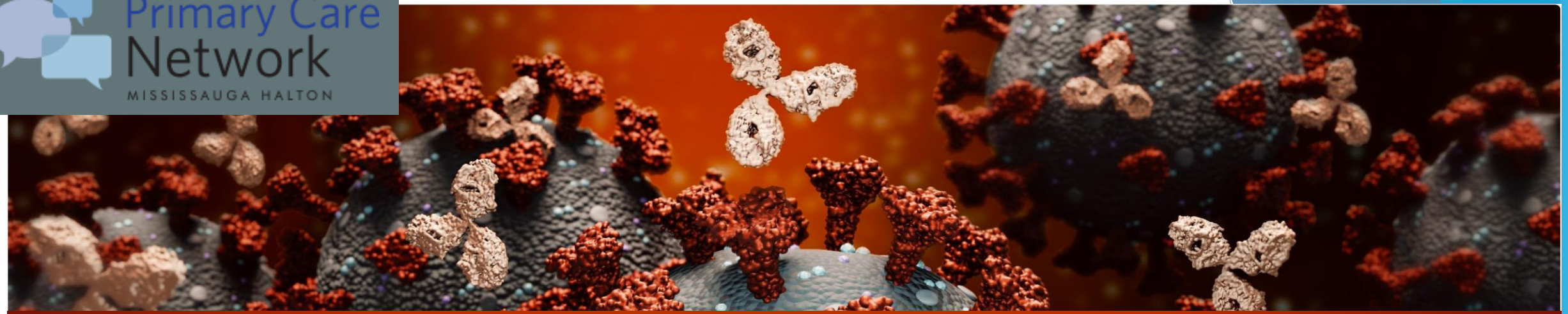
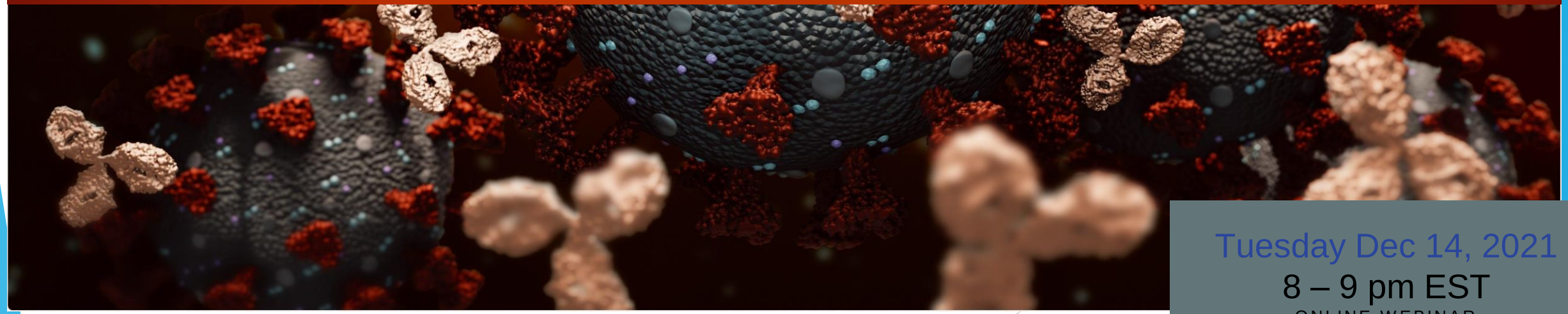
Primary Care Network
MISSISSAUGA HALTON



OH-MY-CRON! There's a treatment available now!

Novel therapies and the future of COVID-19 management



Tuesday Dec 14, 2021

8 – 9 pm EST

ONLINE WEBINAR

Our Board

- All family doctors, from diverse payment models, representing primary care from all over the region


Adithi


Ali


Baldeep


Carolyn


David


Greg


Mike


Richard

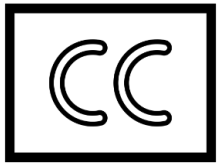

Sohal

Tonight's Agenda

- Welcome
- Introductions
- Speaker Presentations – Dr. Zain Chagla & Dr. Anil Gupta
- Open Q&A
- Closing Remarks

Land Acknowledgement

Participant Tips



Closed Captions

Click on ‘show subtitles’ To see closed captions throughout this session. You can also modify their size and position

Get interactive

Use the chat feature to introduce yourself, interact with other participants and share comments throughout this session

Ask Questions

Direct all in-session questions to the Q&A feature in Zoom. We will provide answers in our post-event summary

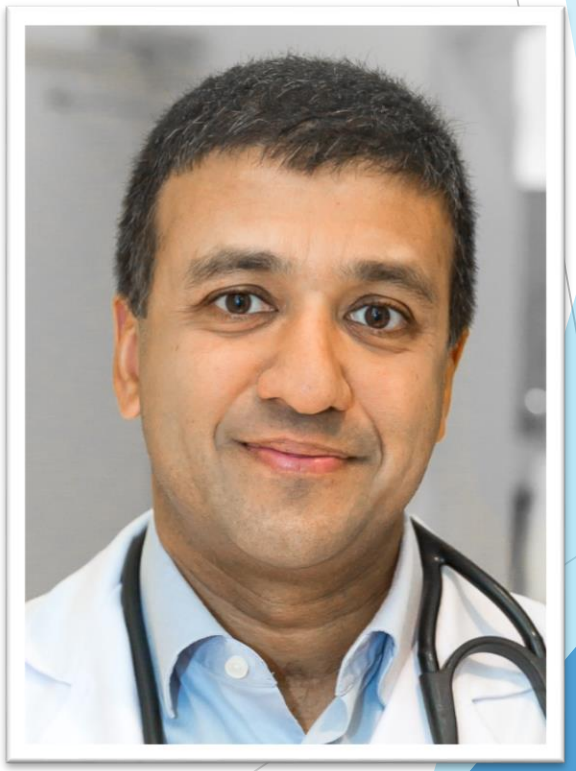
Respect Others

Share respectful feedback and comments when chatting with others and asking questions of our guest speakers and experts

Guest Speakers

Dr. Zain Chagla

Dr. Anil Gupta



Speaker Disclosures

Dr. Anil Gupta, Dr. Zain Chagla and Dr. Sohal Goyal

No sponsors

No pharma

No funding for tonight

Current Covid-19 Patient Pathway

- individual gets symptoms then gets tested
- if positive, receives phone call from testing site, public health, primary care provider
- receives message to stay home and isolate
- if progression, go to hospital
- creates tremendous fear

Current Covid-19 patient Pathway

- as pandemic progressed, other programs developed
- “Covid at home”
- this provided more objective measures for patient to make clinical decisions (O2 sat.)
- Ongoing pathways need to be established

My Clinic's Approach

- team of 3 doctors and staff wanted to provide more
- home visits for patients
- early morning assessments in the office before regular hours
- LTC home outbreak assessments
- performed NP swabs early when testing not routinely available
- patients were extremely grateful

- opportunity to participate in a Covid treatment clinical trial

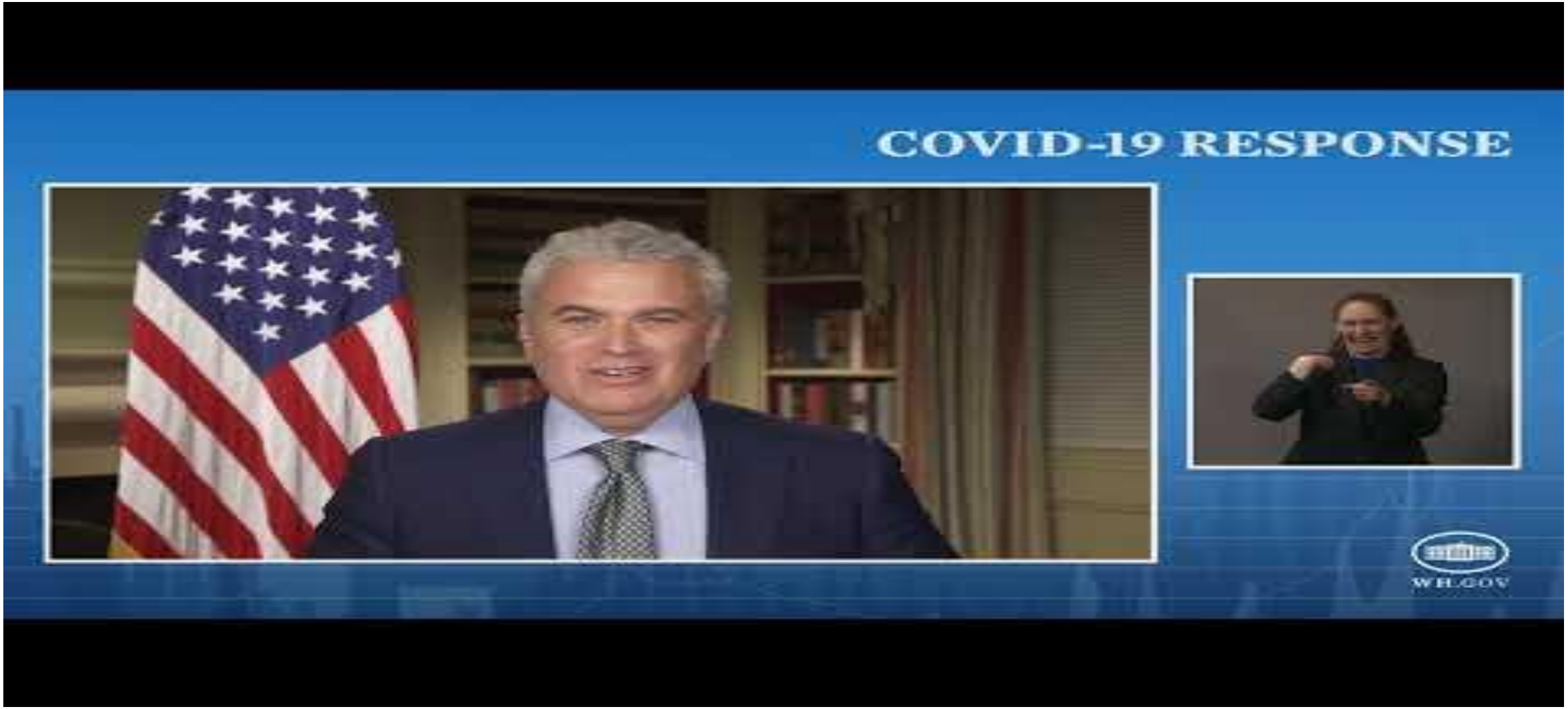
Need for Therapeutics

- **ALTERNATIVES NEEDED BESIDES**

(1) STAYING AT HOME or

(2) GOING TO HOSPITAL

White House Covid-19 Response Team Briefing June 2021



Early Covid Therapeutics

MODIFYING HOST RESPONSE

- fluvoxamine
- inhaled steroids

TARGETING THE VIRUS

- ivermectin
- molnupiravir
- monoclonal antibodies

Fluvoxamine

- Along with psychiatric effects – S1R modulation leading to lowered cytokine storm
- Small phase II clinical trial
  - 100mg TID of fluvoxamine vs. placebo (N=152 ▫ 117 completed trial)
  - Endpoint of clinical deterioration (SoB/hopsitalizations/O2/<92%)
  - 0 patients in fluvoxamine, 6 in placebo (p=0.009)
- Need for further study…

Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial. *JAMA*. 2020;324(22):2292–2300. doi:10.1001/jama.2020.22760

TOGETHER - Fluvoxamine

- Multiplatform adaptive placebo controlled RCT in Brazilian outpatients > 18 with 1 risk factor for deterioration
- Fluvoxamine 100mg PO BID (N=739) x 10 days vs. Placebo (N=733)
  - ED Stay/Hospitalization - (77/739 vs 108/733; Relative Risk [RR]: 0.71; 95% 44 Bayesian Credible Interval [95% BCI]: 0.54 - 0.93) – mostly hospital
    - NNT of 24
  - No differences in viral clearance, mortality (small no), time to death, days in hospital, or days ventilated
- Signal towards reduced hospitalization in high risk patients
  - 2 more clinical trials enrolling – may be a viable outpatient early therapy

Reis, G. *et al. Effect of Early Treatment with Fluvoxamine on Risk of Emergency Care and Hospitalization Among Patients with COVID-19: The TOGETHER Randomized Platform Clinical Trial.* http://medrxiv.org/lookup/doi/10.1101/2021.08.19.21262323 (2021) doi:10.1101/2021.08.19.21262323.

Inhaled Steroids

- PRINCIPLE trial
  - Open label inhaled budesonide in > 65 or those > 50 with comorbidities vs. controls, those with COVID symptoms < 14 days
  - N= 1073 vs. N = 1988 vs. N = 1639 (other arms)
  - Reduction in self reported recovery by 3 days (over BA interval), 2% reduction in hospitalization (not significant)
- STOIC trial
  - Open label inhaled budesonide vs. no treatment (n=73 in each group)
  - Primary endpoint (urgent care/ED/Hopsitalization) 1 vs 14%.
  - Lower fever, faster symptom resolution

Yu, L.-M. *et al*. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *The Lancet* **398**, 843–855 (2021).

Ramakrishnan, S. *et al*. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. *The Lancet Respiratory Medicine* **9**, 763–772 (2021).

Inhaled Steroids

- Double blind RCT of ciclesonide (197) vs. placebo (203) – multicenter USA
- Inclusion > 12 with symptomatic COVID-19
- No difference in primary outcome (time to symptom resolution by day 30 of all COVID-19 symptoms)
- Secondary endpoint – ED / hospitalization
  - 1.0 vs. 5.4% - mixture of ED and hospitalization
- No clear symptom resolution benefit (funny primary endpoint) – but some blinded data around less healthcare utilization…

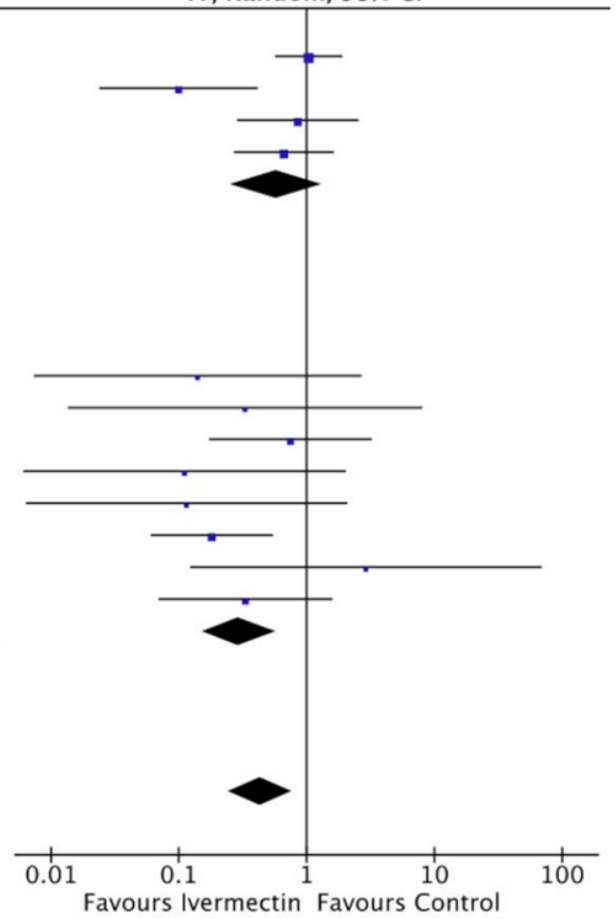
Clemency, B. M. *et al. A randomized controlled trial of inhaled ciclesonide for outpatient treatment of symptomatic COVID-19 infections*. http://medrxiv.org/lookup/doi/10.1101/2021.09.07.21261811 (2021) doi:10.1101/2021.09.07.21261811.

Ivermectin

- One of the most contentious drugs through pandemic
- In vitro data suggested significant reductions in virus
  - Human levels above MIC would be toxic
- Large observational analysis from surgisphere showing reduced mortality ▫ Part of 3 papers that were eventually retracted for overt fraud
- Several poorly designed small studies that came later, put together by metaanalysis

1G)

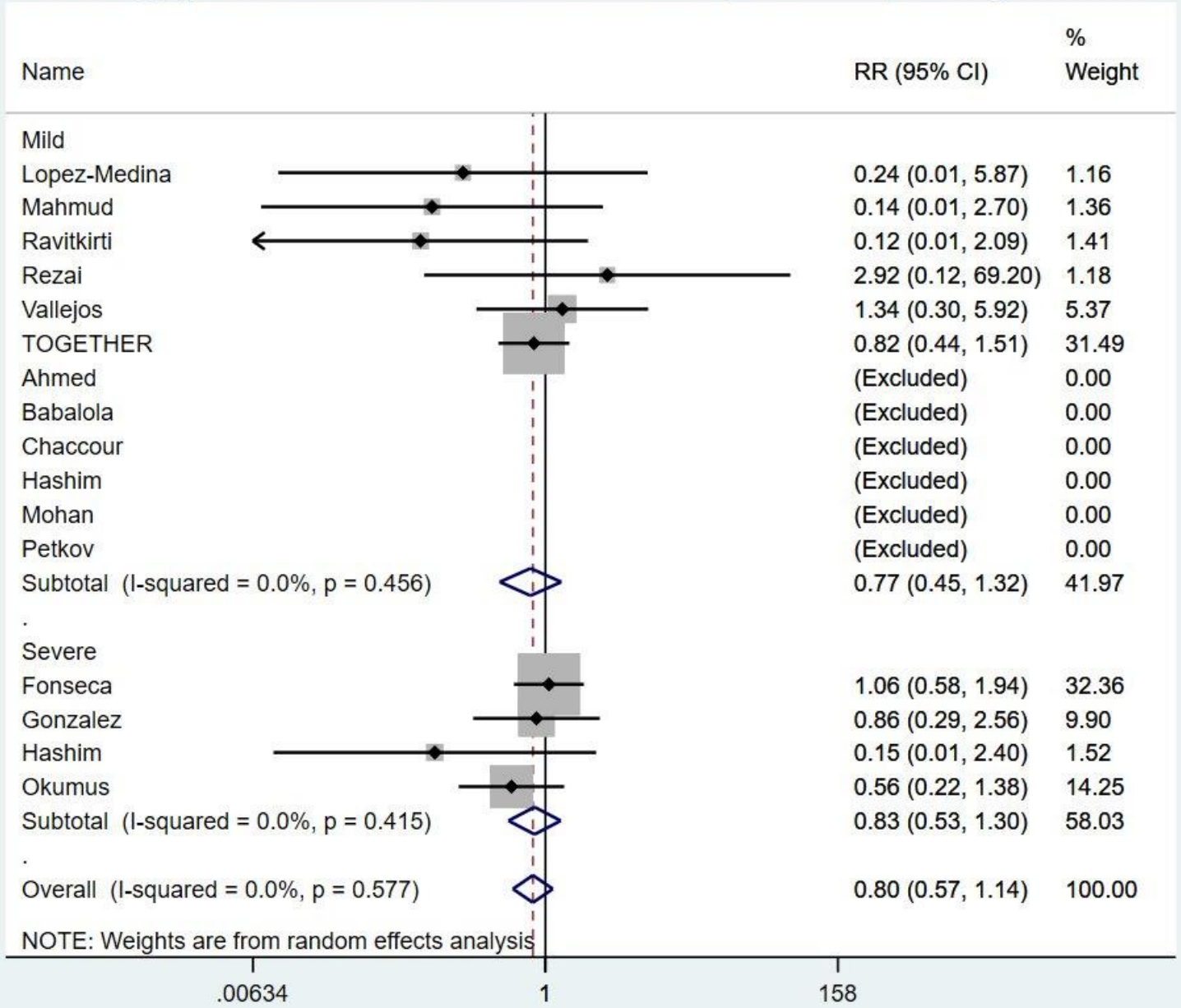
Study or Subgroup	Ivermectin Events	Ivermectin Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
4.3.1 Severe						
Brazil Fonseca et al	12	53	25	115	18.4%	1.04 [0.57, 1.91]
Egypt Elgazzar Severe	2	100	20	100	9.4%	0.10 [0.02, 0.42]
Mexico Gonzalez et al	5	36	6	37	12.5%	0.86 [0.29, 2.56]
Turkey Okumus et al	6	30	9	30	14.7%	0.67 [0.27, 1.64]
Subtotal (95% CI)		**219**		**282**	**55.0%**	**0.58 [0.25, 1.32]**
Total events	25		60			
Heterogeneity: $Tau^2 = 0.45$; $Chi^2 = 8.90$, df = 3 (P = 0.03); $I^2 = 66\%$						
Test for overall effect: Z = 1.30 (P = 0.19)						
4.3.2 Mild/moderate						
Bangladesh Mahmud et al	0	183	3	180	3.2%	0.14 [0.01, 2.70]
Colombia Lopez-Medina et al	0	200	1	198	2.8%	0.33 [0.01, 8.05]
Egypt Abd-Elsalam et al	3	82	4	82	9.1%	0.75 [0.17, 3.25]
Egypt Elgazzar Moderate	0	100	4	100	3.2%	0.11 [0.01, 2.04]
India Kirti et al	0	55	4	57	3.3%	0.12 [0.01, 2.09]
Iran Niaee et al	4	120	11	60	12.4%	0.18 [0.06, 0.55]
Iran Rezai et al	1	35	0	34	2.8%	2.92 [0.12, 69.20]
Iraq Hashim et al	2	70	6	70	8.4%	0.33 [0.07, 1.60]
Subtotal (95% CI)		**845**		**781**	**45.0%**	**0.30 [0.15, 0.58]**
Total events	10		33			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.42$, df = 7 (P = 0.61); $I^2 = 0\%$						
Test for overall effect: Z = 3.57 (P = 0.0004)						
Total (95% CI)		**1064**		**1063**	**100.0%**	**0.44 [0.25, 0.77]**
Total events	35		93			
Heterogeneity: $Tau^2 = 0.35$; $Chi^2 = 19.24$, df = 11 (P = 0.06); $I^2 = 43\%$						
Test for overall effect: Z = 2.85 (P = 0.004)						
Test for subgroup differences: $Chi^2 = 1.54$, df = 1 (P = 0.21), $I^2 = 35.1\%$						



Questionable studies

- Elgazzar et al.
  - Major data inconsistency errors from raw data to published data
  - Complete imbalance between treatment and placebo group
  - Multiple instances of data being copied and pasted
  - Mathematically impossible standard deviations
  - Recruitment pre-REB approval
  - Given this – eventually retracted
- Niaee et al
  - Issues with concealment, bias, baseline mismatch to placebo, median calculations

Gid's quick reanalysis of ivermectin for COVID-19 excluding probable fraud and very-low quality research

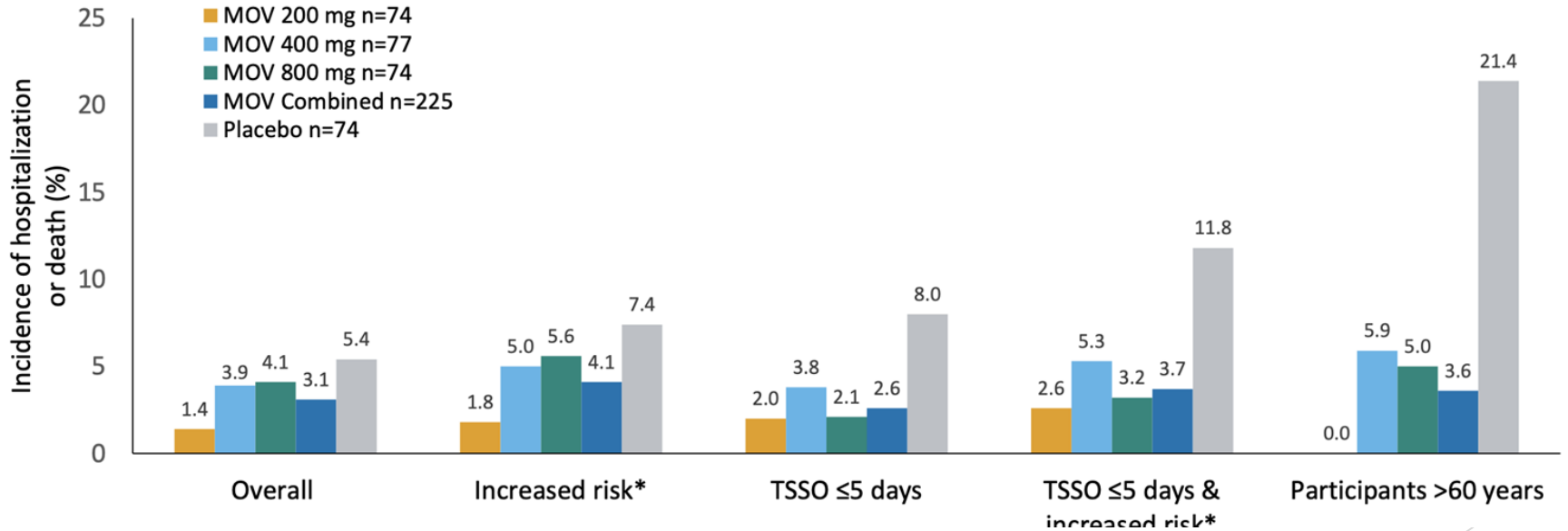


Molnupiravir

- Phase II study - 1:1:1:1 different doses vs. Placebo (~ 300 participants)

Primary Efficacy Endpoint (MITT Population)

MOV reduced the incidence of hospitalization or death through Day 29, particularly in subgroups with risk factors



Caraco Y et al – Phase 2 Results from a Phase 2/3 Study evaluating Treatment of COVID-19 in Non-hospitalizated adults. ECCMID 2021.

Molnupiravir

- Press release October 1st
- Large RCT (continuation of the phase II study)
  - ~ 700 people per group
  - Hospitalization 14% in placebo, 7% in intervention
  - IMB stopped trial due to potential benefits
- Second press release Late November much lower effects (9 vs. 6% after full analysis – 30% RRR)
- Likely of some benefit still, although smaller magnitude

Paxlovid

- Protease inhibitor along with Ritonavir (HIV protease inhibitor – inhibits metabolism to ”boosts” level in vivo)
- Large multicenter RCT - interim analysis of first 1200 patients
  - Given within 3 days – 0.8 vs. 7% hospitalization
  - Given within 5 days – 1 vs. 6.7% hospitalization
  - 0 deaths vs. 10 deaths in placebo
  - Well tolerated with minimal ADE (less than placebo)
  - Need to consider DDI particularly with R
    - DOAC’s, Statins, anti seizure medications

The potential role of mAbs in the treatment of COVID-19

Prevention and Treatment across the COVID-19 spectrum

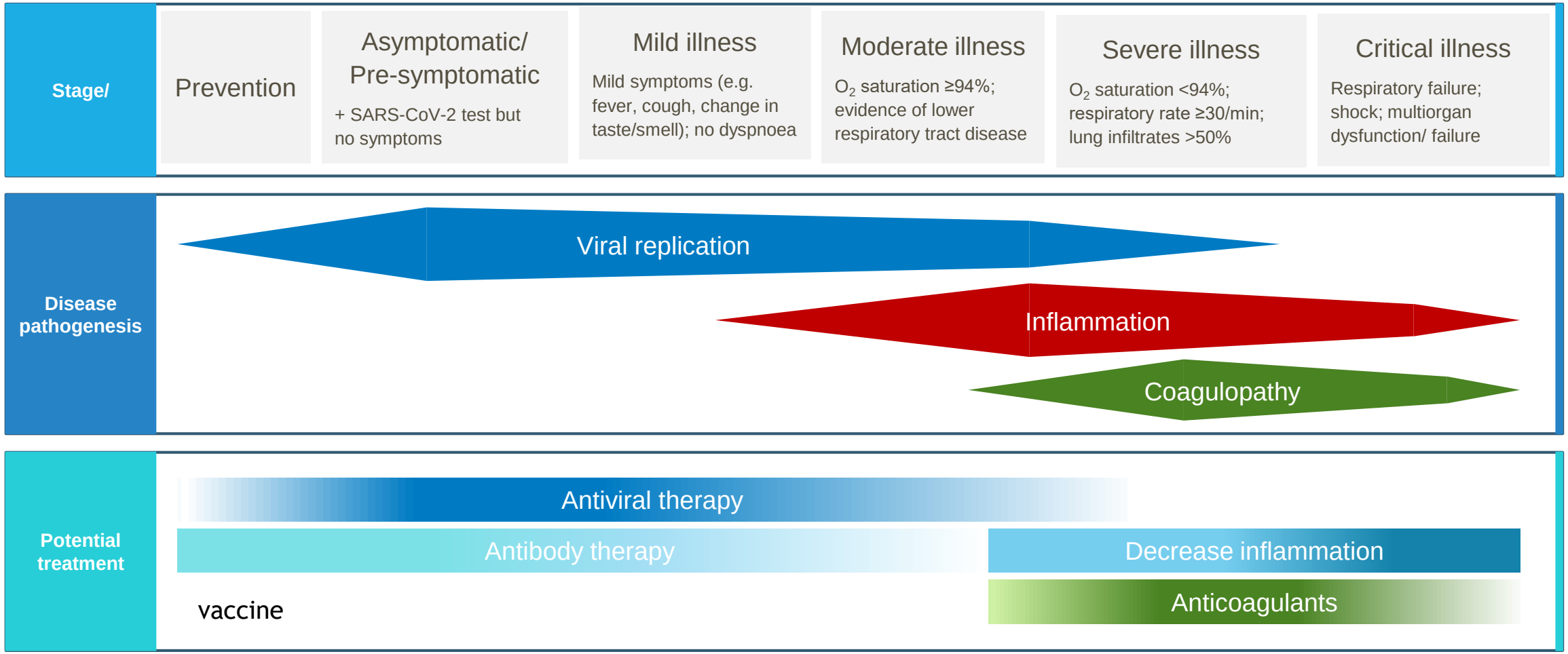


Figure adapted from Gandhi RT. Clin Infect Dis 2020. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

1. Gandhi RT. Clin Infect Dis 2020 Jul 31;ciaa1132. doi: 10.1093/cid/ciaa1132 (ePub ahead of print); 2. Gandhi RT, et al. N Engl J Med. 2020;383:1757-1766. 3. Corti D Cell Review. 2021;184(12)-3086-3108_

Early intervention with monoclonal antibodies aims to prevent progression of COVID-19 in those at risk of severe disease[1,2]

Treating people early in the course of SARS-CoV-2 infection is likely to speed recovery, reduce the likelihood of severe outcomes, and reduce demand on the healthcare system[3]

Data suggest that early treatment with SARS-CoV-2 mAbs may help to[1,4]:

ED, emergency department; mAb, monoclonal antibody.

1. NIH, COVID-19 Treatment Guidelines (accessed May 25, 2021); 2. Cohen MS. *N Engl J Med*. 2021;384(3):289-291; 3. NIH, Press release November 11, 2020 (accessed May 26, 2021); 4. Tuccori M, et al. *mAbs*. 2020;12(1):e1854149.

Which Patients Are Considered at high-risk for progression to severe COVID-19 disease?

Health Canada : Underlying medical conditions associated with more severe COVID-19 disease[1]:

- asthma (moderate to severe)
- cancer
- chronic kidney and end-stage disease
- chronic lung diseases
- cystic fibrosis
- dementia or other neurological conditions
- diabetes (type 1 or type 2)
- Down syndrome
- epilepsy
- heart conditions eg. such as heart failure, coronary artery disease, cardiomyopathies or hypertension
- HIV infection
- immunocompromised state
- interstitial lung disease
- liver disease
- motor neuron diseases
- overweight and obesity*
- pregnancy
- pulmonary hypertension
- sickle cell disease or thalassemia
- smoking, current or former
- solid organ or blood stem cell transplant
- stroke or cerebrovascular disease
- substance use disorders

*Overweight = body mass index (BMI) > 25 kg/m2 but < 30 kg/m2), obesity (BMI ≥30 kg/m2 but < 40 kg/m2), or severe obesity (BMI of ≥40 kg/m2)

Health Canada (June 17, 2021) ***COVID-19 signs, symptoms and severity of disease: A clinician guide***
https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/guidance-documents/signs-symptoms-severity.html

Which Patients Meet Criteria for the use of Anti-SARS-CoV-2 mAbs?

Original EUA Criteria

- Aged ≥65 years
- Obesity (BMI ≥35 kg/m^2)
- Diabetes
- CVD (including congenital heart disease) or hypertension
- Chronic lung diseases

Expanded EUA Criteria

- An immunocompromising condition or immunosuppressive treatment
- Being overweight (BMI >25 kg/m^2) as the sole risk factor
- CKD
- Pregnancy
- Sickle cell disease
- Neurodevelopmental disorders or other conditions that confer medical complexity
- Medical-related technological dependence

- **EUA criteria apply to any patient aged ≥12 years.**
- **Anti-SARS-CoV-2 mAb may be used in a patient hospitalized for a reason other than COVID-19 if they meet other EUA criteria.**

CKD, chronic kidney disease; CVD, cardiovascular disease

NIH. https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/. Accessed August 4, 2021.

Characteristics of Anti-SARS-CoV-2 mAbs

mAb	Status	Binding Site	Route of Administration	Characteristics
BAM + ETE[1] HC Pending	EUA for treatment	ACE2 receptor interface on spike protein	IV	• Bind to different but overlapping epitopes • No Fc modifications for BAM; amino acid substitutions in Fc region for ETE
CAS + IMD[2] Granted Health Canada IO auth for treatment	EUA for treatment and postexposure prophylaxis	ACE2 receptor interface on spike protein	IV (can be SQ)	• Bind to nonoverlapping sites • No modifications in Fc region
SOT[3] Granted Health Canada IO auth for treatment	EUA for treatment	Highly conserved epitope on spike protein	IV	• Does not compete with ACE2 receptor binding • Amino acid substitutions in Fc region to extend half-life
AZD7442 (tixagevimab + cilgavimab)[4] HC Pending	Emerging	ACE2 receptor interface on spike protein	IM	• Components bind to 2 noncompeting sites • Long-acting mAb (up to 12 months) • Reduced Fc receptor binding

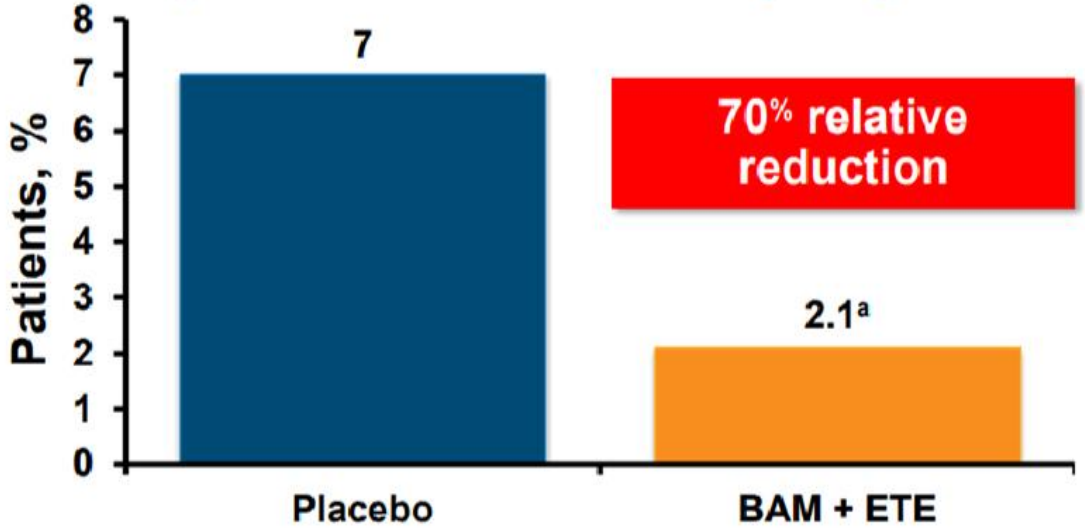
1. US Food and Drug Administration (FDA). https://www.fda.gov/media/145802/download. Accessed September 8, 2021; 2. FDA. https://www.fda.gov/media/145611/download. Accessed September 8, 2021; 3. FDA. https://www.fda.gov/media/149534/download. Accessed September 8, 2021; 4. Precision Vaccinations. https://www.precisionvaccinations.com/vaccines/covid-19-antibody-azd7442. Accessed September 8, 2021.

In vitro studies indicate that BAM+ETE, CAS+IMD, Sotrovimab, and AZD7442 mAbs retain activity against the Delta variant.[1,2,3,4]

BAM + ETE for Treatment of Mild or Moderate COVID-19

BLAZE-1 Phase 3 Trial

BAM + ETE Reduced COVID-19-Related Hospitalization or Death by Day 29[1]



- No patients in the BAM + ETE group died
- Viral load reduction by day 7 was ~16 times higher in BAM + ETE[a]
- Time to symptom resolution was 1 day shorter in BAM + ETE[b]
- Among those hospitalized, duration was 4 days shorter with BAM + ETE

[a]*P*<0.001; [b]*P*<0.01.

N=1035 ambulatory adolescents and adults who tested positive for SARS-CoV-2 and had >1 risk factor for severe COVID-19 were randomly assigned to 1 dose of placebo or 2800 mg BAM + 2800 mg ETE IV within 3 days of positive test result.

Dougan M, et al. *N Engl J Med*. 2021. [Epub ahead of print].

Evidence for Monoclonal Antibodies in Early COVID – Regen-Cov

- Regen- Cov
- mAb Combination
  - Casirivimab with Imdevimab
  - Study evolved as trial progressed
  - 3 arms - 2400mg, 1200 mg, placebo
  - Onset of symptoms < 7 days
- Independent monitoring Committee recommended to stop enrollment in Placebo Arm

Weinreich, D. M., et al. (2021). REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19, *New England Journal of Medicine*. https://doi.org/10.1056/NEJMoa2108163.

Regen-Cov

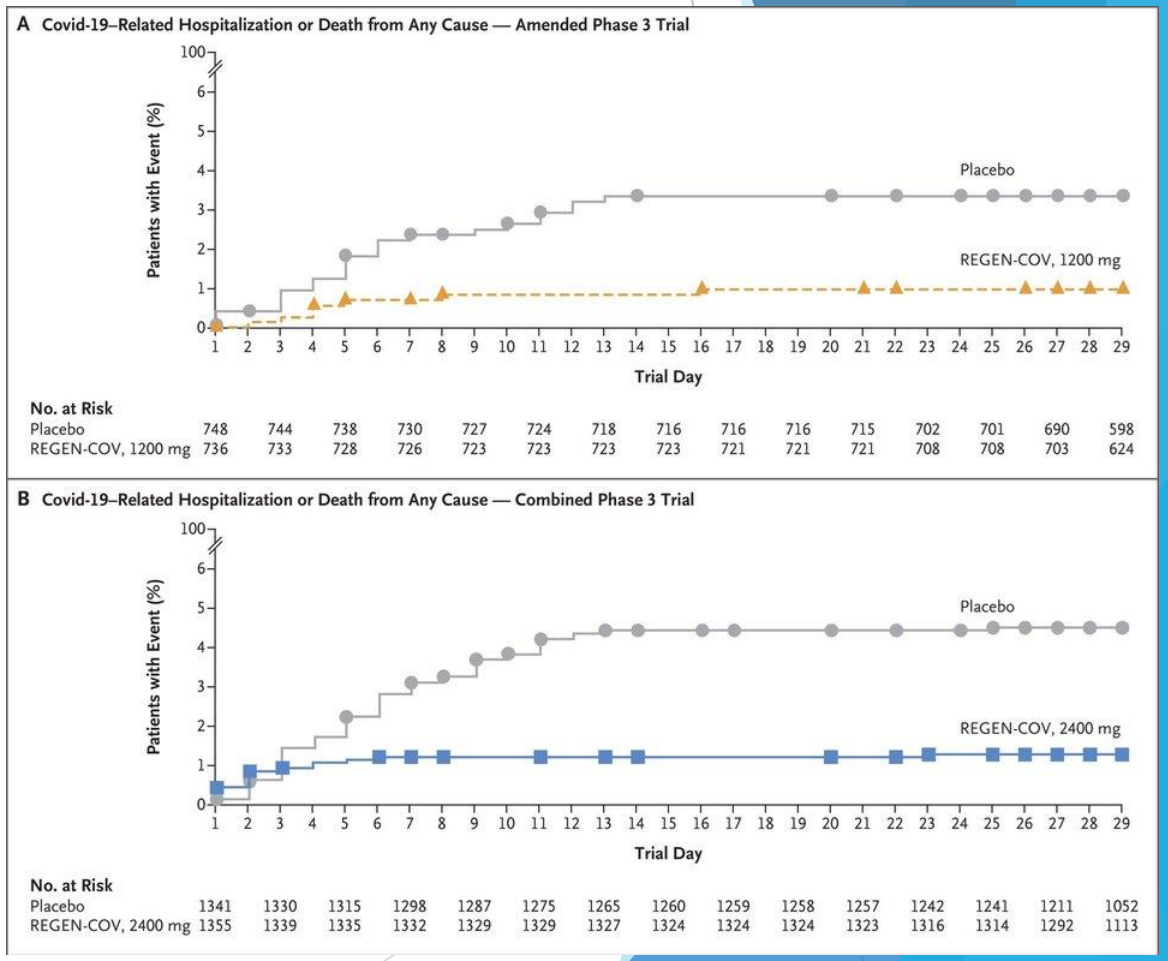
- In the primary efficacy population
  - Obesity
  - CV disease, including hypertension
  - Chronic lung, liver, kidney disease
  - Chronic metabolic disease, Diabetes
  - Immunosuppressed, investigator judgement

- OR age >50

Weinreich, D. M., et al. (2021). REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19, *New England Journal of Medicine*. https://doi.org/10.1056/NEJMoa2108163.

Treating COVID-19 With CAS + IMD in High-Risk Patients

- Reductions in hospitalization or death
- Results similar with 2400 mg and 1200 mg
- 2400 mg – 71.3% reduction (1.3 vs. 4.6%)
- 1200 mg – 70.4% reduction (1 vs. 3.2%)
- Safe
- Serious adverse events more in placebo group – 4% vs. 1.1 - 1.7%
- Thought to be related to Covid, not the drug
- Grade ≥ 2 infusion related reactions negligible
- 0 in placebo vs. 2, 1 in active arms



Weinreich, D. M., et al. (2021). REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19, *New England Journal of Medicine*. https://doi.org/10.1056/NEJMoa2108163.

Evidence for Monoclonal Antibodies in Early COVID – Sotrovimab

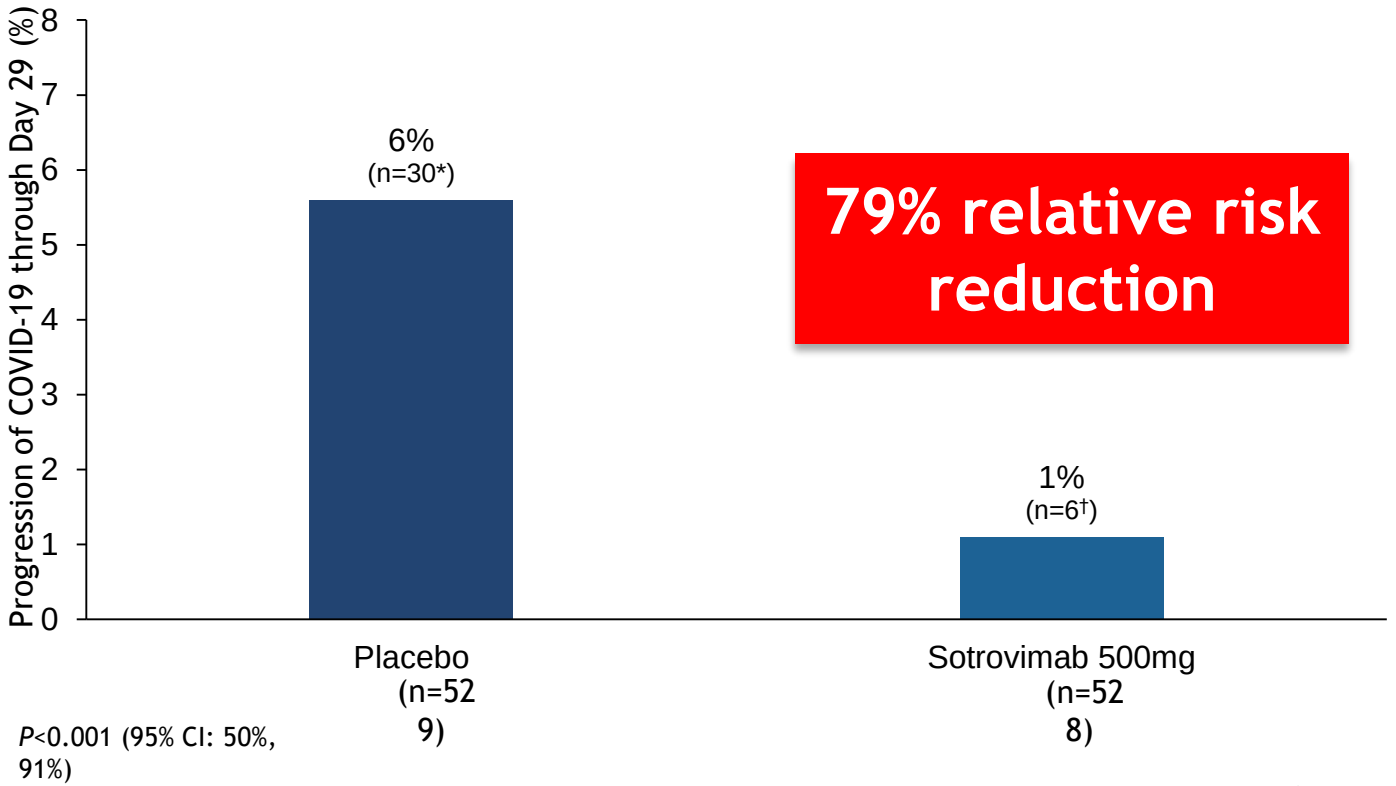
- Sotrovimab

- Outpatient study
- At risk for progression of Covid
  - Obesity (BMI > 30)
  - Chronic kidney disease (eGFR < 60)
  - Congestive heart failure
  - COPD or asthma
  - Diabetic
  - Or age ≥ 55 years
- Symptom onset < 5 days

Gupta, A., et al. (2021). Early Covid-19 Treatment With SARS-CoV-2 Neutralizing Antibody Sotrovimab, *medRxiv*, 2021.2005.2027.21257096. https://doi.org/10.1101/2021.05.27.21257096

Sotrovimab impact in Covid-19 High Risk patients

COMET-ICE primary endpoint : Reduction of hospitalization >24h for acute management of illness or death from any cause through Day 29 (ITT population)



P<0.001 (95% CI: 50%, 91%)

- Hospitalization, ER visits reduced by **66%**
- **74%** risk reduction risk of severe and/or critical COVID 19
- No participants treated with sotrovimab required high-flow O_2, non-rebreather mask or mechanical ventilation
- Most common AEs: diarrhoea (2%) and rash (1%); all Grade 1(mild) or Grade 2 (moderate)
- No SAEs reported considered related to treatment

*Of the 30 participants in the placebo group who met the primary endpoint, 29 were hospitalized and two died; †Of the six participants in the sotrovimab group who were hospitalized, three were likely hospitalized due to non-COVID-19 causes including small bowel obstruction, lung cancer and a diabetic foot ulcer.

CI, confidence interval; ITT, Intent-to-Treat

1. Sotrovimab Product Monograph (14 Sept 2021) https://ca.gsk.com/media/1741008/sotrovimab_pm-2021-07-30.pdf; 2. GSK, Data on File REF-133050.

Secondary endpoints (1 of 2)

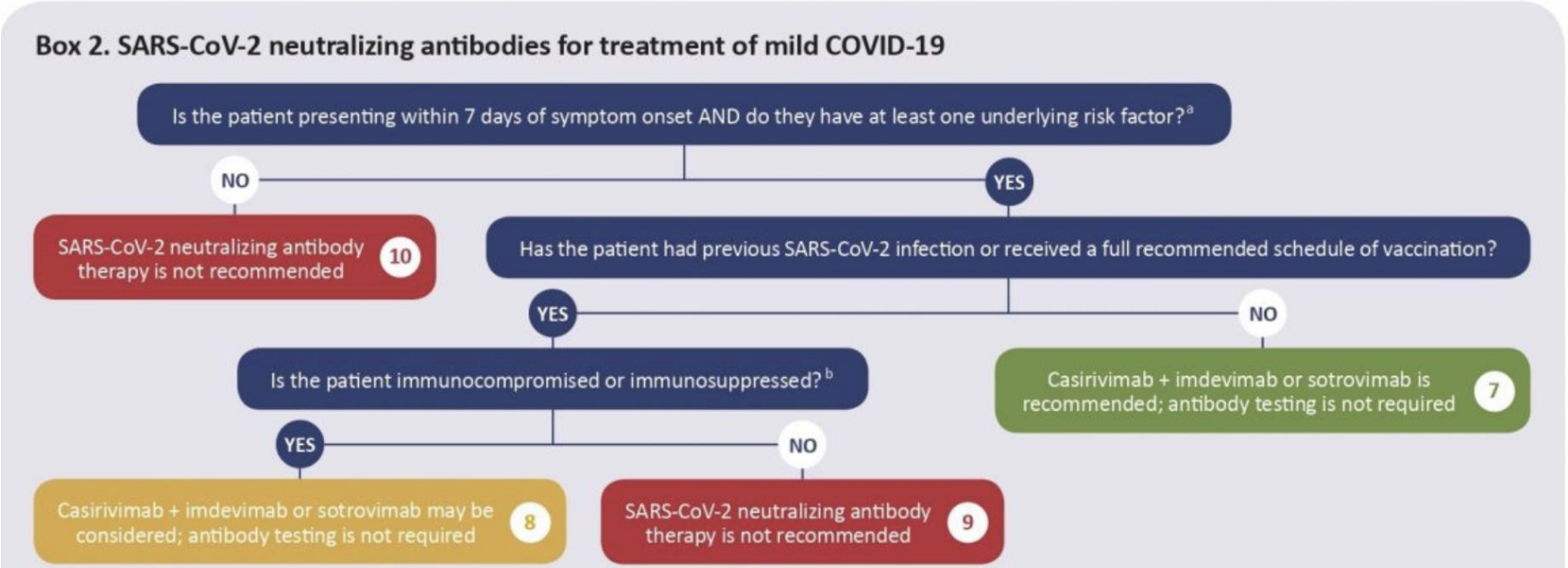
Progression of COVID-19 through Day 29 defined as visit to ER, hospitalization or death (ITT population)

Sotrovimab resulted in a 66% reduction in the need for hospitalization (of any duration), ER visit or death compared with placebo

	Placebo (n=529)	Sotrovimab 500mg (n=528)
Progression status, n (%)		
Hospitalized, ER visit and/or death due to any cause	**39 (7%)**	**13 (2%)**
• Hospitalized	29 (5%)	7 (1%)
• ER visit	10 (2%)	6 (1%)
• Death	2 (<1%)	0
Alive and not hospitalized and no ER visit	485 (92%)	508 (96%)
Missing	5 (<1%)	7 (1%)
Sotrovimab 500mg vs. Placebo		
Adjusted relative risk reduction	**66%**	
• 95% CI	37%, 81%	
• *P*-value	**<0.001**	

CI, confidence interval; ITT, Intent-to-Treat
GSK, Data on File REF-133050.

Ontario Science Table Recommendations



SCENARIO	RECOMMENDATION[a]
No history of vaccination or SARS-CoV-2 infection, with risk factors[b]	● 7 Casirivimab + imdevimab 1200 mg IV/SC OR sotrovimab 500 mg IV **is recommended** for mildly ill patients who meet the following criteria: (1) no history of SARS-CoV-2 infection or having received a full recommended schedule of vaccination, AND (2) confirmed, symptomatic COVID-19, AND (3) within 7 days of onset of any COVID-19 symptom, AND (4) at least one underlying risk factor[b]. Anti-spike antibody testing is not required.
History of vaccination or SARS-CoV-2 infection, immunocompromised or immunosuppressed[c]	▲ 8 Casirivimab + imdevimab 1200 mg IV/SC OR sotrovimab 500 mg IV **may be considered** for mildly ill patients who meet the following criteria: (1) history of SARS-CoV-2 infection or having received a full recommended schedule of vaccination, AND (2) confirmed, symptomatic COVID-19, AND (3) within 7 days of onset of any COVID-19 symptom, AND (4) immunocompromised or immunosuppressed[c]. Anti-spike antibody testing is not required.
History of vaccination or SARS-CoV-2 infection, with risk factors[b] other than immunocompromise or immunosuppression	■ 9 Monoclonal antibody therapy is **not recommended** for mildly ill patients who are not immunocompromised or immunosuppressed and are presumed to have immunity (through receiving a full recommended schedule of vaccination or previous infection).
No risk factors[b]	■ 10 Monoclonal antibody therapy is **not recommended** for patients at low risk of adverse outcomes, whether or not they are presumed to have immunity.

Omicron and it’s impact

b

	D614G	Alpha	Gamma	Beta	Delta	Omicron
LY−CoV555	0.013	0.008	>10	>10	>10	>10
LY−CoV016	0.032	1.707	>10	>10	0.024	>10
REGN10933	0.005	0.007	0.055	0.098	0.003	>10
REGN10987	0.005	0.003	0.003	0.002	0.005	>10
AZD8895	0.001	0.002	0.012	0.014	0.002	6.860
AZD1061	0.001	0.001	0.002	0.003	0.004	>10
VIR−7831	0.058	0.080	0.066	0.050	0.073	0.181
BRII−196	0.053	0.031	0.041	0.030	0.042	7.258
DXP−604	0.010	0.007	0.005	0.065	0.016	0.287

IC50 (ng/μL)

0 5 10

B.1.1.529 escapes the majority of SARS-CoV-2 neutralizing antibodies of diverse epitopes https://www.biorxiv.org/content/10.1101/2021.12.07.470392v1