COMET-ICE Study

Interim Analysis and Headline Results of Final Day 29 Data

For Medical Reactive Use

Date of Preparation – June 2021

Please note that some information in this slide deck is subject to change and might not be accurate at a future date

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Risk factors for severe COVID-19–related disease

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COVID-19–related disease: Risk factors for infection and severe disease

Age: Risk for infection and severe disease with increasing age[1-3]

Sex: Similar rate of infection among males and females;[2] however, rates of severe disease are higher among males than females[2,3]

Comorbidities: Underlying health conditions including **obesity** further increase the risk for severe COVID-19[1,3]

Ethnicity: Racial and ethnic minorities have higher risk for infection and severe disease[1]

1. NIH, COVID-19 Treatment Guidelines (accessed June 23, 2021); 2. Stokes EK, et al. *MMWR Morb Mortal Wkly Rep*. 2020;69:759–65; 3. Garg S, et al. *MMWR Morb Mortal Wkly Rep*. 2020;69:458–64.

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Age and pre-existing co-morbidities are risk factors for critical disease and death

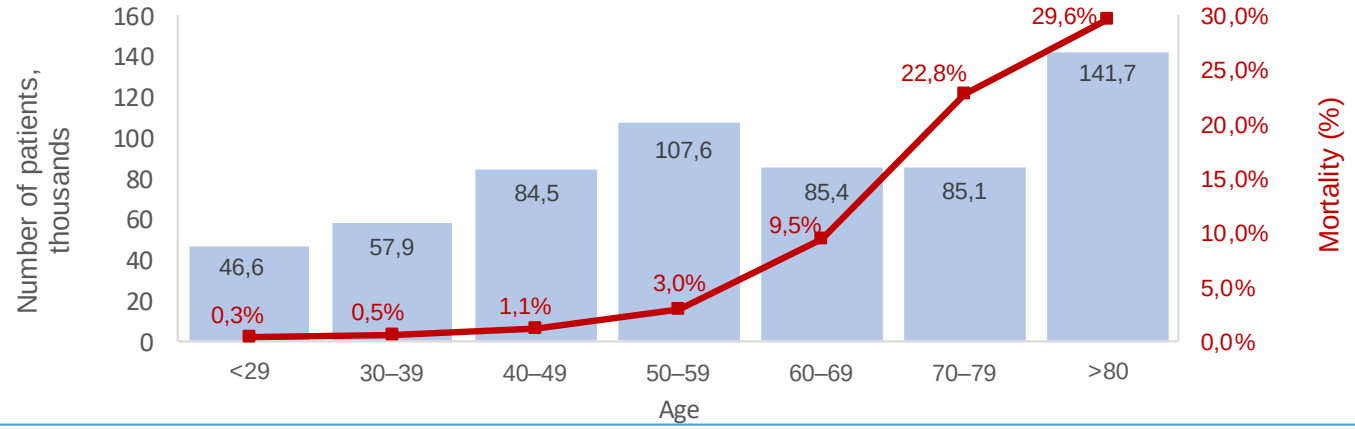
Increasing age

- Risk of critical disease/death increases with age[1-3]
- Risk of critical disease/death at >65 years: OR 6.01 (95% CI 3.95–9.16*)[4]

Smoking status

- Smoking increases risk of critical disease/ death (OR 2.04; 95% CI 1.32–3.15)*[4]
- Smoking impairs lung function and ability to fight SARS-CoV-2[1,5]

Age and crude mortality rates†[3]



Comorbid disease[6]

Comorbidity	Risk of serious events (odds ratio)‡
COPD	6.66
CKD	5.32
CVD	4.58
Diabetes	3.07
Hypertension	2.95

Figure reprinted from Bonanad C, et al. The Effect of Age on Mortality in Patients With COVID-19:A Meta-Analysis With 611,583 Subjects. *JAMDA*. 2020;21:915–18, with permission from Elsevier.

*Based on a systematic review and meta-analysis of 13 studies including 3027 patients; †based on a systematic review and meta-analysis of 17 studies including 611,583 patients; ‡based on a meta-analysis of 16 studies including 3,994 patients; results are ORs demonstrating a significant association of serious events in patients with COVID-19.

CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

1. WHO, Clinical Management of COVID-19 (accessed June 11, 2021); 2. NIH, COVID-19 Treatment Guidelines (accessed June 23, 2021); 3. Bonanad C, et al. JAMDA. 2020;21:915–18; 4. Zheng Z, et al. J Infect. 2020;81:e16-e25; 5. WHO, Statement on tobacco use and COVID-19 (accessed June 11, 2021); 6. Nandy K, et al. Diabetes Metab Syndr. 2020;14:1017–25.

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Sotrovimab (VIR-7831): Background and rationale in COVID-19

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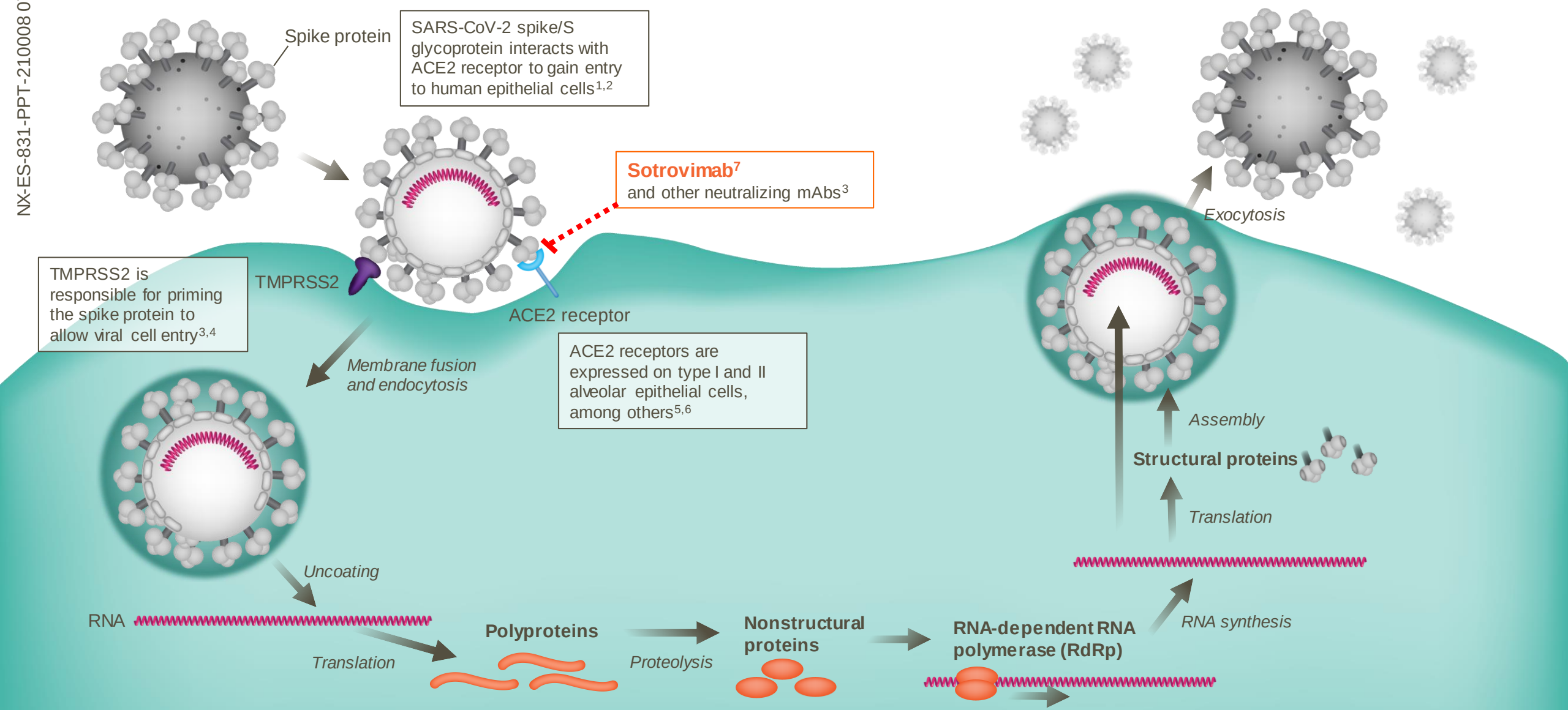
SARS-CoV-2 viral infection and replication

Sotrovimab binds to the SARS-CoV-2 spike protein and prevents viral entry into host cells



ACE2, angiotensin-converting enzyme 2; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, type 2 transmembrane serine protease.

1. Bergmann CC & Silverman RH. *Cleve Clin J Med*. 2020;87:321–7; 2. Jiang S, et al. *Trends Immunol*. 2020;41:355–9; 3. Elshabrawy HA. *Vaccines*. 2020;8:335; 4. Hoffman M, et al. *Cell.* 2020;181(2):271–280; 5. Sun P, et al. *J Med Virol*. 2020;92:548-551; 6. Zhao Y, et al. *Am J Resp Crit Care Med* 2020;202:756–9;. 7. Pinto D, et al. Nature. 2020;583:290–5.

Dual action of sotrovimab: Neutralization and effector functions

Sotrovimab has demonstrated potent neutralization activity against SARS-CoV-2 in vitro and in vivo, which protects uninfected cells from becoming infected[1]

- Data show sotrovimab has broad neutralizing activity against multiple sarbecorviruses (including SARS-CoV-2 and SARS-CoV-1)[2]

Sotrovimab has preserved effector functions in vitro that may recruit the host immune system to kill already infected cells[1]

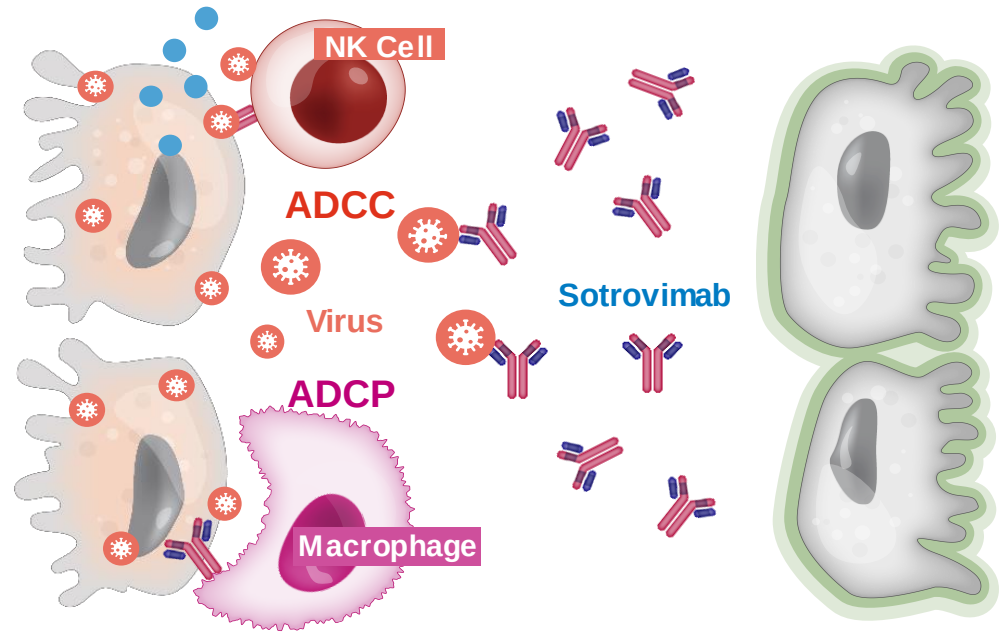
Antibody-dependent cell cytotoxicity (ADCC)[1–3]:

- mediated by natural killer cells
- triggers apoptosis of virus-infected target cells

Antibody-dependent cellular phagocytosis (ADCP)[1,2,4]:

- mediated by macrophages or dendritic cells
- helps clear virus and infected cells by engulfing/ destroying viral particles and stimulating a T-cell response

Neutralizing Activity and Antibody Effector Mechanisms



NK, natural killer; SARS-CoV, severe acute respiratory syndrome coronavirus.

1. Cathcart AL, et al. *bioRxiv* (preprint). doi: 10.1101/2021.03.09.434607; 2. Pinto D, et al. *Nature*. 2020;583:290–5; 3. Jegaskanda S, et al. *J Immunol*. 2014;193(2):469-475; 4. Sicca F, et al. *Expert Rev Vaccines*. 2018;17:785–95.

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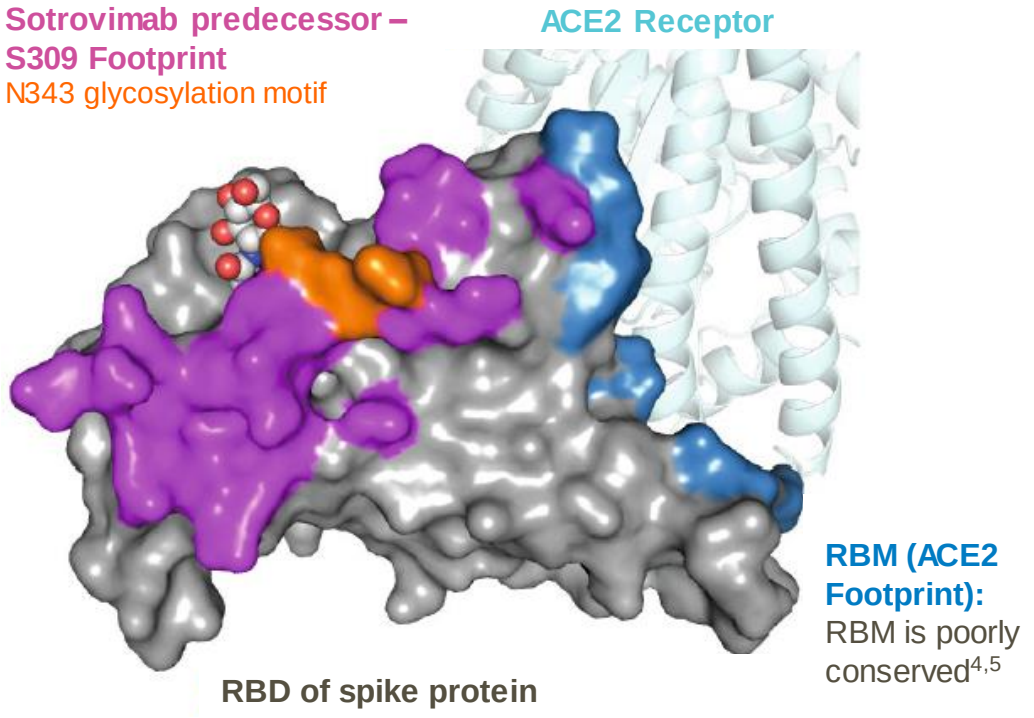
Binding to a highly conserved site on the spike protein

Genomic variations in SARS-CoV-2 may be linked to **pathogenesis, immune evasion** and **drug resistance**[1]

Evaluating mutations is crucial for drug/vaccine development to identify and target conserved regions less likely to change over time or **develop resistance**[1]

Sotrovimab binding site on the spike protein is highly conserved between coronaviruses, indicating the potential for a high barrier to virus resistance[2,3]



The illustration has been reproduced with the permission of Springer Pinto D, et al. *Nature* 2020;583:290–5. Copyright © 2020

ACE2, angiotensin converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

1. Laamarti M, et al. *PLoS One*. 2020;15(11):e0240345; 2. Pinto D, et al. *Nature*. 2020;583:290–5; 3. Cathcart AL, et al. *bioRxiv* (preprint). doi: 10.1101/2021.03.09.434607; 4. Chen Y, et al. *Biochem Biophys Res Commun*. 2020;525:135–40; 5. Robson B, *Comput Biol Med*. 2020;121:103749.

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Sotrovimab in the context of viral mutant emergence

- SARS-CoV-2 is rapidly evolving: treatments and vaccines need to retain activity against emergent variants of concern (VOCs)[1]

- Some mAbs bind to RBM (receptor-binding motif). This is the most structurally plastic, poorly conserved domain of the spike[2]; the non-RBM RBD is more conserved

- Sotrovimab was derived from an antibody isolated from a SARS-CoV-1 survivor and binds to the same highly conserved target epitope on the RBD (receptor-binding domain) of both viruses - which may make it more difficult for resistance to develop[3,4]

- Scientific analysis in pseudotyped virus systems demonstrates sotrovimab in vitro retains activity against emergent variants of concern[4]

mAb, monoclonal antibody; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

1. GISAID, https://www.gisaid.org (accessed May 14, 2021); 2. Thomson EC, et al. *Cell* 2021;184(5):1171-1187.e20. 3. Pinto D, et al. *Nature*. 2020;583:290–5; 4. Cathcart AL, et al. *bioRxiv* (preprint). doi: 10.1101/2021.03.09.434607.

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Sotrovimab retains *in vitro* neutralization activity against key SARS-CoV-2 variants in pseudotyped virus system[1,2]

WHO Label[3]	SARS-CoV-2 Variant Name	Variants in Tested Spike Sequence	Average Fold Change in EC_{50} vs Wild-type*	Neutralization, Retained/Lost*
Alpha	UK (B.1.1.7)	H69-, V70-, Y144-, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H	2.3	Retained activity
Beta	South Africa (B.1.351)	L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, A701V	0.6	Retained activity
Gamma	Brazil (P.1)	D138Y, D614G, E484K, H655Y, K417T, L18F, N501Y, P26S, R190S, T1027I, T20N, V1176F	0.4	Retained activity
Delta	India (B.1.617.2)	T19R, G142D, E156G, F157-, R158-, L452R, T478K, D614G, P681R, D950N	1.0	Retained activity
Kappa	India (B.1.617.1)	T95I, G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H	0.7	Retained activity
Epsilon	California (B.1.427/B.1.429)	S13I, W152C, L452R, D614G	0.7	Retained activity
Eta	Nigeria (B.1.525)	Q52R, A67V, H69-, V70-, Y144-, E484K, D614G, Q677H, F888L	0.9	Retained activity
Iota	New York (B.1.526)	L5F, T95I, D253G, E484K, D614G, A701V	0.6	Retained activity
N/A	Mexico/Swiss (B.1.1.519)	T478K, D614G, P681H, T732A	0.8	Retained activity
N/A	Scotland (B.1.258)	H69-, V70-, N439K, D614G	0.9	Retained activity
N/A	US (R.2)	E484K, D614G, Q677H, T732S, E1202Q	0.8	Retained activity
N/A	Liverpool (A.23.1)	R102I, F157L, V367F, E484K, Q613H, P681R	1.1	Retained activity
N/A	Bristol (B.1.1.7 + E484K)	H69-, V70-, Y144-, E484K, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H	1.7	Retained activity
N/A	Cameroon (B.1.619)	I210T, N440K, E484K, D614G, D936N, S939F, T1027I	1.3	Retained activity

*Retained activity = <3-fold reduction in average fold change.[2]

EC_{50}, half maximal effective concentration; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2

1. US Food and Drug Administration, Sotrovimab Fact Sheet for Healthcare Providers (accessed June 11, 2021); 2. Cathcart AL, et al. *bioRxiv* (preprint). doi: 10.1101/2021.03.09.434607; 3. WHO, Tracking SARS-CoV-2 Variants (accessed June 10, 2021)

COMET-ICE

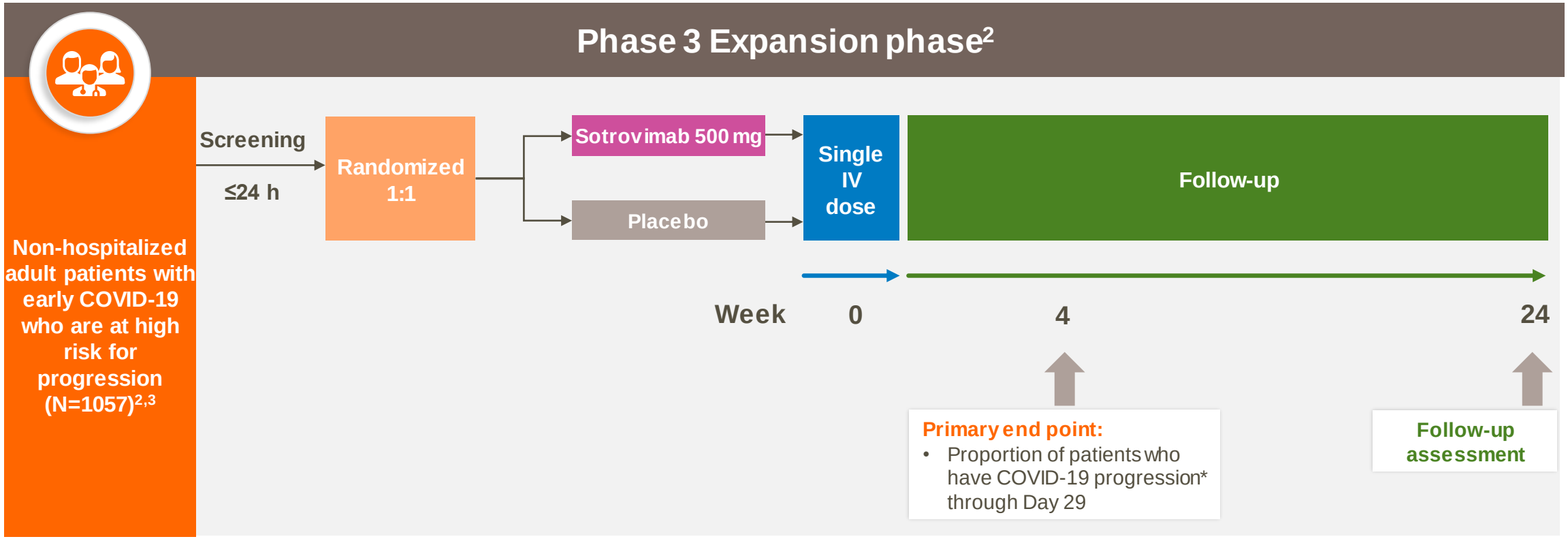
(**CO**VID-19 **M**onoclonal antibody **E**fficacy **T**rial – **I**ntent to **C**are **E**arly **NCT04545060)**

Study design

COMET-ICE: Study design

Expansion phase

Following a positive evaluation of data from the Phase 2 Lead-in phase, the Independent Data Monitoring Committee recommended on September 30, 2020 that the study continue into Phase 3[1]



*Progression defined by the need for hospitalization >24 hours for acute management of any illness or death due to any cause.[2]

ER, emergency room; IV, intravenous.

1. GSK, Press Release October 06, 2020 (accessed June 10, 2021); 2. Gupta A, et al. *medRxiv* (preprint). doi: 10.1101/2021.05.27.21257096; 3. GSK, Press release June 21, 2021 (accessed June 23, 2021).

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COMET-ICE: Objectives and endpoints

Objectives	Endpoints[1,2]
Primary	
Efficacy	• **Proportion of patients who have COVID-19 progression through Day 29 (defined as hospitalization >24 hours for acute management of any illness or death due to any cause)**
Secondary	
Efficacy	• Proportion of patients with progression of COVID-19, defined by ER visit for management of illness, hospitalization for acute management of illness, or death, through Day 29 • Mean change in FLU-PRO Plus total score comparing sotrovimab vs placebo (AUC through Day 7) • Time to symptom alleviation using FLU-PRO Plus • Change from baseline in viral load in nasal secretions by qRT-PCR at Day 8 • Proportion of patients with progression to severe and/or critical respiratory COVID-19 as manifest by requirement for and method of supplemental oxygen at Day 8, Day 15, Day 22 or Day 29 • 29-, 60-, and 90-day all-cause mortality
Safety	• AEs, SAEs, and AESI • Incidence and titers of serum ADA (if applicable)
Pharmacokinetics	• Sotrovimab pharmacokinetics in serum
Select exploratory endpoints	
Efficacy, viral characteristics, immunogenicity, and health-related quality of life	• Number of ventilator days • Total length of stay in hospital and intensive care • Proportion of patients hospitalized for non-respiratory complications (includes COVID-19–related cardiac, renal, neurologic, and hematologic events) • Work productivity and quality of life • Emergence of viral resistance • Detection of SARS-CoV-2 in nasal secretions and blood • Host immune responses and biomarkers

ADA, anti-drug antibody; AEs, adverse events; AESI, adverse events of special interest; AUC, area under the curve; ER, emergency room; FLU-PRO, influenza patient-reported outcome; qRT-PCR, quantitative reverse transcription polymerase chain reaction; SAEs, serious adverse events; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

1. ClinialTrials.gov, NCT04545060 (accessed June 10, 2021); 2. Data on file [001a]. Vir Biotechnology, San Francisco.

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COMET-ICE: Summary of inclusion criteria

Disease characteristics[1]

- Positive SARS-CoV-2 result (e.g. RT-PCR on any specimen type)
- **AND** oxygen saturation ≥94% on room air
- **AND** have COVID-19 symptoms
- **AND** ≤5 days from symptom onset

Age[1]

- ≥18 years with ≥1 risk factor for COVID-19 progression *or*
- ≥55 years

Sex[1,2]

No restriction*

*Female participants must meet and agree to abide by the contraceptive criteria detailed in the protocol[2]

RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

1. ClinicalTrials.gov, NCT04545060 (accessed June 10, 2021); 2. Gupta A, et al. *medRxiv* (preprint). doi: 10.1101/2021.05.27.21257096.

COMET-ICE: High-risk patient population

Patients ≥18 years are considered at high risk for progression of COVID-19 based on the presence of one or more of the following[1,2]:

- Diabetes (requiring medication)
- Obesity (BMI >30 kg/m^2)
- Chronic kidney disease (i.e., eGFR <60 mL/min/1.72m^2 by MDRD)
- Congestive heart failure (NYHA class II or more)
- Chronic obstructive pulmonary disease (history of chronic bronchitis, chronic obstructive lung disease, or emphysema with dyspnea on physical exertion)
- Moderate to severe asthma (participant requires an inhaled steroid to control symptoms or has been prescribed a course of oral steroids in the past year)

BMI, body mass index; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; NYHA, New York Heart Association.

1. ClinicalTrials.gov, NCT04545060 (accessed June 10, 2021); 2. Gupta A, et al. *medRxiv* (preprint). doi: 10.1101/2021.05.27.21257096.

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COMET-ICE: Summary of exclusion criteria

Medical conditions

- Current hospitalization or judged as likely to be hospitalized in 24 hours
- Symptoms consistent with severe COVID-19, including requirement for supplemental oxygen
- Participants judged likely to die in next 7 days
- Participants who are severely immunocompromised
- Known hypersensitivity to sotrovimab or any constituent in the product
- Previous anaphylaxis or hypersensitivity to a mAb

Prior/concurrent clinical study experience

- Enrollment in any investigational vaccine trial in last 180 days or any investigational drug trial within 30 days prior to Day 1 or within 5 half-lives of the investigational compound
- Enrollment in any SARS-CoV-2 vaccine trial

Other

- Receipt of any vaccine within 48 hours prior to enrollment
- Receipt of a SARS-CoV-2 vaccine prior to randomization at any timepoint
- Receipt of convalescent plasma from a recovered COVID-19 patient or anti-SARS-CoV-2 mAb within last 3 months
- Participants who will be unlikely or unable to comply with protocol requirements through Day 29

mAb, monoclonal antibody; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Gupta A, et al. *medRxiv* (preprint). doi: 10.1101/2021.05.27.21257096.

COMET-ICE: Medications during the study

Medication NOT PERMITTED during the study

- Hydroxychloroquine and chloroquine
- Convalescent plasma from COVID-19 patient or anti-SARS-CoV-2 monoclonal antibody
- Any vaccine within 4 weeks after dosing
- Any investigational or approved SARS-CoV-2 vaccine within 4 weeks after dosing

Medication PERMITTED during the study

- All medication received as local, established standard of care for acute COVID-19

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Data on file [001a]. Vir Biotechnology, San Francisco.

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COMET-ICE

(**CO**VID-19 **M**onoclonal antibody **E**fficacy **T**rial – **I**ntent to **C**are **E**arly **NCT04545060**)

Interim Analysis

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COMET-ICE: Study populations

Efficacy and safety populations for interim and final analyses

	Placebo	Sotrovimab	Total
Intent-to-Treat (ITT)[1,2]	529	528	1057
Intent-to-Treat - Interim analysis[3,4]	292	291	583
Safety[1]	526	523	1049
Safety - Interim analysis[3,4]	438	430	868

- ITT: all subjects who were randomly assigned to study treatment[1]
- ITT (IA): All participants who were randomly assigned to study intervention by 19 January 2021[4]
- Safety: All subjects who received study treatment (presented by actual treatment)[1]
- Safety (IA): All randomized participants who were exposed to study intervention up to 17 February 2021 (29 days after the ITT [IA] cut off). Includes safety data for these participants up to 04 March 2021[4]

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IA, interim analysis

1. GSK, Data on File REF-125366; 2. GSK, Press release June 21, 2021 (accessed June 23, 2021); 3. US Food and Drug Administration, Sotrovimab Fact Sheet for Healthcare Providers (accessed June 11, 2021);
4. Gupta A, et al. *medRxiv* (preprint). doi: 10.1101/2021.05.27.21257096.

COMET-ICE (Interim Analysis): Baseline characteristics[1]

Baseline demographics were well balanced between treatment arms

	ITT (Interim Analysis) Population			Safety (Interim Analysis) Population		
	Placebo (n = 292)	Sotrovimab (n = 291)	Total (N = 583)	Placebo (n = 438)	Sotrovimab (n = 430)	Total (N = 868)
Age (y), median (range)	53 (18-88)	53 (18-96)	53 (18-96)	52 (17-88)	53 (18-96)	53 (17-96)
≥65 yrs, n (%)	65 (22%)	63 (22%)	128 (22%)	88 (20%)	84 (20%)	172 (20%)
>70 yrs, n (%)	32 (11%)	33 (11%)	65 (11%)	42 (10%)	42 (10%)	84 (10%)
Male Gender, n (%)	131 (45%)	135 (46%)	266 (46%)	212 (48%)	194 (45%)	406 (47%)
Race, n (%)						
White	252 (87%)	254 (88%)	506 (87%)	384 (88%)	374 (87%)	758 (88%)
Black or African American	22 (8%)	16 (6%)	38 (7%)	33 (8%)	27 (6%)	60 (7%)
Asian*	17 (6%)	17 (6%)	34 (6%)	19 (4%)	21 (5%)	40 (5%)
Ethnicity Hispanic/Latino, n (%)	178 (61%)	190 (65%)	368 (63%)	280 (64%)	280 (65%)	560 (65%)
BMI (kg/m^2)						
Mean ± SD	32.1 (6.3)	32.0 (6.4)	32.1 (6.3)	32.5 (6.7)	32.1 (6.4)	32.3 (6.5)
Duration of Symptoms, n (%)						
≤ 3 days	171 (59)	167 (57)	388 (58)	260 (59)	254 (59)	514 (59)
4-5 days	121 (41)	123 (42)	244 (42)	178 (41)	173 (40)	351 (40)

*COMET-ICE has not recruited any Japanese participants. ITT (IA) Population includes Asian: 3 (<1%) of SE Asian Heritage, 6 (1%) East Asian Heritage.[2]

BMI, body mass index; ITT, Intent-to-Treat; SD, standard deviation

1. Gupta A, et al. *medRxiv* (preprint). doi: 10.1101/2021.05.27.21257096; 2. GSK, Data on file. 2021N472668_00.

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COMET-ICE (Interim Analysis): Baseline risk factors

The most common predefined risk factors were obesity, age ≥55 years, and diabetes

	ITT (Interim Analysis) Population			Safety (Interim Analysis) Population		
	Placebo (n = 292)	Sotrovimab (n = 291)	Total (N = 583)	Placebo (n = 438)	Sotrovimab (n = 430)	Total (N = 868)
Any condition, n (%)	290 (>99%)	291 (100%)	581 (>99%)	434 (>99%)	427 (>99%)	861 (>99%)
Age ≥55 yrs	141 (48%)	135 (46%)	276 (47%)	205 (47%)	195 (45%)	400 (46%)
Diabetes requiring medication	66 (23%)	66 (23%)	132 (23%)	88 (20%)	93 (22%)	181 (21%)
Obesity (BMI >30 kg/m^2)	187 (64%)	182 (63%)	369 (63%)	292 (67%)	267 (62%)	559 (64%)
Chronic kidney disease (eGFR <60 by MDRD)	4 (1%)	1 (<1%)	5 (<1%)	5 (1%)	2 (<1%)	7 (<1%)
Congestive heart failure (NYHA class II or more)	3 (1%)	1 (<1%)	4 (<1%)	3 (<1%)	4 (<1%)	7 (<1%)
COPD	10 (3%)	14 (5%)	24 (4%)	18 (4%)	24 (6%)	42 (5%)
Moderate to severe asthma	46 (16%)	46 (16%)	92 (16%)	72 (16%)	69 (16%)	141 (16%)
Number of conditions met, n (%)						
0	2 (<1%)	0	2 (<1%)	4 (<1%)	3 (<1%)	7 (<1%)
1	168 (58%)	170 (58%)	338 (58%)	250 (57%)	251 (58%)	501 (58%)
2	86 (29%)	91 (31%)	177 (30%)	130 (30%)	132 (31%)	262 (30%)
≥3	36 (12%)	30 (10%)	66 (11%)	54 (13%)	44 (10%)	98 (11%)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; NYHA, New York Heart Association; ITT, Intent-to-Treat

Gupta A, et al. *medRxiv* (preprint). doi: 10.1101/2021.05.27.21257096.

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COMET-ICE (Interim Analysis): Baseline characteristics

Baseline demographics were well balanced between treatment arms

ITT population (N = 583)

In the overall ITT population:

- **46%** of participants were male
- **63%** were Hispanic/Latinx
- **7%** were Black or African American

The median age was **53 (range: 18-96) years**

The mean BMI was **32.1 (SD: 6.3) kg/m²**

Safety population (N = 868)

In the overall Safety population:

- **47%** of participants were male
- **65%** were Hispanic/Latinx
- **7%** were Black or African American

The median age was **53 (range: 17-96) years**

The mean BMI was **32.3 (SD: 6.5) kg/m²**

The most common pre-defined risk factors at baseline were

Obesity (BMI >30 kg/m²) – reported in **63%** and **64%** of the ITT and safety populations, respectively

Age ≥55 years – reported in **47%** and **46%** of the ITT and safety populations, respectively

Diabetes requiring medication – reported in **23%** and **21%** of the ITT and safety populations, respectively

BMI, body mass index; ITT, intent-to-treat; SD, standard deviation

Gupta A, et al. *medRxiv* (preprint). doi: 10.1101/2021.05.27.21257096.

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COMET-ICE (Interim Analysis): Primary endpoint

Hospitalization >24 hours for acute management of illness or death through Day 29

Treatment with sotrovimab resulted in an 85% reduction in hospitalization >24 hours or death compared to placebo (*P*=0.002)

	Placebo (n = 292)	Sotrovimab (n = 291)
Progression Status, n (%)		
Hospitalized >24 hours or death for any cause	**21 (7%)**	**3 (1%)**
Hospitalized >24 hours for any cause	21 (7%)	3 (1%)
Death by any cause	1 (<1%)	0
Alive and not hospitalized	270 (92%)	284 (98%)
Missing	1 (<1%)	4 (1%)
Withdrew consent prior to dosing	1 (<1%)	3 (1%)
Sotrovimab 500 mg vs. placebo		
Adjusted relative risk reduction		**85%**
(97.24% CI)		(44%, 96%)
p-value		**0.002**

CI, confidence interval

Gupta A, et al. *medRxiv* (preprint). doi: 10.1101/2021.05.27.21257096.

COMET-ICE (Interim Analysis): Key secondary endpoint*

Hospital emergency room (ER), hospitalization or death through Day 29

Treatment with sotrovimab resulted in a numerical reduction in need for ER visit, hospitalization (for any duration), or death compared to placebo

	Placebo (n = 292)	Sotrovimab (n = 291)
Progression Status, n (%)		
Hospitalized, ER visit or Death for any cause	**28 (10%)**	**6 (2%)**
Hospitalized (for any cause or duration)	21 (7%)	4 (1%)†
ER visit for any cause	8 (3%)	2 (<1%)
Death by any cause	1 (<1%)	0
Alive and not hospitalized	263 (90%)	281 (97%)
Missing	1 (<1%)	4 (1%)

*Results are descriptive only. No inferences can be made until results of full analyses are known for all endpoints within the testing hierarchy; †One patient was hospitalized for <24 hours for diabetes management.

ER, emergency room

Gupta A, et al. *medRxiv* (preprint). doi: 10.1101/2021.05.27.21257096.

COMET-ICE (Interim Analysis): Key secondary endpoint*

Development of severe and/or critical respiratory COVID-19 (Day 29)

- **Treatment with sotrovimab resulted in a numerical reduction in the risk of severe and/or critical respiratory COVID-19 compared to placebo**
- **No participants treated with sotrovimab required use of high-flow oxygen, non-rebreather mask or mechanical ventilation**

	Placebo (n = 292)	Sotrovimab (n = 291)
No need for supplemental oxygen, n (%)	272 (93%)	285 (98%)
Need for supplemental oxygen, n (%)	19 (7%)	2 (<1%)
Category 2: Low flow nasal cannula/face mask	11 (4%)	2 (<1%)
Category 3: Non-re-breather mask or high flow nasal cannula/non-invasive ventilation	5 (2%)	0
Category 4: Mechanical ventilation/extra-corporeal membrane oxygenation	2 (<1%)	0
Death	1 (<1%)	0
Missing, n (%)	1 (<1%)	4 (1%)

*Results are descriptive only. No inferences can be made until results of full analyses are known for all endpoints within the testing hierarchy.

Gupta A, et al. *medRxiv* (preprint). doi: 10.1101/2021.05.27.21257096.

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COMET-ICE (Interim Analysis): Key secondary endpoint*

All-cause mortality (up to Day 29)

- No deaths occurred in the sotrovimab treatment arm (n = 291) up to Day 29
- 1 death (<1%) occurred in the placebo arm (n = 292) up to Day 29

*Results are descriptive only. No inferences can be made until results of full analyses are known for all endpoints within the testing hierarchy.

Gupta A, et al. *medRxiv* (preprint). doi: 10.1101/2021.05.27.21257096.

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COMET-ICE: Ongoing evaluation of resistance

Limited nucleotide sequencing data (N = 218)

Variant	Mutations	Baseline			Progressed to hospitalization		
		Sotrovimab	Placebo	Total	Sotrovimab	Placebo	Total
CAL.20C	S13I, W152C, L452R	4	5	9	1	0	1

- Two additional participants in the placebo group carried the L452R variant only
- None of the participants were infected with SARS-CoV-2 that contained the full complement of spike substitutions characteristic of the UK (B.1.1.7), South African (B.1.351), or Brazilian (P.1) variants
- One participant in the placebo group carried the N501Y variant at baseline

Post-baseline epitope variants detected in 8 participants in sotrovimab group

Participant	Post-baseline mutations	Allele frequency
#1	E340K	≥99.7%
#2	E340K	≥99.7%
#3	E340K	≥99.7%
#4	E340K	≥99.7%
#5	A344V	6.2%
#6	K356R	7.5%
#7	S359G	12.2%
#8	S359G	8.3%

Phenotypic assessment of sotrovimab activity in pseudotyped VLP system

Baseline and post-baseline mutation	Fold Change in EC_{50}
L335F	0.8
G339C	1.2
E340A	>100
E340K	>297
R346I	1.7
K356N	1.1
K356R	0.8
R357I	1
I358V	0.7
S359G	0.8

The clinical impact of these variants is not yet known. Data collection and analysis is still ongoing.

EC50 = Half maximal effective concentration; FC = fold change; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; VLP = virus-like particles.
US Food and Drug Administration, Sotrovimab Fact Sheet for Healthcare Providers (accessed June 11, 2021).

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COMET-ICE (Interim Analysis): Overview of adverse events

Interim Analysis, Safety Population (N = 868)

	Placebo (n = 438)	Sotrovimab (n = 430)
Any AE, n (%)	**85 (19%)**	**73 (17%)**
AEs related to study treatment	8 (2%)	8 (2%)
AEs leading to permanent discontinuation of study treatment	0	0
AEs leading to dose interruption/delay	0	2 (<1%)
Any infusion-related reaction, n (%)	**5 (1%)**	**6 (1%)**
Infusion-related reactions related to study treatment	2 (<1%)	1 (<1%)
Infusion-related reactions leading to permanent discontinuation of study treatment	0	0
Infusion-related reactions leading to dose interruption/delay	0	0
Any Grade 3 or 4 AE, n (%)	**27 (6%)**	**7 (2%)**
Any SAE, n (%)	**26 (6%)**	**7 (2%)**
SAEs related to study treatment	1 (<1%)	0
Fatal SAEs	2 (<1%)	0
Fatal SAEs related to study treatment	0	0

AE, adverse event; SAE, serious adverse event.
Gupta A, et al. *medRxiv* (preprint). doi: 10.1101/2021.05.27.21257096.

COMET-ICE (Interim Analysis): Serious adverse events

Interim Analysis, Safety Population (N = 868)

System Organ Class	Preferred Term	Placebo (n = 438) n (%)	Sotrovimab (n = 430) n (%)
Any Event		**26 (6%)**	**7 (2%)**
Infections and infestations	COVID-19 pneumonia	13 (3%)	1 (<1%)
	Pneumonia	6 (1%)	0
	Diverticulitis	0	2 (<1%)
	COVID-19	0	1 (<1%)
Metabolism and nutrition disorders	Dehydration	2 (<1%)	0
	Diabetes mellitus	0	1 (<1%)
	Hyperglycemia	0	1 (<1%)
	Hypovolaemia	1 (<1%)	0
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	1 (<1%)	0
	Dyspnea	1 (<1%)	0
	Hypoxia	1 (<1%)	0
	Pulmonary embolism	1 (<1%)	0
	Respiratory distress	1 (<1%)	0

GSK, Data on file. 2021N472668_00.

COMET-ICE (Interim Analysis): Serious adverse events (cont)

Interim Analysis, Safety Population (N = 868)

System Organ Class	Preferred Term	Placebo (n = 438) n (%)	Sotrovimab (n = 430) n (%)
Gastrointestinal disorders	Obstructive pancreatitis	1 (<1%)	0
	Small intestinal obstruction	0	1 (<1%)
Investigations	Oxygen saturation decreased	1 (<1%)	0
Neoplasms benign, malignant and unspecified	Non-small cell lung cancer	0	1 (<1%)
Renal and urinary disorders	Acute kidney injury	1 (<1%)	0

GSK, Data on file. 2021N472668_00.

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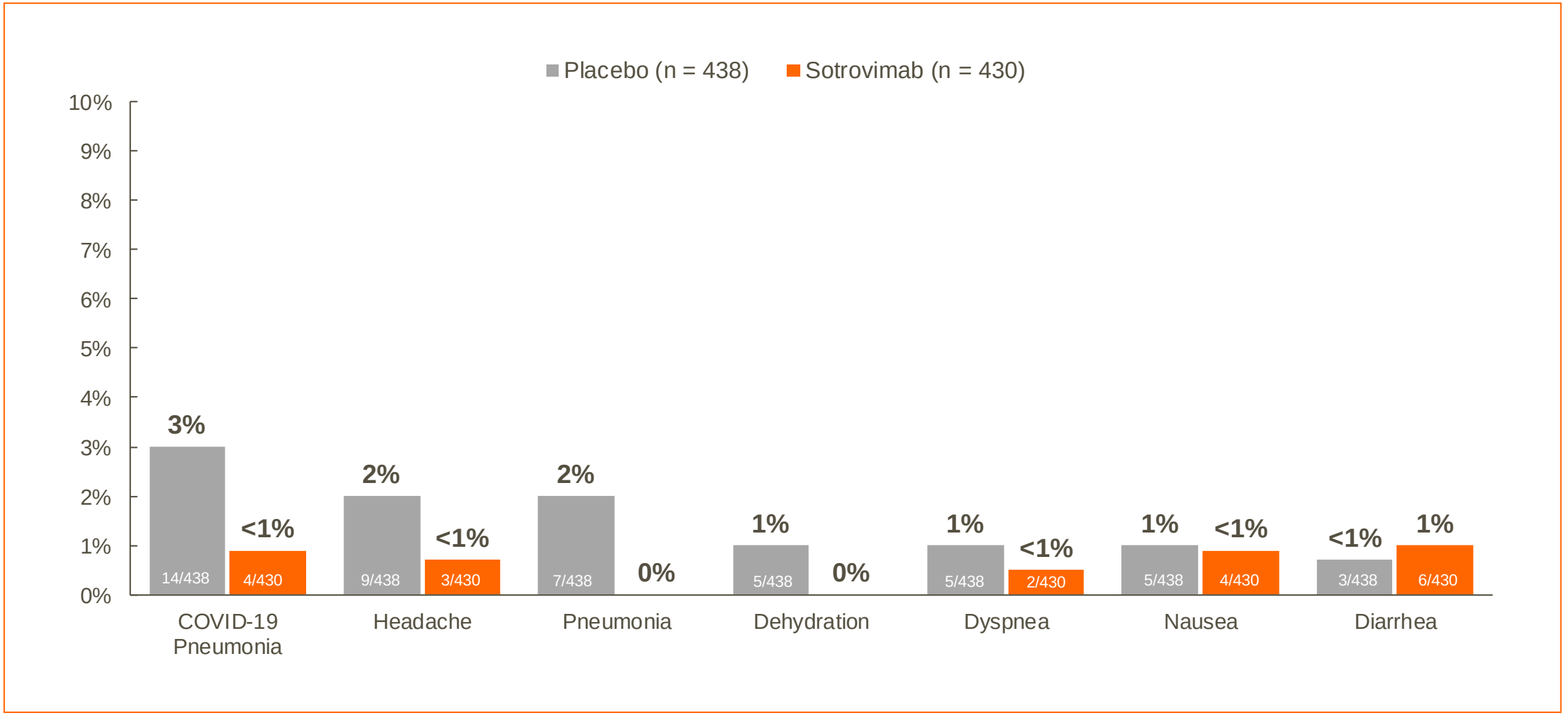
COMET-ICE (Interim Analysis): Adverse events ≥1% in either treatment arm[1]

Interim Analysis, Safety Population (N = 868)[2]



1. GSK, Data on file 2021N473826_00; 2. Gupta A, et al. *medRxiv* (preprint). doi: 10.1101/2021.05.27.21257096.

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COMET-ICE (Interim Analysis): Safety

Interim analysis results

Safety Population

- Of the 868 participants in the safety population, 583 have been followed to at least Day 29[1]
- Two patients experienced treatment interruption due to infusion-site extravasation. In each case, the infusion was completed[1]

Serious Adverse Events

- SAEs were reported in 2% (7/430) of patients in the sotrovimab group and 6% (26/438) of patients in the placebo group[1]
- Treatment-related SAEs were reported in 0% (0/430) of patients in the sotrovimab group and <1% (1/438) of patients in the placebo group[1]
- No events consistent with antibody dependent enhancement (ADE) were observed[1]

Infusion Reactions

- Immediate, non-serious hypersensitivity events were observed in 1% of patients in each treatment group[1]
- No cases of anaphylaxis following infusion of sotrovimab were reported[2]
- All events were Grade 1 (mild) or Grade 2 (moderate)[1,3]

1. Gupta A, et al. *medRxiv* (preprint). doi: 10.1101/2021.05.27.21257096; 2. GSK, Data on file. 2021N472668_00; 3. US Food and Drug Administration, Sotrovimab Fact Sheet for Healthcare Providers (accessed June 11, 2021).

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COMET-ICE

(**CO**VID-19 **M**onoclonal antibody **E**fficacy **T**rial – **I**ntent to **C**are **E**arly **NCT04545060**)

Headline Results of Final Day 29 Data

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COMET-ICE: Results of final analysis consistent with interim analysis

Interim efficacy analysis conducted on 583 randomized participants (ITT [IA]) in COMET-ICE who were followed through Day 29 for hospitalization >24h for acute management of any illness or death due to any cause[1]

- 3/291 (1%) sotrovimab treated participants compared to 21/292 (7%) placebo participants were hospitalized >24h or died through Day 29
- 85% reduction in the risk of hospitalization >24h or death by Day 29, *P*=0.002 compared to placebo
- IDMC recommended stopping enrollment due to profound efficacy on the primary endpoint of reduction in the risk of hospitalization >24h or death by Day 29

Intent-to-Treat analysis conducted on 1057 randomized participants in COMET-ICE who were followed through Day 29 for hospitalization >24h for acute management of any illness or death due to any cause[2,3]

- 6/528 (1%) sotrovimab treated participants compared to 30/529 (6%) placebo participants were hospitalized >24h or died through Day 29
- 79% reduction in the risk of hospitalization >24h or death by Day 29, *P*<0.001 compared to placebo
- Results consistent in magnitude and direction of effect with the Interim Analysis

1. Gupta A, et al. *medRxiv* (preprint). doi: 10.1101/2021.05.27.21257096; 2. GSK, Data on File REF-125366; 3. GSK, Press release June 21, 2021 (accessed June 23, 2021).

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Primary endpoint (ITT Population)

Hospitalization >24h for acute management of illness or death through Day 29[1]

Treatment with sotrovimab resulted in 79% reduction in the need for hospitalization >24h or death compared to placebo (*P*<0.001)[1]

	Placebo (n = 529)[1,2]	Sotrovimab 500mg* (n = 528)[1,2]
Progression Status, n (%)		
Hospitalized > 24 hours or death for any cause	**30 (6%)**	**6 (1%)***
Sotrovimab 500mg vs. Placebo		
Relative Risk Ratio		**0.21**
p-value		**<0.001**

*Among the six sotrovimab-treated patients who were hospitalized, three were likely hospitalized due to non-COVID-19 causes including small bowel obstruction, lung cancer and a diabetic foot ulcer.[1]

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

1. GSK, Press release June 21, 2021 (accessed June 23, 2021); 2. GSK, Data on File REF-125366.

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Overview of Adverse Events (Safety Population)

Safety Population N=1049 (followed through at least Day 29, N=1037)[1]

Most common AEs[2,*]	Sotrovimab
Rash	1%
Diarrhea	2%

No other treatment-emergent adverse events were reported at a higher rate with sotrovimab compared to placebo[2]

*All Grade 1 (mild) or Grade 2 (moderate).

AE, adverse event;3

1. GSK, Data on File REF-125366; 2.GSK, Press release June 21, 2021 (accessed June 23, 2021).

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COMET-ICE

(**CO**VID-19 **M**onoclonal antibody **E**fficacy **T**rial – **I**ntent to **C**are **E**arly **NCT04545060)**

Summary

Preclinical attributes of sotrovimab

Mechanism of Action

- Sotrovimab is a dual-action monoclonal antibody:
  - Demonstrated potent neutralization activity in vitro and in vivo against SARS-CoV-2, protecting uninfected cells from becoming infected
  - Effector function has been demonstrated in vitro, and may contribute to clinical efficacy by engagement of the immune system to eliminate infected host cells

Activity Against Variants of Concern

- Sotrovimab binds to a highly conserved epitope on the receptor binding domain (RBD), which may make it more difficult for SARS-CoV-2 resistance to develop
- Sotrovimab retained activity in vitro with pseudotyped virus against emergent variants of concern

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Cathcart AL, et al. *bioRxiv* (preprint). doi:10.1101/2021.03.09.434607.

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In early treatment of adults at risk of progression to severe COVID-19 sotrovimab reduced hospitalization or death versus placebo

Primary and Secondary Endpoint Results: Interim Analysis

- **Interim efficacy analysis conducted on 583 randomized participants who were followed through Day 29[1,2]**
- 3/291 (1%) sotrovimab-treated participants compared to 21/292 (7%) placebo participants were hospitalized >24 hour through Day 29[1]
  - 1 participant in the placebo arm was hospitalized and then died prior to Day 29[1]
- **Primary endpoint: 85% reduction in the risk of hospitalization >24 hour or death by Day 29, *P*=0.002 compared to placebo[1]**
- IDMC recommended stopping enrollment due to profound efficacy on the primary endpoint[1]
- **Key Secondary Endpoints*:**
  - Treatment with sotrovimab resulted in a numerical reduction in need for hospitalization (for any duration), ER visit or death compared to placebo[1]
  - Treatment with sotrovimab resulted in a numerical reduction in the risk of severe and/or critical respiratory COVID-19[1]
  - No participants treated with sotrovimab required use of high-flow oxygen, non-rebreather mask or mechanical ventilation versus 7 participants who received placebo[1]

ITT Analysis results (full population) through Day 29 consistent in magnitude and direction of effect with Interim Analysis[3]

*Results are descriptive only. No inferences can be made until results of full analyses are known for all endpoints within the testing hierarchy.

1. Gupta A, et al. *medRxiv* (preprint). doi: 10.1101/2021.05.27.21257096; 2. US Food and Drug Administration, Sotrovimab Fact Sheet for Healthcare Providers (accessed June 11, 2021); 3. GSK, Press release. June 21, 2021 (accessed June 23, 2021).

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Safety Results from the Interim Analysis

Safety Results: Interim Analysis

- 868 participants are included in the interim analysis safety population[1,2]
- Any AE was reported in 17% of patients in the sotrovimab arm and 19% of patients in the placebo arm[1]
  - The most common adverse events in the sotrovimab treatment group were diarrhea (1%), COVID-19 pneumonia, headache, dyspnea, nausea (each <1%)[1,3]
- Any serious AE was reported in 2% of patients in the sotrovimab arm and 6% of patients in the placebo arm[1]
- Immediate, non-serious hypersensitivity events were observed in 1% of patients in each treatment group[1]
- There were no cases of anaphylaxis and no events consistent with antibody dependent enhancement (ADE) were observed[1,2]

In the safety analysis population, the most common adverse events in the sotrovimab group were diarrhea (2%) and rash (1%)[4]

AE, adverse event.

1. Gupta A, et al. *medRxiv* (preprint). doi: 10.1101/2021.05.27.21257096; 2. US Food and Drug Administration, Sotrovimab Fact Sheet for Healthcare Providers (accessed June 11, 2021); 3. GSK, Data on file. 2021N472668_00; 4. GSK, Press release. June 21, 2021 (accessed June 23, 2021).

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END

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