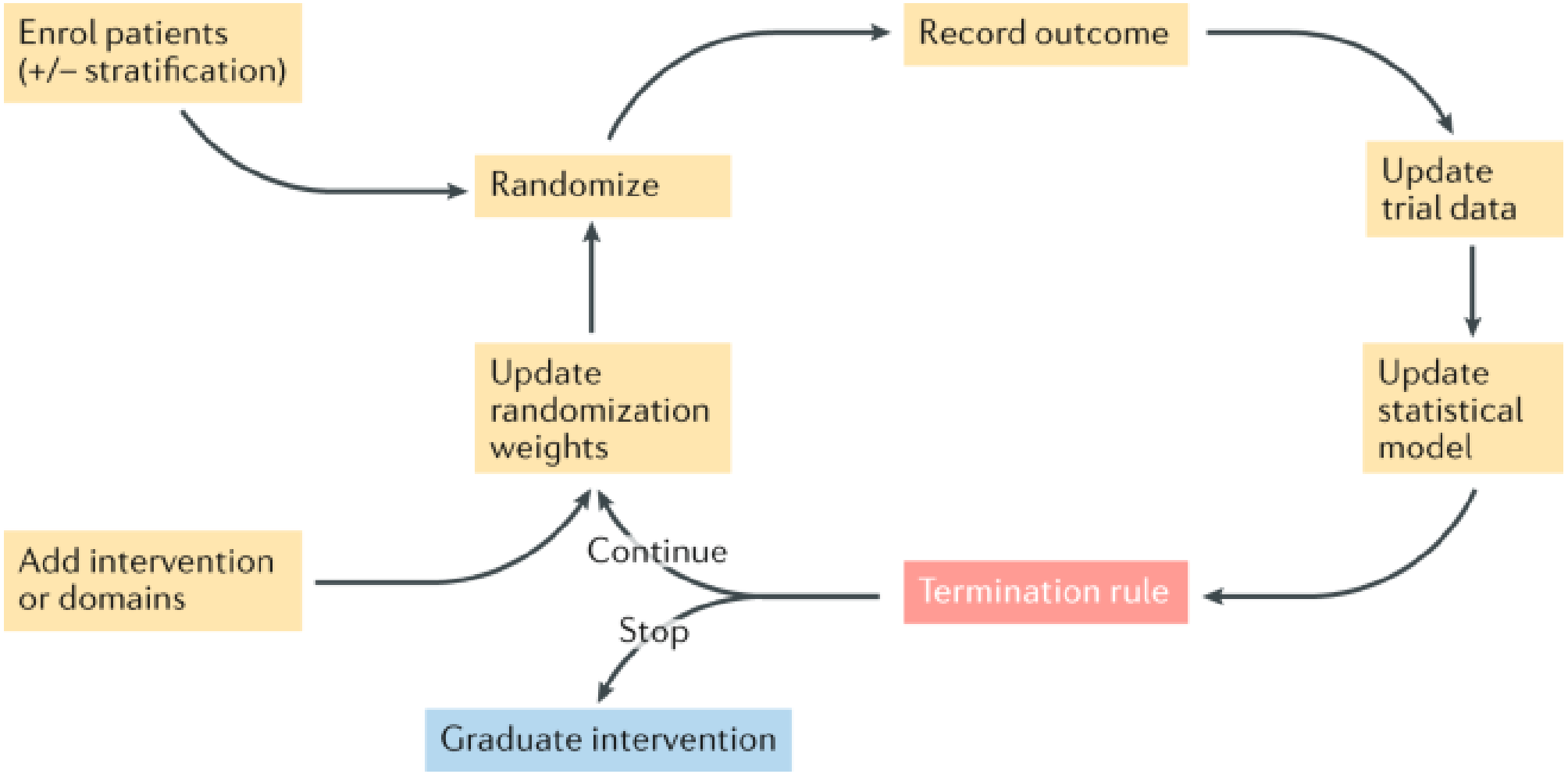


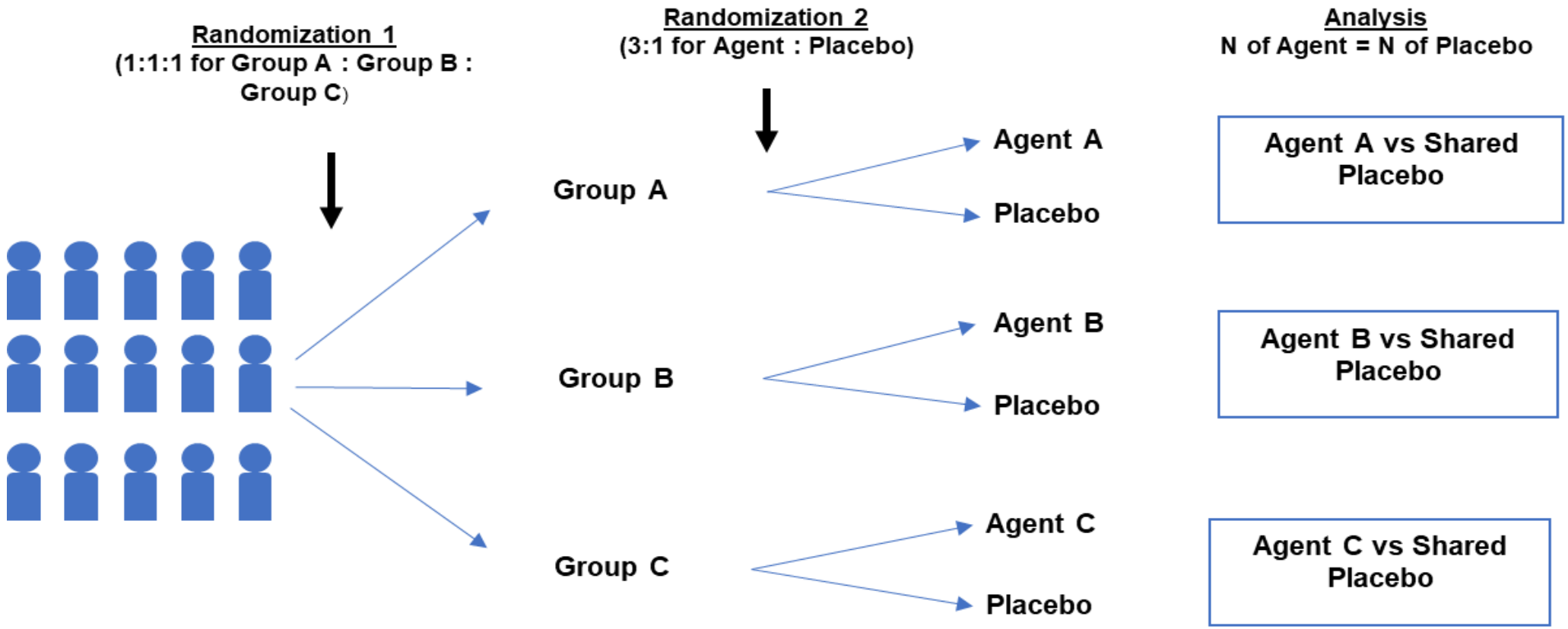
Woodcock, J. & LaVange, L. M. *N. Engl. J. Med.* **377**, 62–70 (2017).

Adaptation



The Adaptive Platform Trials Coalition., Angus, D.C., Alexander, B.M. *et al.* Adaptive platform trials: definition, design, conduct and reporting considerations. *Nat Rev Drug Discov* **18,** 797–807 (2019).

Randomization and Placebo Efficiency



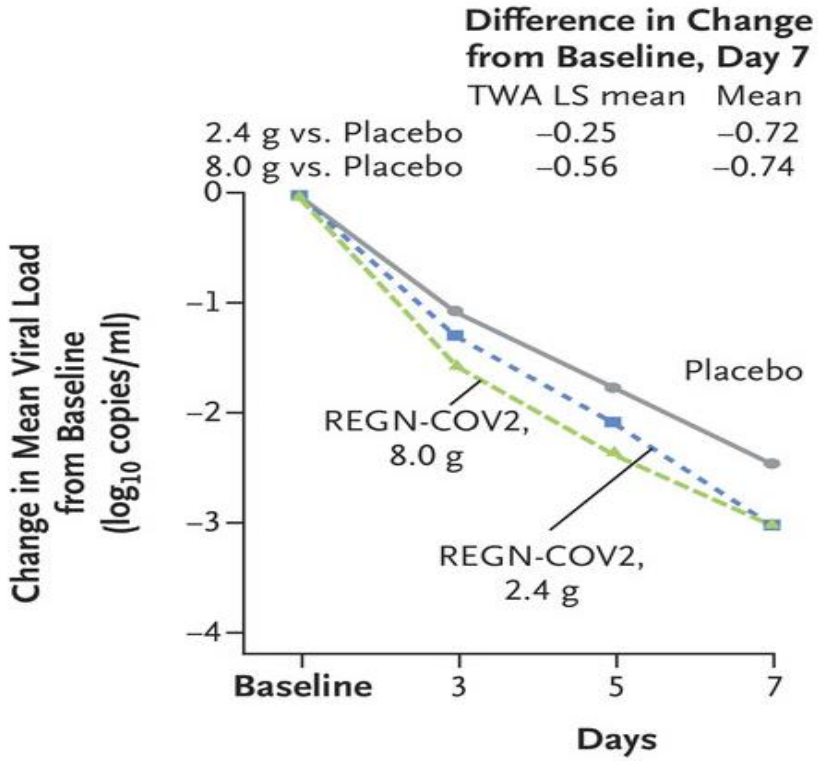
- When Agents A, B and C are enrolling in either Phase II or Phase III
- When participants are eligible for each agent

How do we know if an antiviral works?

- Anti-virus
  - Reduce viral replication
- Clinically
  - Reduce symptoms
  - Reduce disease
    - Hospitalizations
    - Death

Casirivimab and Imdevimab

- **Viral Loads**
  - 275 patients randomized 1:1:1 to receive 8 g cocktail (n=90), 2.4 g cocktail (n=92) or placebo (n=93).



No. at Risk				
Placebo	81	70	78	78
REGN-COV2, 2.4 g	73	66	69	70
REGN-COV2, 8.0 g	74	70	73	73

Weinreich et al. NEJM Dec 2020.

Casirivimab and Imdevimab

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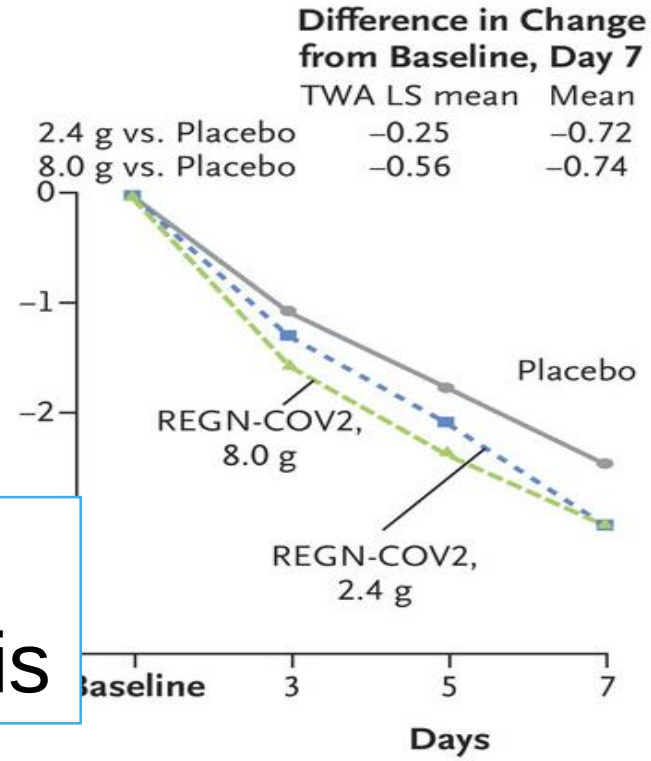
  - 275 patients randomized 1:1:1 to receive 8 g cocktail (n=90), 2.4 g cocktail (n=9), placebo (n=93)

President Trump was treated with this



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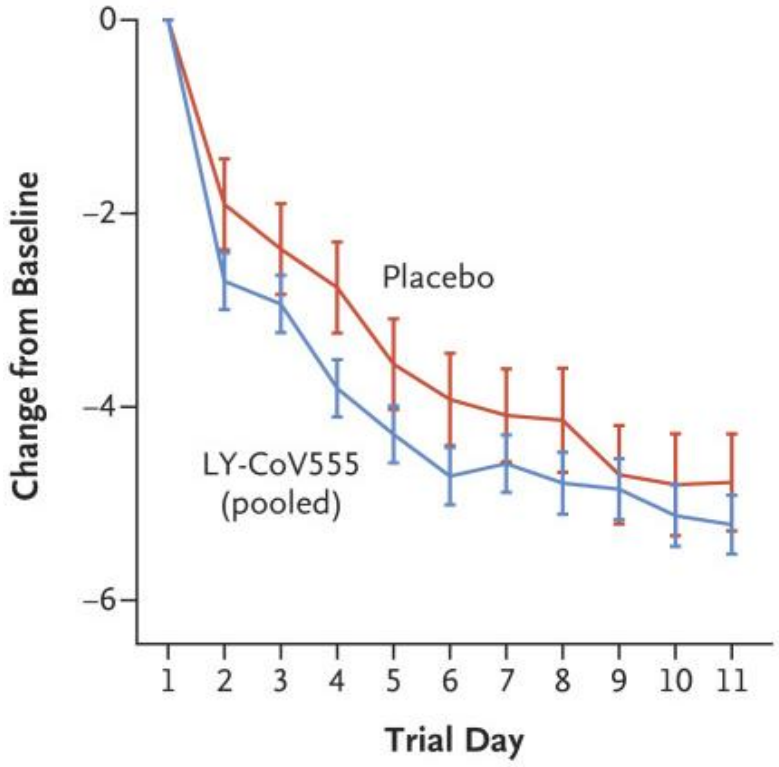
Bamlanivimab (LY-CoV555)

- **Symptom scores**
  - 452 persons received LY-CoV555 in one of three doses (700 mg, 2800 mg, or 7000 mg) or placebo



	Delta Value (95% CI)
Day 2	−0.79 (−1.35 to −0.24)
Day 3	−0.57 (−1.12 to −0.01)
Day 4	−1.04 (−1.60 to −0.49)
Day 5	−0.73 (−1.28 to −0.17)
Day 6	−0.79 (−1.35 to −0.23)
Day 7	−0.50 (−1.06 to 0.07)
Day 8	−0.65 (−1.28 to −0.02)
Day 9	−0.15 (−0.75 to 0.45)
Day 10	−0.32 (−0.94 to 0.29)
Day 11	−0.44 (−1.02 to 0.15)

Chen et al. NEJM Oct 2020.

Bamlanivimab (LY-CoV555)

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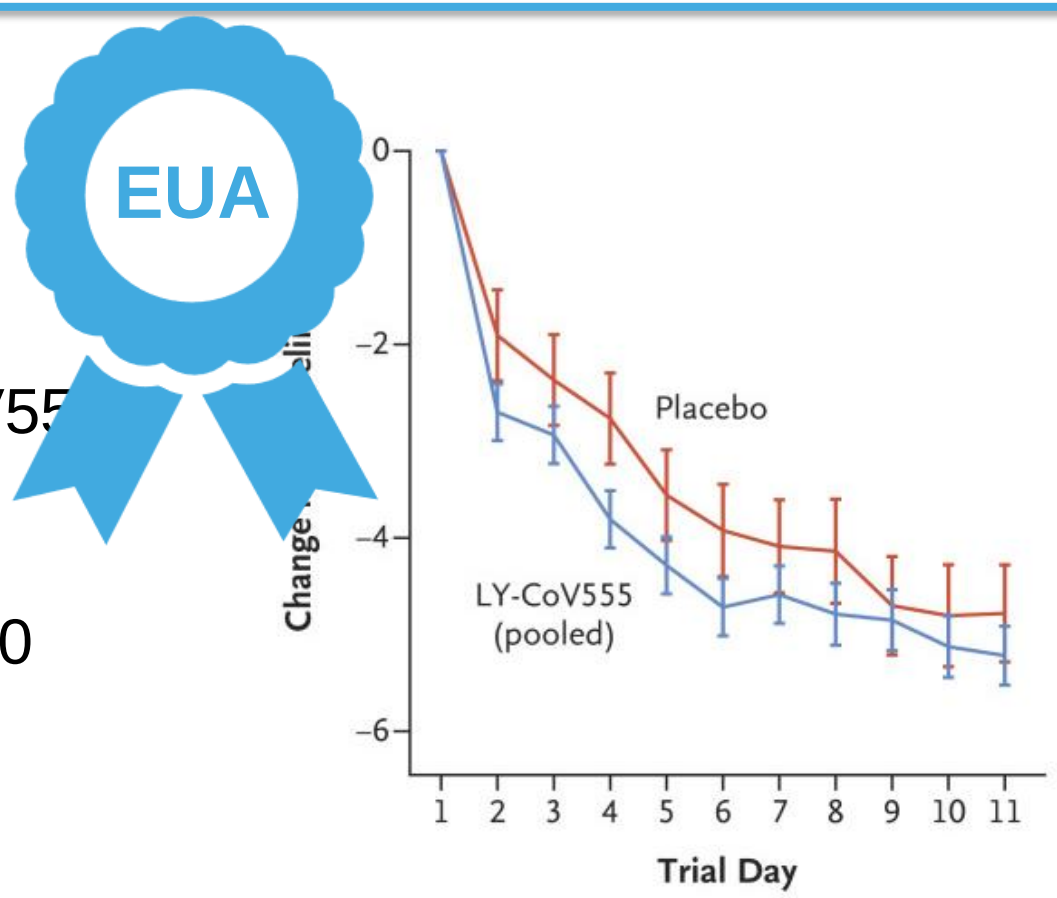

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Chen et al. NEJM Oct 2020.

Bamlanivimab (LY-CoV555)

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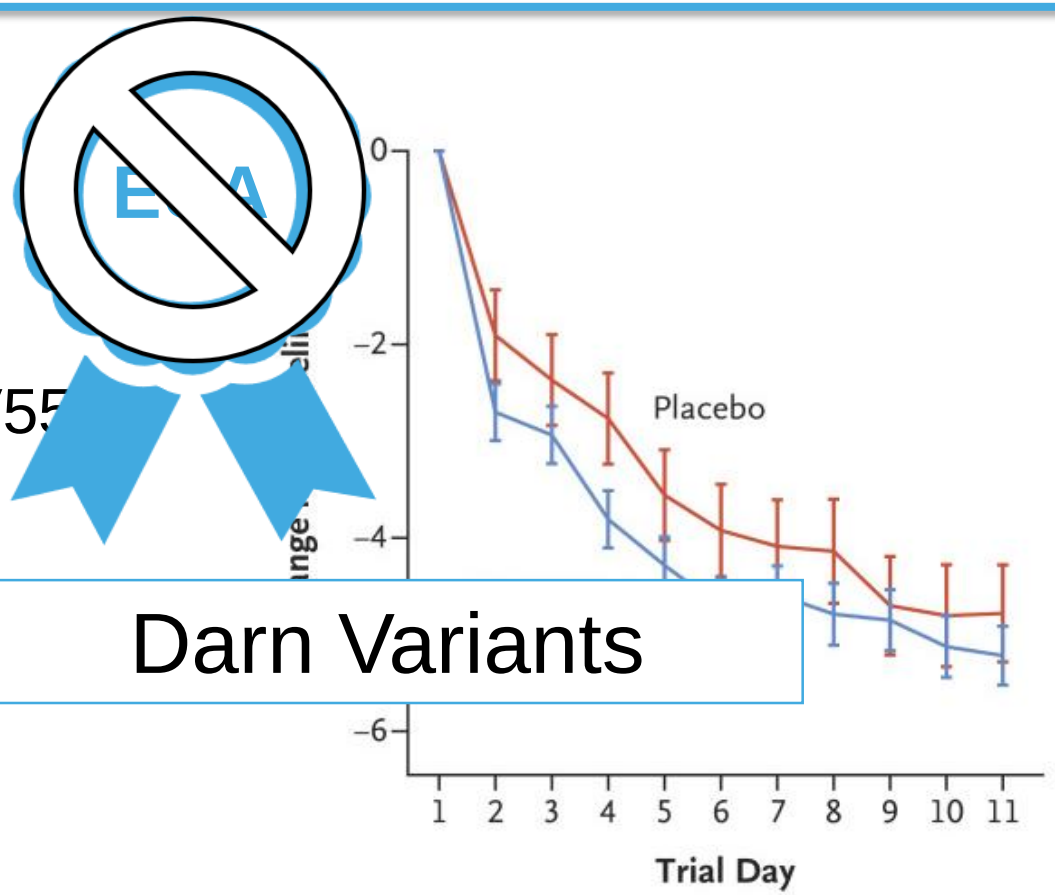

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Darn Variants

Chen et al. NEJM Oct 2020.

Bamlanivimab + Etesevimab

COVID-19 RELATED HOSPITALIZATION OR DEATH BY ANY CAUSE BY DAY 29

	N	Events	Rate	*p*
Placebo	517	36	7.0%	-
Bamlanivimab 2800 mg + Etesevimab 2800 mg	518	11	2.1%	0.0004

70% reduction vs. placebo

DEATH BY ANY CAUSE BY DAY 29

	N	Events	Rate
Placebo	517	10[†]	1.9%
Bamlanivimab 2800 mg + Etesevimab 2800 mg	518	0	0%

No deaths of any cause with antibody therapy

Lily Press Release Jan 26, 2021

Bamlanivimab + Etesevimab

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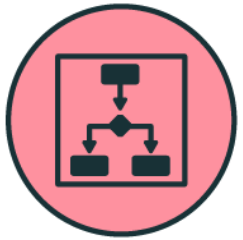

Randomized, blinded, controlled platform that allows agents to be added and dropped during the study

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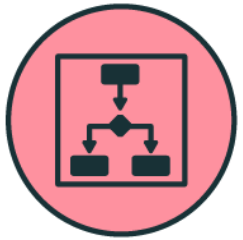

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Begins with **phase II** followed by a larger **phase III** for promising agents

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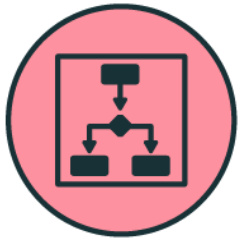


Randomized, blinded, controlled platform that allows agents to be added and dropped during the study

Begins with **phase II** followed by a larger **phase III** for promising agents

When two or more new agents are being tested concurrently, the **same placebo will be used**, if feasible

AGENT SELECTION

PRIORITIZED BASED ON:

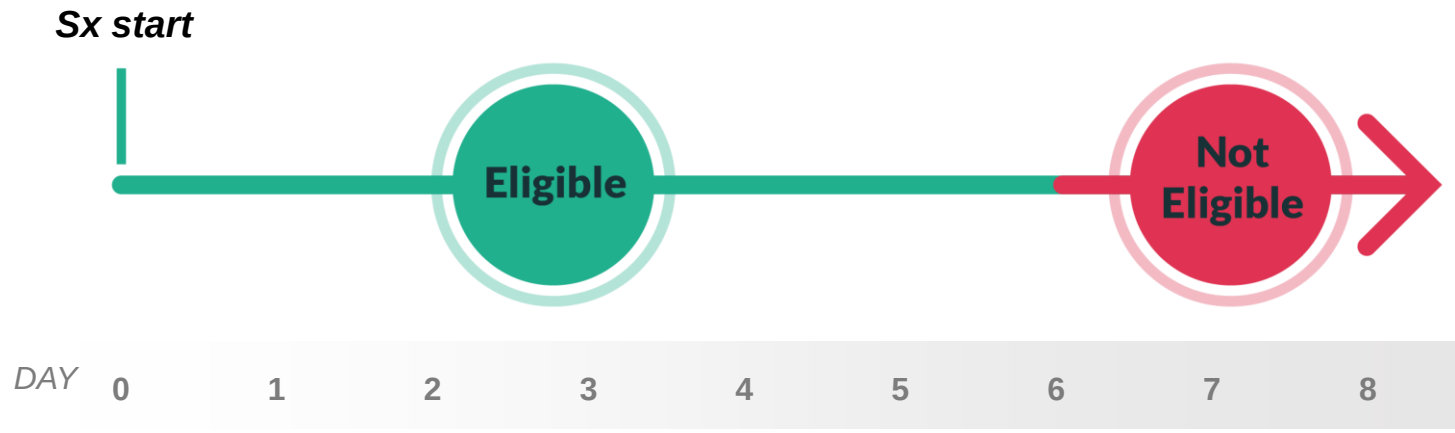
Activity against SARS CoV-2 entry or replication

Phase I pharmacokinetic and safety data

Potential to expand to Phase III if found effective

STUDY ELIGIBILITY

- Ambulatory Adult (≥18 years)
- Diagnosis of active CoV-2 infection ≤10 days prior to Entry
- At least one COVID-19 symptom for **≤10** days prior to Entry, and at least one symptom present within 24 hours of entry
- Infused Agents: Higher Risk Only
- Non-infused agents: All Risk



Over the study the start of symptoms reduced from 10 to 8 to 7

STRATIFICATION

Higher risk of COVID-19 progression:

- Age ≥60 years
- Or any age with a protocol-specified condition or co-morbidities
- Unvaccinated (new)

Time from symptom onset (≤ or >5 days)

SYMPTOM DIARY FOR SEVERITY SCORE

Now in an ***electronic form***!

POST ACUTE COVID

- Feeling feverish
- Cough
- Shortness of breath or difficulty breathing
- Sore throat
- Body pain or muscle pain/aches
- Fatigue
- Headache
- Chills
- Nasal obstruction or congestion
- Nasal discharge
- Nausea
- Vomiting
- Diarrhea

PHASE II

Active Drug
or Placebo

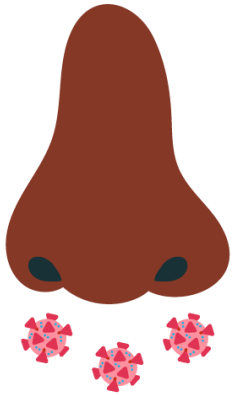
Post Acute COVID Survey

DAY **0**	DAY **3**	DAY **7**	DAY **14**	DAY **28**	WEEK **12**	WEEK **24**	WEEK **36**	WEEK **48**	WEEK **72**
	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood	✓	✓	✓	✓		✓			
O_2 NP	✓	✓	✓	✓					

Study Diary every day thru Day 28

Anterior Nasal Swabs
every day thru Day 14

Daily reminder for diaries and swabs



Phase II: 1^0 Objectives

Determine safety and efficacy of an agent to reduce the duration of COVID-19 symptoms and nasopharyngeal SARS-CoV-2 RNA detection through 28 days after study entry.

PHASE II GRADUATION

Based on Bayesian probability (agent is better than placebo by at least X) is greater than 0.6 where X is defined for each outcome measure in **bold**.

Virology: NP Swabs

- Proportion **<LLoQ** by ≥20%
- Decrease of **≥0.5** log10 copies/mL
- Reduction in median **AUC**

Symptoms: Diary

- Relative reduction of **≥20**%

Other considerations:

- Safety
- Dynamics of virology and symptoms
- Viral rebound
- Hospitalization/death

Sample Size and Precision Analysis

Proposed sample size:

220 (110 per investigational agent and 110 on concurrent placebo)

→ Assume 100 of the 110 would have evaluations

Participants at risk of severe COVID-19 will no longer be randomized to placebo

PHASE III

Evals (e.g. safety) added per agent in agent specific appendix

Investigational Agent or Active Comparator in Higher Risk

DAY **0**	DAY **3**	DAY **7**	DAY **14**	DAY **28**	WEEK **12**	WEEK **24**	WEEK **48**
Blood							
O_2 NP		O_2 NP		O_2 NP			

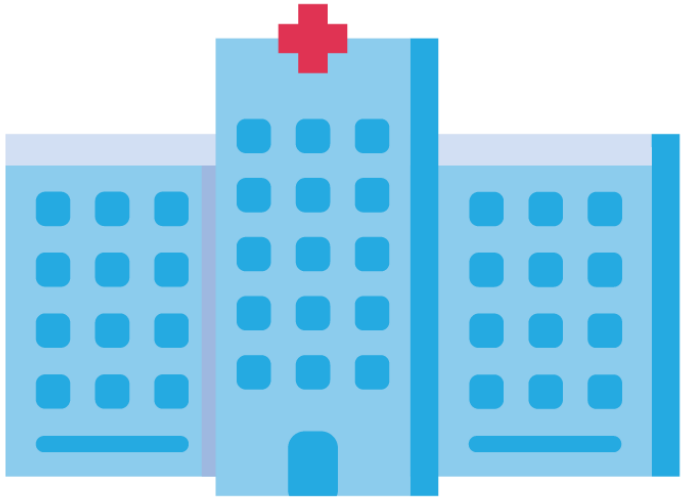
Study Diary every day thru Day 28

Daily reminder for diaries and swabs

PASC

PASC

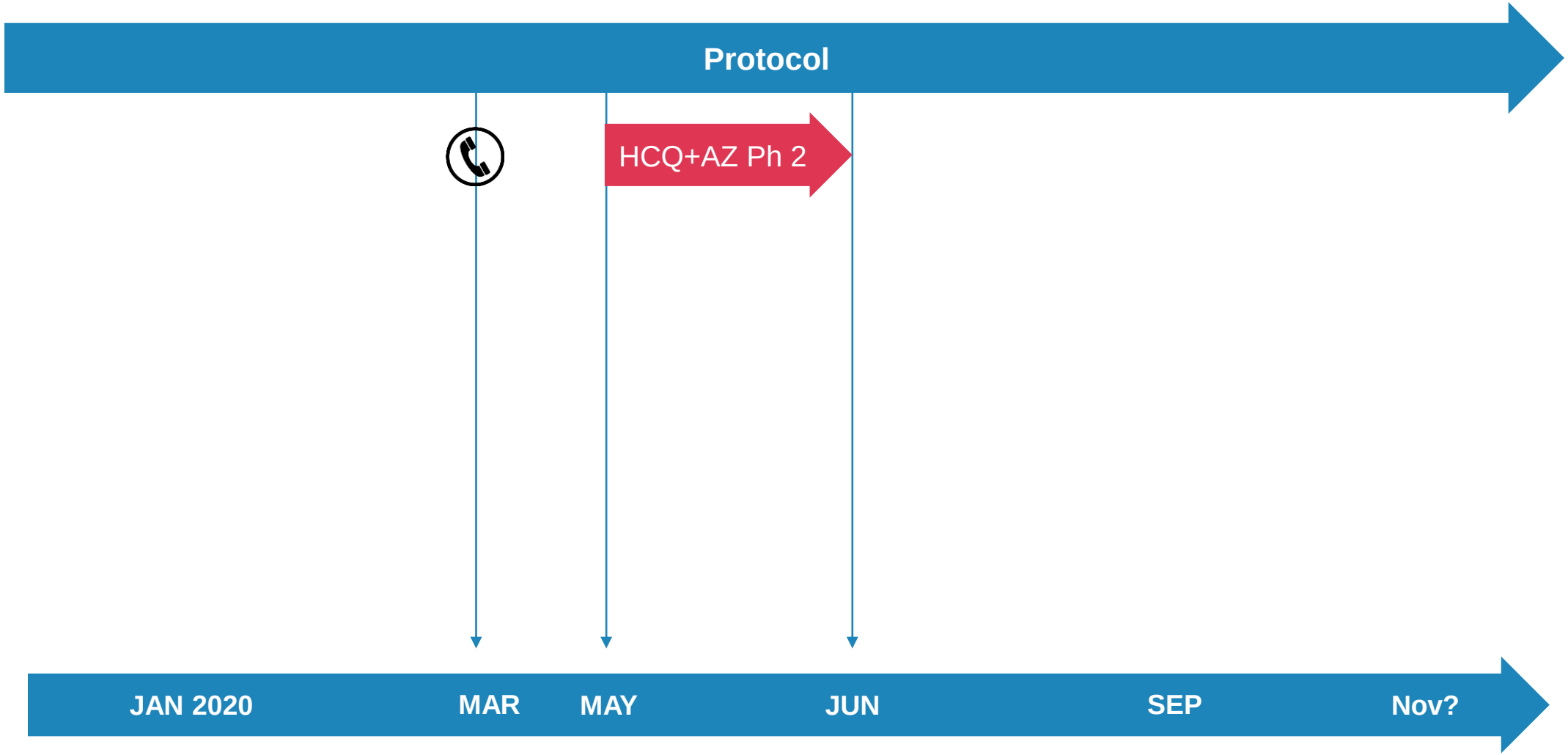
PASC



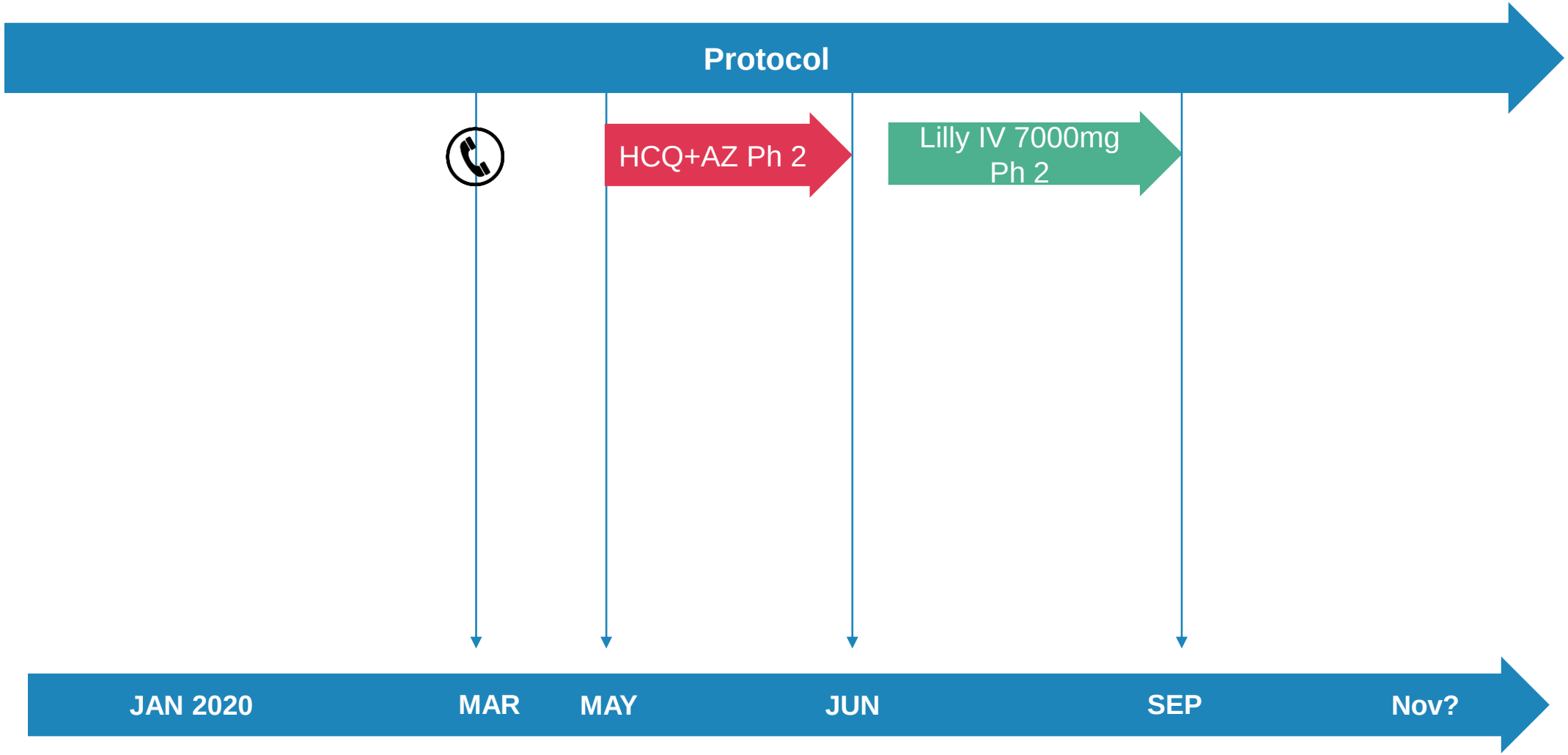
Phase III: 1^0 Objective

Determine if an agent will prevent either hospitalization or death through 28 days after study entry.

Timeline



ACTIV-2 Flow Chart



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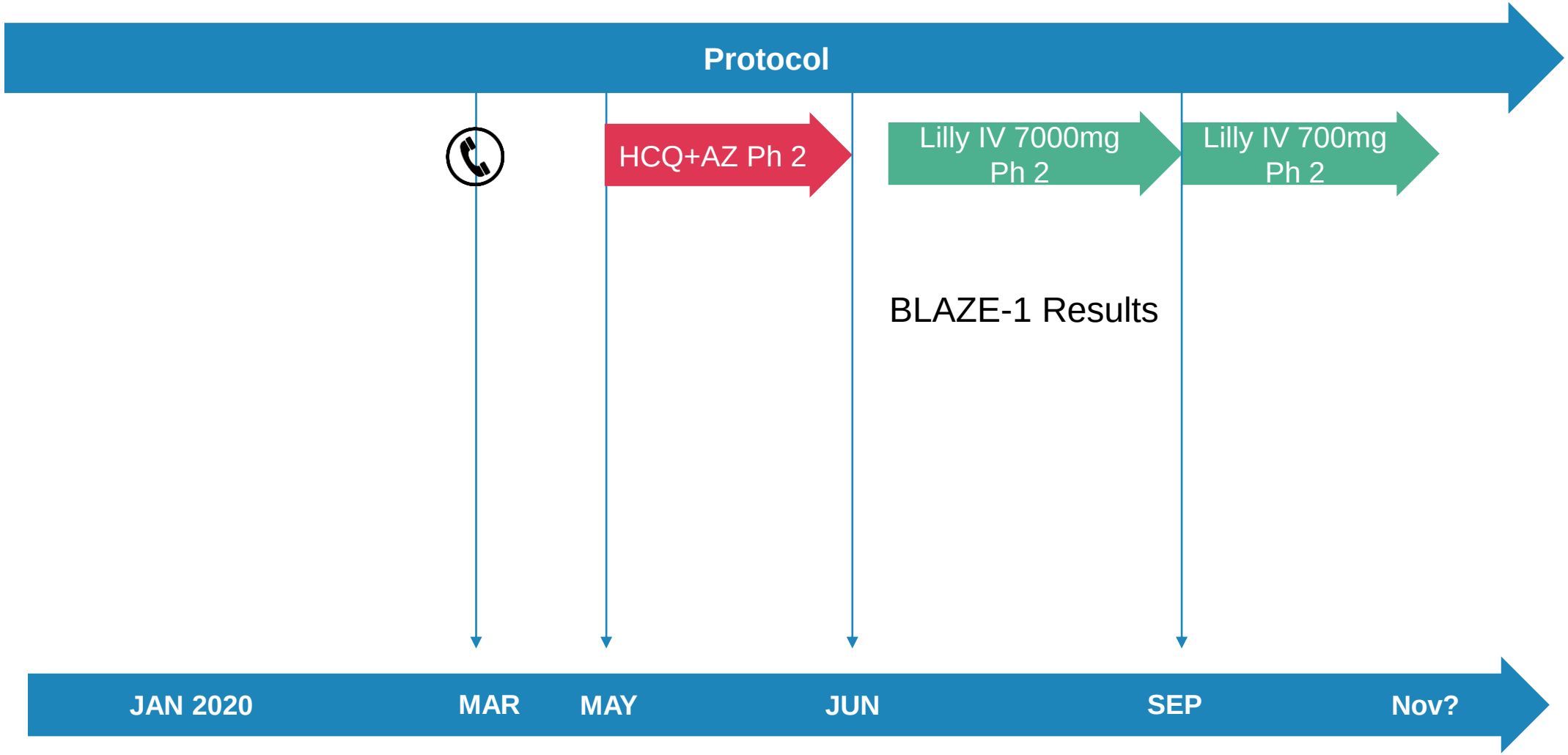
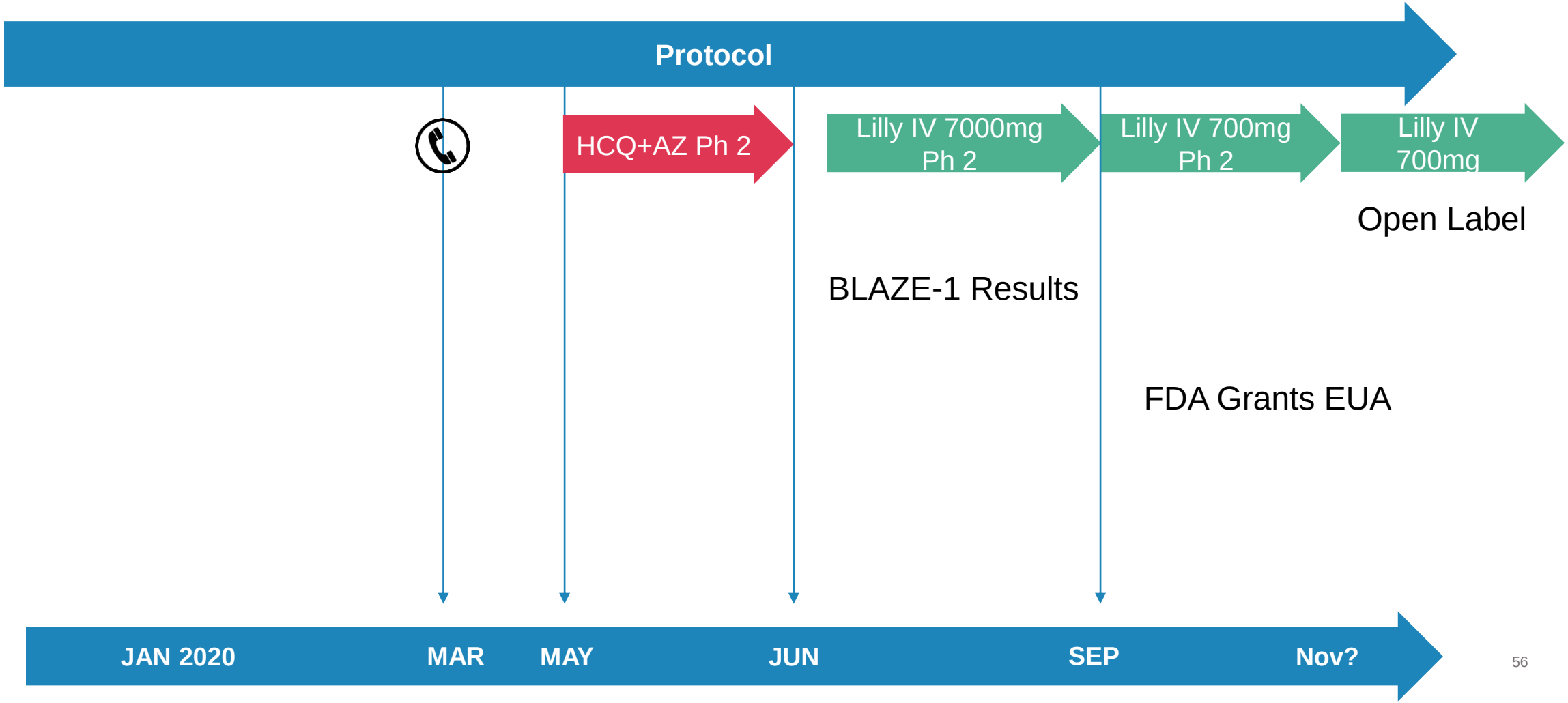
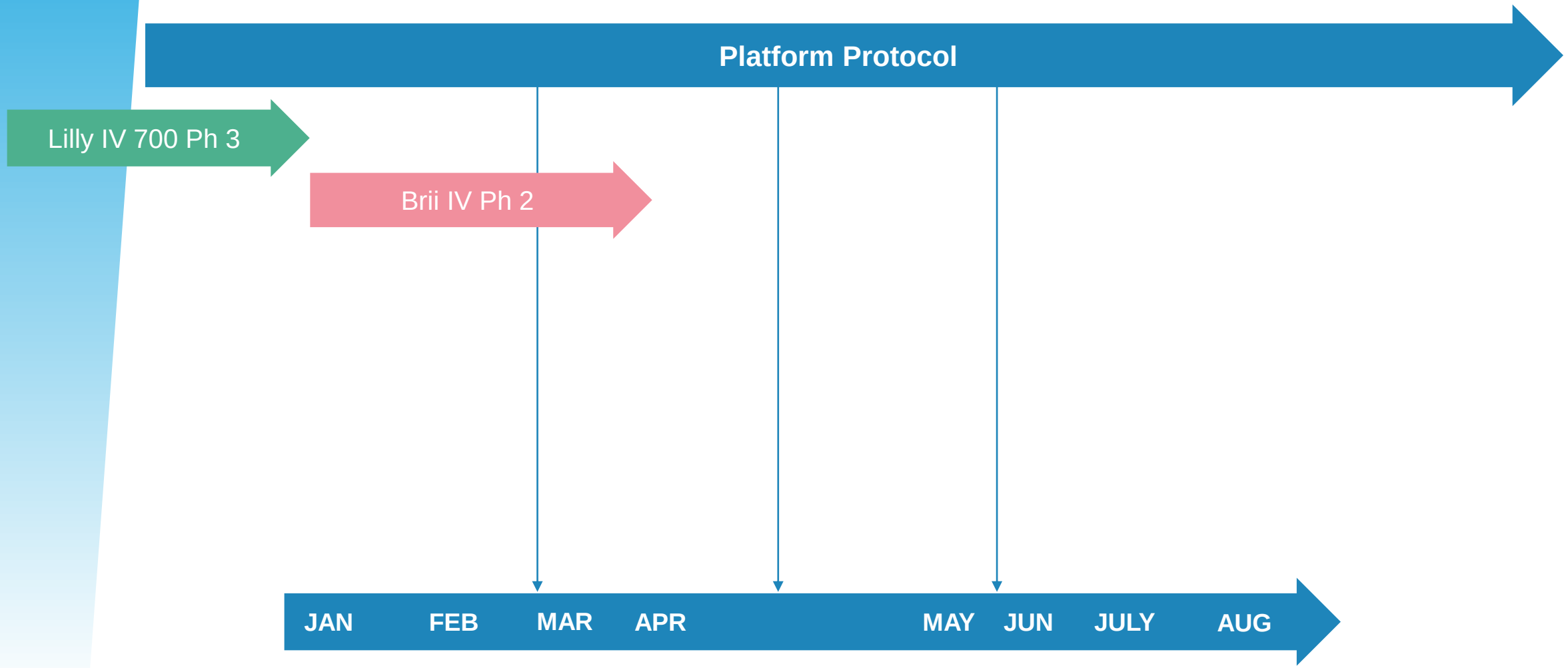


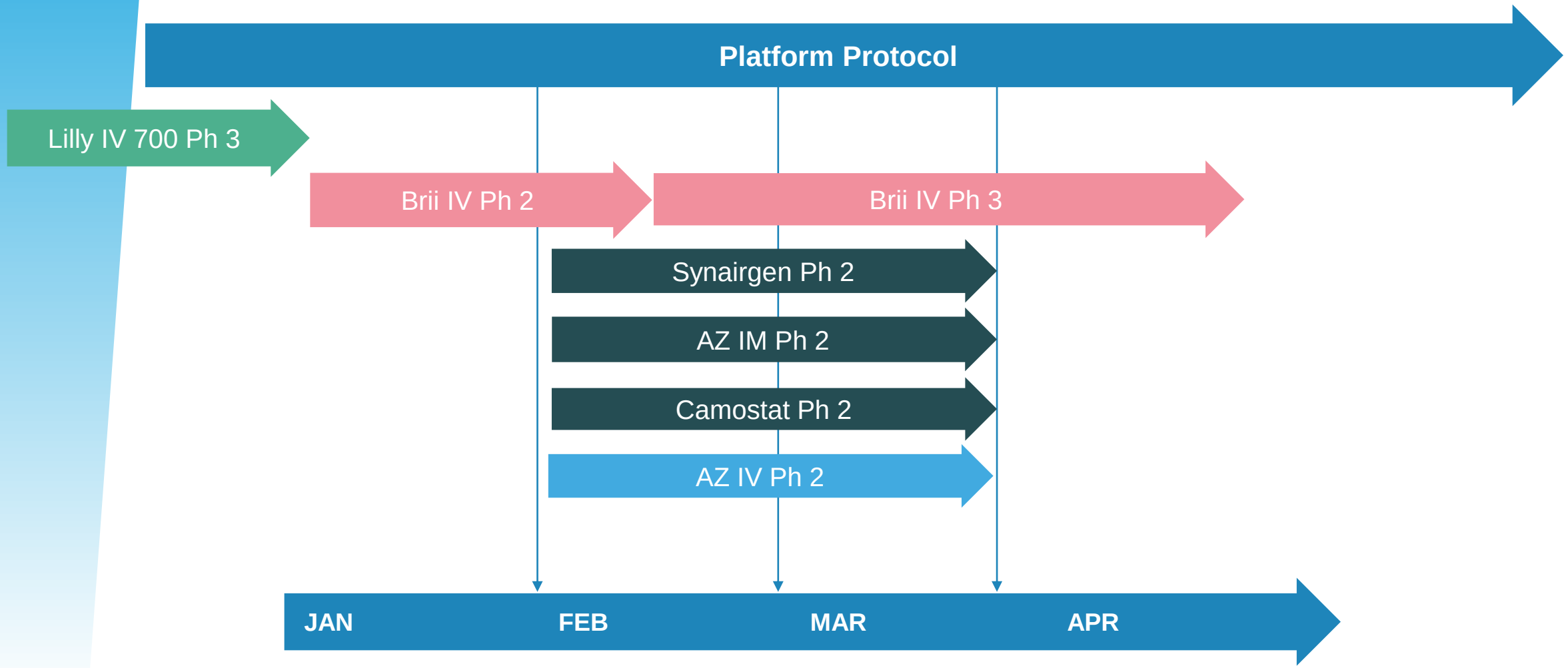
ACTIV-2 Flow Chart



ACTIV-2 IP Flow Chart



ACTIV-2 IP Flow Chart



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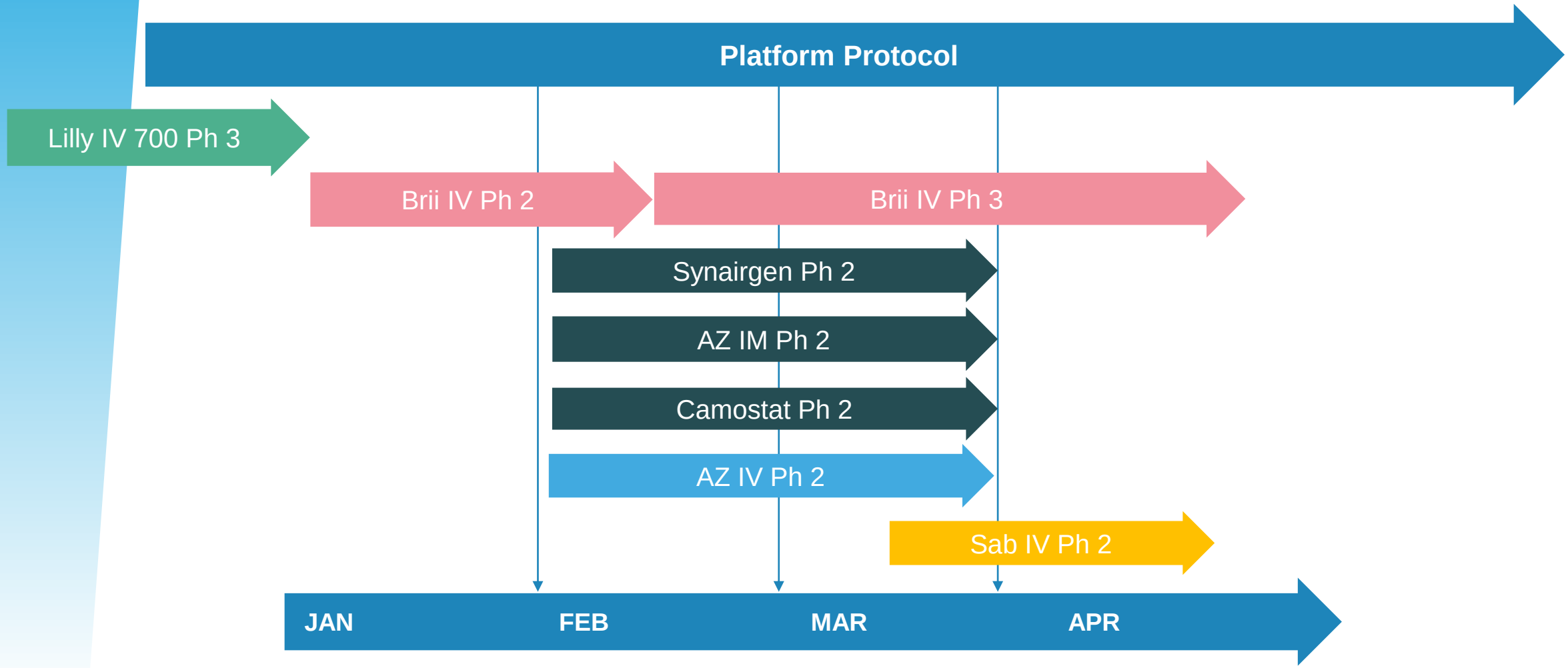
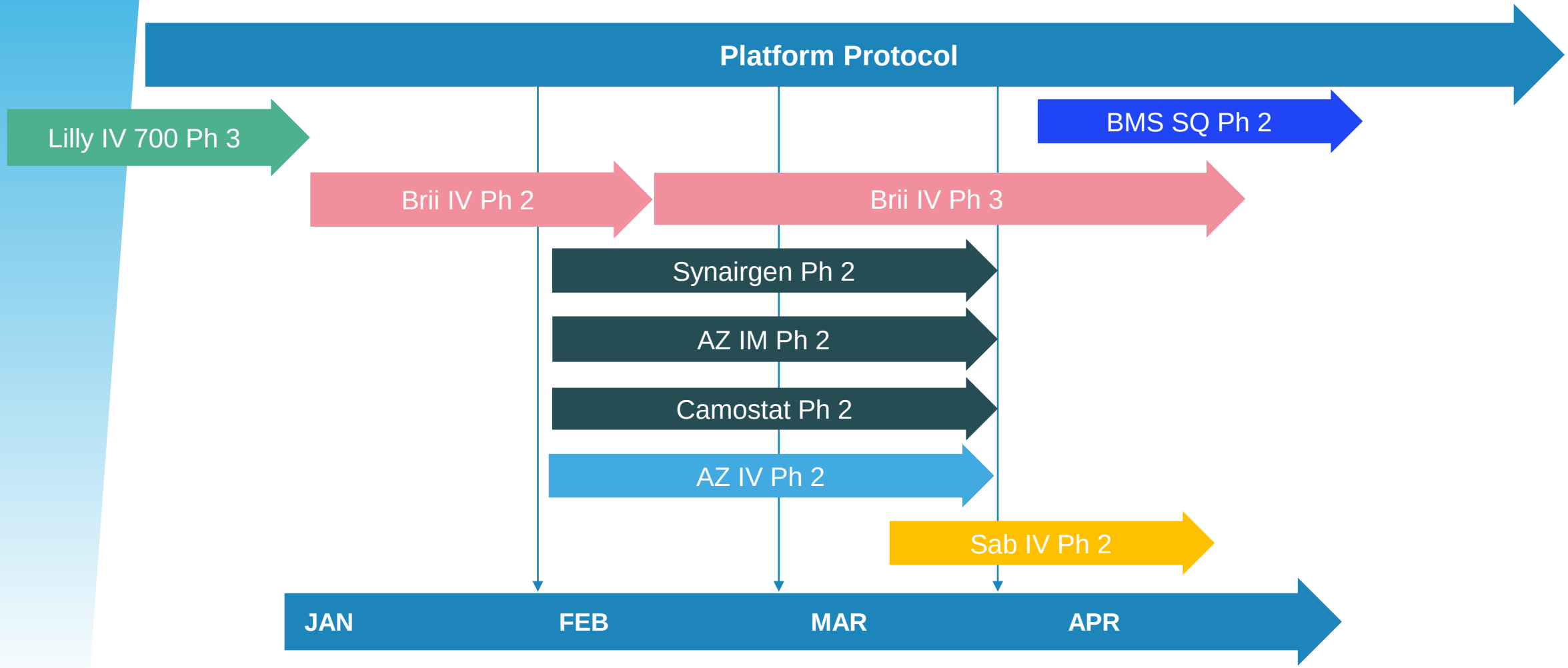
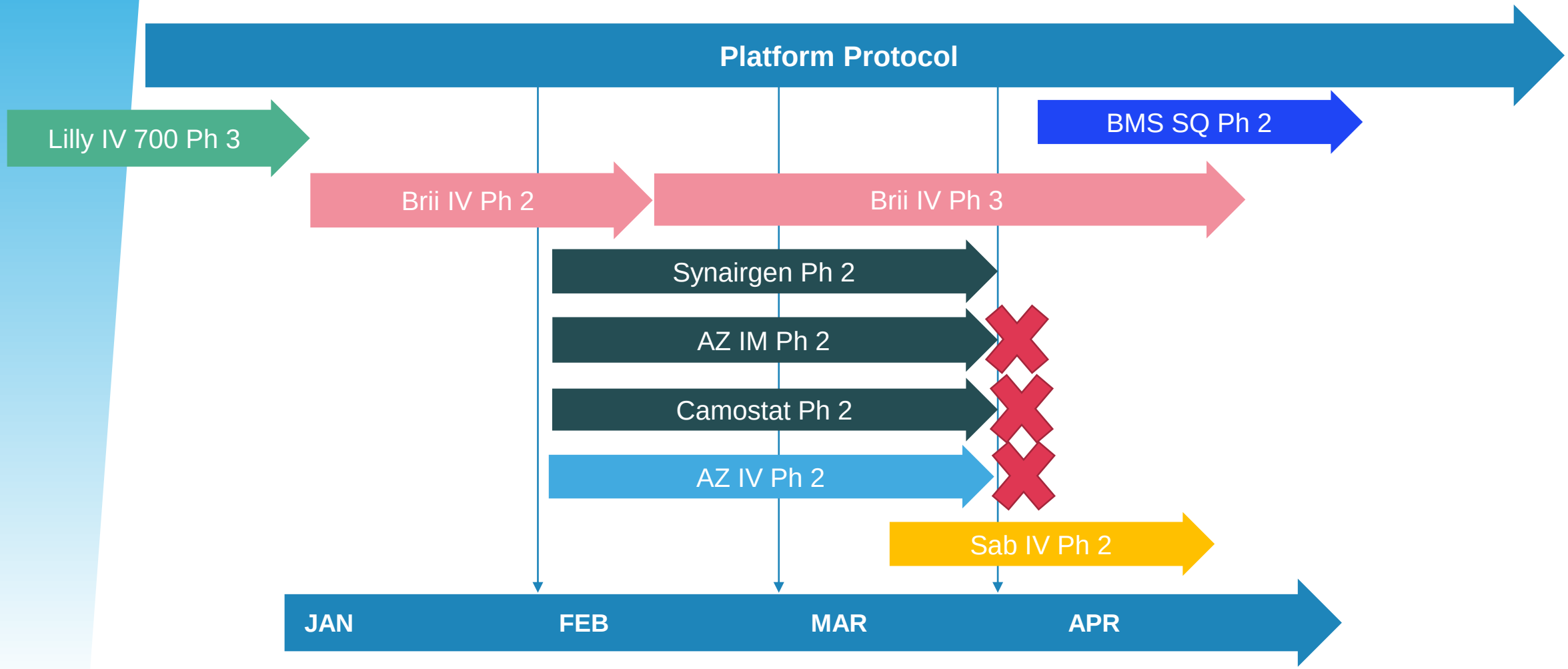


ACTIV-2 IP Flow Chart



ACTIV-2 IP Flow Chart



RISE ABOVE COVID

Adapt Out COVID Version 7

Non-inferiority Trial

- Monoclonal antibodies (mAbs) have received FDA EUA for treatment of COVID-19 in the outpatient setting for persons at higher risk for progression to hospitalization or death.
- Standard of Care for higher risk persons

Clinical Efficacy of Casi+Imdev		
	2400mg vs Placebo	**1200mg vs Placebo**
COVID-19 related hospital or all-cause death through day 29	18/1355 (1.3%) vs 62/1341 (4.6%); p<0.0001	7/736 (1.0%) vs 24/748 (3.2%); p=0.0024
Time to COVID-19 symptoms resolution	Median 10 vs 14 days; p<0.0001	Median 10 vs 14 days; p<0.0001

ACTIV 2 Overview Design

Phase 2
Lower Risk
Blinded, Shared Placebo
N=110 per active agent
Primary outcome:
Safety, Virology

Graduation analysis: Virology, symptoms/ hosp/death composite, safety

Phase 3
Higher Risk
Open-label, Shared Active Comparator (REGN)
N=600-800 per arm
Primary outcome: Hospitalization and death from any cause

EUA Eligible

Agents can enter at Phase 2 or directly to Phase 3 higher risk trial (if Phase 2 completed elsewhere)

Graduation Criteria

When last participant in agent group/shared placebo has completed **7 days** of follow-up.

Based on Bayesian probability statement: Probability (agent is better than placebo by at least X) is greater than 0.6 where X is defined below for each outcome measure.

Virology: NP Swabs through **Day 7**

- Lower SARS-CoV-2 RNA level of ≥0.5 log10 copies/mL at Day 3 and/or Day 7
- Higher proportion <LLoQ by ≥20% at Day 3 and/or Day 7
- Relative reduction in median AUC of ≥20%

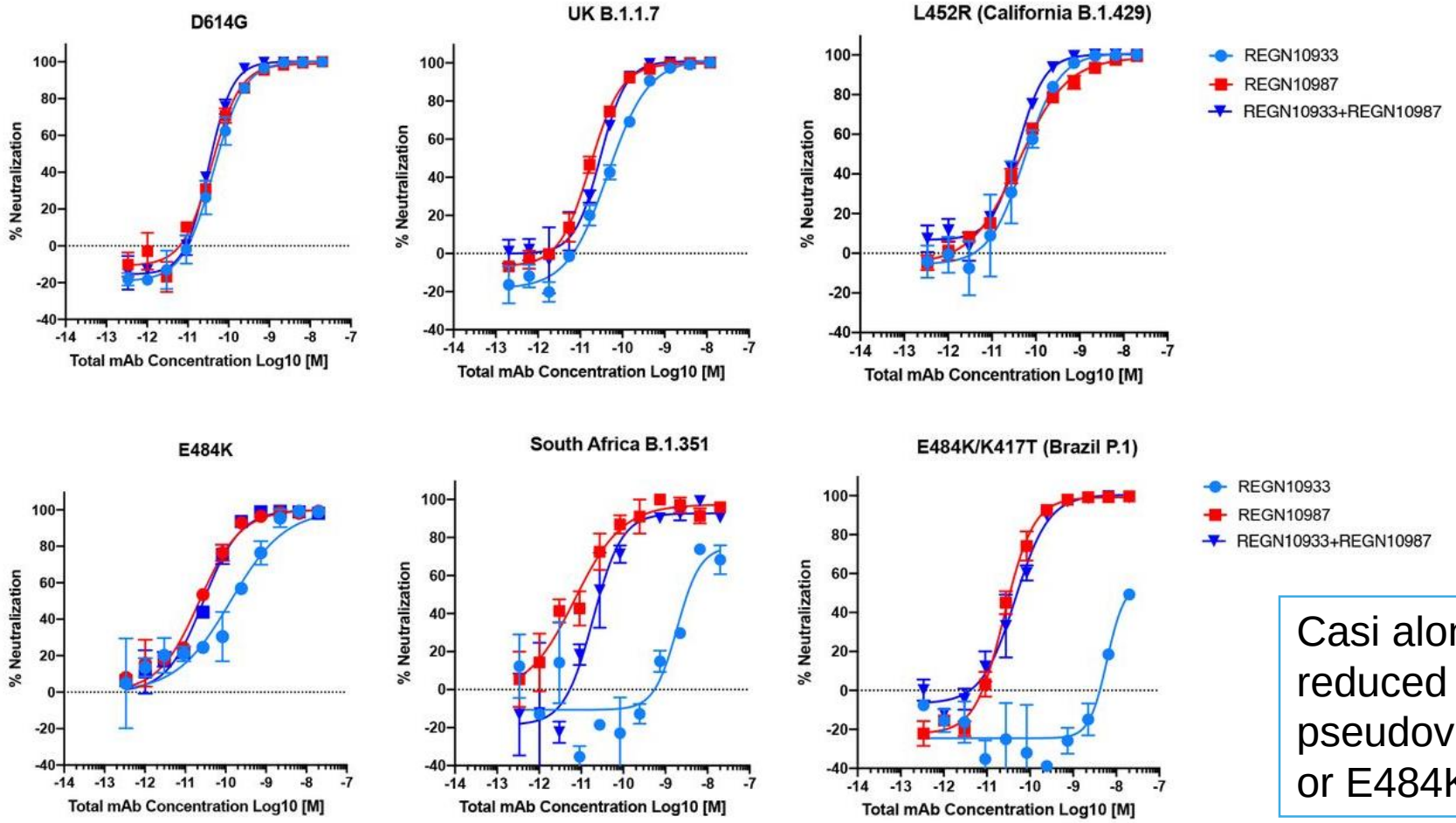
Clinical:

- Relative reduction of **≥40%** in proportion with EITHER (moderate or severe symptoms reported in the study diary at Day 7) or (hospitalization and/or death by Day 7)

Other considerations:

- Safety
- Viral rebound

Active Comparator= Casi + Imdevi



Casi alone, but not imdev, has reduced activity against pseudovirus expressing K417N or E484K

https://www.biorxiv.org/content/10.1101/2021.03.10.434834v2.full

Preliminary FDA Recommendations for Sample Size

Margin / Event Rate	2%	2.5%	3%
1%	611	505	323
1.5%	798	545	403
2%	990	664	484

Assuming:

- 85% Power
- 1:1 Randomization
- Two-sided 5% alpha (no interim analysis)
- Equal event rates in each arm
- Farrington Manning NI Test

Hosp/death			
	Comparison	Placebo	mAb
PYAB Phase 2: Subset of participants meeting EUA high risk criteria	Placebo versus pooled bamlanivimab 700 mg, bamlanivimab 2800 mg, bamlanivimab 7000 mg, and bamlanivimab 2800 mg and etesevimab 2800 mg	6/69 (8.7%)	5/175 (2.9%)
PYAB Phase 3	Placebo versus bamlanivimab 2800 mg and etesevimab 2800 mg	36/517 (7.0%)	11/518 (2.1%)
PYAB Phase 3	Placebo versus bamlanivimab 700 mg and etesevimab 1400 mg	15/258 (5.8%)	4/511 (0.8%)
Trial COV-2067. Subset of participants meeting EUA high risk criteria	Pooled REGEN-COV 8000 mg, REGEN-COV 2400 mg, REGEN-COV 1200 mg	51/684 (7.5%)	32/1392 (2.3%)

Phase 3 Sample Size and Analysis (NI design)

- Open-label non-inferiority design
- Sample size 600 infused agents, 800 for non-infused per arm (minimum of 300 for safety evaluation)
- Non-inferiority margin = absolute risk difference of 3%
- Interim analyses - O'Brien and Fleming stopping guideline assuming four equally spaced analyses
  - Stopping for superiority and inferiority
- Assume 5% loss to follow-up
- 90% power

Summary of Phase Differences

	Phase 2	Phase 3
Study Population	Lower Risk Only	Higher Risk Only
Comparator	Shared Placebo	Shared Open-label Active (Regeneron)
Design	Superiority	Non-inferiority
1^0 Outcomes	Virology thru Day 14 Symptoms & Safety thru Day 28	Safety, Hospitalization and Death Day 28
Sample Size	110 per arm	600-800 per arm
Doses	1 or 2	1 only

STUDY TEAM

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Thank you