September 15, 2021

BY ELECTRONIC DELIVERY

Adagio Therapeutics
303 Wyman Street, Suite 300
Waltham, MA 02451

Institute for Clinical and Economic Review (ICER)
14 Beacon Street, Suite 800
Boston, MA 02108

Dear ICER Review Panel:

Adagio Therapeutics, Inc. appreciates the opportunity to provide comments on ICER's draft scoping document entitled "Treatments for COVID-19." At Adagio, our mission is to provide an effective long-term solution for the global coronavirus challenge by discovering, developing and commercializing antibody-based solutions to address the current COVID-19 pandemic as well as potential future viral diseases with pandemic potential. Our lead product candidate, AGD20, is designed to be a potent, long-acting and broadly neutralizing antibody, and is currently being evaluated in two, Phase 2/3 clinical trials: the STAMP trial for treatment and the EVADE trial for prevention of COVID-19.[1,2] We respectfully offer the following points for consideration regarding the current draft scope of analysis.

Major Comments; We recommend the following:

I. **Include alternative routes of administration, such as intramuscular (IM) and subcutaneous (SQ) injection, to intravenous (IV) infusion and the subsequent impact on accessibility, sites of care, administrative burden, patient convenience, patient willingness to receive treatment, and - ultimately - economic impact.**
   a. As ICER notes, "[a]dditional options for outpatient treatment of mild-moderate disease are therefore needed." These alternative routes of administration to IV infusion are authorized for a subset of monoclonal antibody products available under current EUAs and/or are under evaluation in clinical trials. To exclude this examination from the current analysis would substantially underestimate the potential impact these IM/SQ options can bring to patients, providers, and payers.
      i. Sites of care: Please consider potential cost savings and patient throughput efficiencies associated with the ability to administer treatment via IM/SQ injection in a broad range of community sites of care, including urgent care, pharmacy clinics, primary care offices, emergency rooms and other non-hospital settings.
         1. Existing CMS payment rates for administration and post-administration monitoring range from $450 at a clinical site to $750 in the home setting.[3] Expanding the sites of care eligible to

deliver monoclonal antibody therapy by introducing new routes of administration could reduce cost of care.

2. On September 9th, 2021, the Department of Health and Human Services amended the Public Readiness and Emergency Preparedness (PREP) Act providing liability protection to licensed pharmacists, pharmacy technicians and pharmacy interns who deliver monoclonal antibody therapy.[4] This change combined with the introduction of new IM/SQ routes of administration should support efforts to expand access to monoclonal antibody therapy in the community setting.

ii. Time to administer: As part of your Comparative Value Analysis, please consider potential cost savings and patient throughput efficiencies that may be realized via reduced time to prepare and administer treatment via IM/SQ injection as compared to IV infusion.

iii. Supplies: As part of your Comparative Value Analysis, please consider potential cost savings related to reduced capital supplies necessary to administer treatment via IM/SQ injection as compared to IV infusion.

b. In addition, the number of IM/SQ injections should be considered. This may have implications on the overall resource utilization, administrative time, and site throughput, as well as patient satisfaction and patient willingness to receive treatment.

II. **Also please consider the fluctuating rates of existing variants of concern and potential newly emergent variants throughout the duration of these multiple clinical studies, and the ultimate impact on efficacy and outcomes**.

a. Emerging data demonstrate a clear trend toward decreased efficacy against variant viral strains across treatment and prophylactic modalities.[5] Regardless, any existing or developing efficacy data should consider efficacy against SARS-CoV-2 variants in the clinical summary, and thereby extrapolate such data to the economic analyses.

III. Consider the limitations of small molecule antiviral therapies for patients infected with COVID-19.

a. Small molecule antivirals that inhibit or induce cytochromes and/or drug transporters have the potential for substantial drug-drug interactions (DDIs).[6]

b. Their pharmacokinetics may also be altered by organ impairment, such as renal or hepatic failure. Thus, some antivirals may not be appropriate for a subset of the most vulnerable and underserved patient populations, particularly those with complex medical conditions requiring polypharmacy and/or those with renal and/or hepatic impairment.[7,8]

c. Antivirals may be prone to resistance development in clinical practice, and this risk should be considered when evaluating clinical efficacy and effectiveness.[9]

d. The impact of medical adherence as well as time to effect on both clinical (including transmission) and economic outcomes should be considered as well; race and socioeconomic status play a critical role in both access and compliance.[10,11]

e. Population-level models and estimates of impact should take into account the proportion of patients who would likely be clinically eligible for such therapies.

Minor Comments; We recommend the following:

I. Consider including low risk as well as asymptomatic infected individuals in the population for analysis.[12]
   a. As data continue to emerge, these may also be critical populations both in terms of prevention of transmission as well as prevention of progression to symptomatic/serious disease.

II. While we understand the analysis as currently scoped is focused on treatment, we believe that developing an analysis including prophylaxis would better represent the overall potential value of these emerging products, which are being evaluated for the prevention of COVID-19.[13]

Finally, we would like to note that Adagio expects to have preliminary clinical data regarding AGD20 in the first quarter of 2022. We request ADG20's inclusion in this analysis should that be possible given this project's current timelines.

Adagio appreciates your time and consideration of the enclosed comments. Please know that our team is available should you have additional questions.

Respectfully,

Lynn Connolly, MD, PhD
Chief Medical Officer
lconnolly@adagiotx.com
415-509-6578
On behalf of Adagio Therapeutics

[1] Adagio Therapeutics, Inc. U.S. National Library of Medicine. Evaluation of ADG20 for the Treatment of Mild or Moderate COVID-19 (STAMP). Identifier: NCT04805671. Available: https://clinicaltrials.gov/ct2/show/NCT04805671. Accessed 15Sept2021.
[2] Adagio Therapeutics, Inc. U.S. National Library of Medicine. Evaluation of ADG20 for the Prevention of COVID-19 (EVADE). Identifier: NCT04859517. Available: https://clinicaltrials.gov/ct2/show/NCT04859517. Accessed 15Sept2021.
[3] Centers for Medicare and Medicaid Services. COVID-19 Vaccines and Monoclonal Antibodies. Last updated 9/10/2021. Available: https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/covid-19-vaccines-and-monoclonal-antibodies. Accessed 15Sept2021.
[4] U.S. Department of Health and Human Services. Expanding Access to COVID 19 Therapeutics: HHS PREP Act Declaration: 9th Amendment. September 13, 2021. Available: https://www.phe.gov/Preparedness/legal/prepact/Pages/PREPact-NinethAmendment.aspx. Accessed 15Sept2021.
[5] Planas D, Veyer D, Baidaliuk A, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature. 2021;596(7871):276-280. doi:10.1038/s41586-021-03777-9.
[6] Kumar D, Trivedi N. Disease-drug and drug-drug interaction in COVID-19: Risk and assessment. Biomed Pharmacother. 2021; 139:111642. doi:10.1016/j.biopha.2021.111642. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8078916/. Accessed 15Sept2021.
[7] Merck Sharp & Dohme Corp. U.S. National Library of Medicine. Efficacy and Safety of Molnupiravir (MK-4482) in Non-Hospitalized Adult Participants With COVID-19 (MK-4482-002). Identifier: NCT04575597. Available: https://clinicaltrials.gov/ct2/show/NCT04575597.
[8] Pfizer. U.S. National Library of Medicine. A Study of PF-07321332/Ritonavir in Nonhospitalized High Risk Adult Participants With COVID-19. Identifier: NCT04960202. Available: https://clinicaltrials.gov/ct2/show/NCT04960202.
[9] Han J, Perez J, Schafer A, et.al. Influenza Virus: Small Molecule Therapeutics and Mechanisms of Antiviral Resistance. Current Medicinal Chemistry 2018; 25(38).
[10] Xie Z, St Clair P, Goldman DP, Joyce G. Racial and ethnic disparities in medication adherence among privately insured patients in the United States. PLoS One. 2019;14(2): e0212117. Published 2019 Feb 14. doi:10.1371/journal.pone.0212117. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6375669/pdf/pone.0212117.pdf. Accessed 15Sept2021.
[11] Osborn CY, Kripalani S, Goggins KM, Wallston KA. Financial strain is associated with medication nonadherence and worse self-rated health among cardiovascular patients. J Health Care Poor Underserved. 2017;28(1):499-513. doi:10.1353/hpu.2017.0036. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5492520/pdf/nihms867576.pdf. Accessed 15Sept2021.
[12] Regeneron (2021 Apr 12). Phase 3 Treatment Trial in Recently Infected Asymptomatic Patients Showed REGEN-COV™ (Casirivimb with Imdevimab) Significantly Reduced Progression to Symptomatic COVID-19 [Press Release]. Available: https://investor.regeneron.com/index.php/news-releases/news-release-details/phase-3-treatment-trial-recently-infected-asymptomatic-patients. Accessed 15Sept2021.
[13] O'Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV Antibody Combination for Covid-19 Prevention. Preprint. medRxiv. 2021;2021.06.14.21258567.

Published 2021 Jun 17. doi:10.1101/2021.06.14.21258567. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8219114/. Accessed 15Sept2021.

Sulabha Ramachandran, Ph. D
Vice President, US and Regions
Value, Evidence and Outcomes
GlaxoSmithKline
1001 Intrepid Avenue
Philadelphia, PA 19112
www.gsk.com

September 14, 2021
Steven D. Pearson, MD, MSc
Institute for Clinical and Economic Review
Two Liberty Square, 9th floor
Boston, MA 02109

Re: ICER's Draft Scope for Assessment of COVID-19 Treatments

Dear Dr. Pearson,

The COVID-19 global pandemic has led to tremendous suffering and loss over the past 18 months but also resulted in tremendous partnership and innovation as governments and healthcare institutions, academia, pharmaceutical companies, and many others, strive to find solutions at record breaking pace. As a result of these efforts several therapeutics have received emergency use authorization (EUA) with other assets in development.[1-8] GSK appreciates the opportunity to respond to ICER's Draft Scoping Document for the proposed assessment of the clinical effectiveness and value of COVID-19 therapies.

The SARS-CoV-2 pandemic has challenged populations, decision makers and health systems around the globe, including here in the United States (US). Given the current unpredictable environment, there are foreseen challenges with assessing the clinical and economic value of COVID-19 therapeutics in a robust and fair manner at this time. As we continue to live under the auspices of a viral pandemic, the medical and scientific community continues to feverishly investigate the molecular mechanisms of SARS-CoV-2 infection pathogenesis and virus–host interactions. More remains to be understood about the heterogeneity of disease, the underlying patient characteristics that are predictive of poor outcomes, and predictors of response to vaccines and therapeutics. This dynamic environment is further characterized by the emergence of SARS-CoV-2 variants some of which have the potential to evade vaccines and therapeutics[9]; and no available point of care test that can be used to direct treatment to specific variants. In addition to our disease understanding (or lack thereof), the clinical data supporting EUA interventions is non-traditional, e.g., based on interim analyses from fast-tracked clinical development programs and generated from clinical programs that were conducted at different points in time and across geographies during the pandemic and largely with limited viral sequencing data to identify predominant variants within clinical trial populations at that point in time.

Given the changing and uncertain environment, GSK recommends the following:

- **ICER consider the changes in the pandemic trajectory and the impact on emerging data and medication utilization.**
  - As new variants of SARS-CoV-2 emerge, it will be critical to consider the proportion of specific variants within the population at the time of the ICER draft report and the susceptibility of EUA therapeutics to predominant and predicted future variants.
  - The impact of current vaccination rates and implicitly the impact of vaccine hesitancy.
  - The still developing data on the duration of natural and vaccine induced immunity, the potential waning of these responses, and the likely need for a vaccine booster(s).
  - The uncertainty in the direction of the COVID-19 pandemic and therefore related duration of the current public health emergency (PHE) and potential impact this could have on the availability and utilization of current EUA therapeutics.
  - The uncertainties related to final FDA-approved product labeling and whether the content will remain consistent with that of current EUA Fact Sheets.
- **ICER should ensure flexibility in the assessment and model inputs to account for emerging data that will become available over the course of this review impacting ICER's conclusions and recommendations.**
  - The totality of clinical efficacy and safety data for each intervention may not be fully available, particularly for those treatments still in development making potential comparison inequitable.
  - *In vitro* data to assess monoclonal antibody activity against emerging variants of concern as a possible indicator of therapeutic viability, while not without its limitations, is the most up to date at the time of ICER's assessment.
- **ICER provide clarity and transparency as to the selection of investigational products for this review.**
  - The requirements and objective for selecting interventions for this review are unclear and clarity and transparency are needed as to ICER's selection process. There are a number of investigational therapies with EUA[1-3] and/or currently being evaluated for the early treatment of COVID-19.[4-8]
- **ICER reconsider the interventions included in this review to ensure that the final report and recommendations reflect the current and future treatments available for use in the United States.**
  - As of September 2, 2021, the Assistant Secretary for Preparedness and Response (ASPR) along with the Food and Drug Administration (FDA) announced that bamlanivimab/etesevimab "can be used in all U.S. states, territories, and jurisdictions under the conditions of authorization for EUA 94. ASPR will resume the distribution of bamlanivimab and etesevimab together and etesevimab alone (to pair with existing supply of bamlanivimab at a facility for use under EUA 094) to all U.S. states, territories, and jurisdictions."[10]
- **In the instance that ICER includes outcomes data from outside the United States, ensure that the rigor of these trials is consistent with US FDA guidance for good clinical practice and human subject protection and accounts for differences in patient populations, treatment practices, variants across countries, and overall applicability of the data to the US healthcare system.**

The differences outlined above are likely to complicate attempts to evaluate interventions as part of the clinical and economic review that ICER proposes and will have implications on policy recommendations by ICER.

GSK shares these recommendations with the intent of informing ICER's process at this stage.

Please feel free to contact us should you wish to discuss these recommendations in further detail.

Sincerely,

Sulabha Ramachandran

Sulabha Ramachandran, PhD
VP, US and Regions, Value, Evidence and Outcomes

Sotrovimab Emergency Use Authorization

Sotrovimab is a monoclonal antibody being developed in a collaboration between GSK and Vir Biotechnology.

Sotrovimab has not been approved but has been authorized for emergency use by the FDA under an EUA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Sotrovimab is not authorized for use in patients who are hospitalized due to COVID-19, who require oxygen therapy due to COVID-19, or who require an increase in baseline oxygen flow rate due to COVID-19 (in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity). Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

The emergency use of sotrovimab is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

For information on the authorized use of sotrovimab and mandatory requirements under the Emergency Use Authorization (EUA), please review the attached FDA Letter of Emergency Use Authorization and Fact Sheet for Healthcare Providers that includes the Fact Sheet for Patients, Parents, and Caregivers, which are also available here.

References

1. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Sotrovimab. Available at: https://www.fda.gov/media/149534/download. Accessed 13 June 2021.
2. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Casirivimab and Imdevimab. Available at: https://www.fda.gov/media/145611/download. Accessed 5 August 2021.
3. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab. Available at: https://www.fda.gov/media/145802/download. Accessed 5 August 2021.
4. Pfizer. Pfizer Initiates Phase 1 Study of Novel Oral Antiviral Therapeutic Agent Against SARS-CoV-2. March 23, 2021. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-initiates-phase-1-study-novel-oral-antiviral. Accessed August 5, 2021.
5. AstraZeneca. AstraZeneca to supply the US with up to half a million additional doses of the potential COVID-19 antibody treatment AZD7442. March 16, 2021. https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2021/us-supply-agreement-for-additional-azd7442-doses.html. Accessed August 5, 2021.
6. Merck. Merck Announces Supply Agreement with U.S. Government for Molnupiravir, an Investigational Oral Antiviral Candidate for Treatment of Mild to Moderate COVID-19. June 9, 2021. https://www.merck.com/news/merck-announces-supply-agreement-with-u-s-government-for-molnupiravir-an-investigational-oral-antiviral-candidate-for-treatment-of-mild-to-moderate-covid-19/. Accessed August 5, 2021.
7. Celltrion. Celltrion announces positive top-line results from global Phase III trial of regdanvimab (CT-P59), an anti-COVID-19 monoclonal antibody treatment. June 14, 2021. https://www.businesswire.com/news/home/20210614005275/en/Celltrion-announces-positive-top-line-results-from-global-Phase-III-trial-of-regdanvimab-CT-P59-an-anti-COVID-19-monoclonal-antibody-treatment. Accessed August 5, 2021.
8. Brii Biosciences. Brii Biosciences Announces Positive Data from the Phase 3 ACTIV-2 Trial Evaluating Combination BRII-196 and BRII-198 in Non-Hospitalized COVID-19 Patients. August 25, 2021. https://www.briibio.com/news-detial.php?id=328#news. Accessed September 8, 2021.
9. Centers for Disease Control and Prevention (CDC). SARS-CoV-2 Variant Classifications and Definitions. Updated September 7, 2021. https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html. Accessed September 9, 2021.
10. US Department of Health and Human Services. Resumption in Use and Distribution of Bamlanivimab/Etesevimab in all U.S. States, Territories, and Jurisdictions. September 2, 2021. https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab-etesevimab/Pages/resume-distribution-bamlanivimabetesevimab-all-states-2sept2021.aspx

September 15, 2021

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

Re: ICER to Assess Treatments for COVID-19

Dear Dr. Pearson:

Thank you for the continued opportunity to provide comments on the proposed ICER analysis of COVID-19 Treatments. At this time, we would like to provide feedback on the scoping document released on Aug 20, 2021

1. Population and comparators:

- ICER intends to compare each treatment to outpatient "usual care" involving only symptomatic treatments, as found in the clinical trials of each treatment. ICER proposed that the population may include adults and adolescents ages 12 and older with mild-to-moderate COVID-19. Please note that the phase 3 randomized controlled trials of Molnupiravir consists of adults (18 years and above).

Recommendations:

- We agree that ICER should compare each treatment to outpatient usual care. The sources of the clinical outcomes data should be limited to phase 3 pivotal clinical trial(s) of each product. The inclusion of the population should depend on the inclusion and exclusion criteria of each clinical trial and note limitations, differences between populations and potential impacts on results if comparisons are attempted. If ICER conducts any indirect comparisons of intervention in a cost effectiveness (CE) analysis, we recommend this approach only when phase 3 data are sufficient to achieve the most robust assessment.
- In order to conduct network meta-analyses, ICER should ensure consistency in terms of comparable outcomes, characteristics of patients in the clinical trials across different treatments, and differences in standards of care.

2. Outcomes:

- Clinical trials may not have collected all the outcomes listed in the draft Scoping document. Data from phase 3 randomized controlled trials may be limited.
- Long COVID (post-acute sequelae of COVID-19 - PASC) outcomes are not captured in most clinical trials. The definition of long COVID has not been well defined and research methods to assess Long COVID have not been standardized. In addition, the long term outcomes and duration of symptoms and healthcare resource utilization monitoring/reporting are not available or comparable between studies.

Recommendations:

In the absence of clinical data such as health care resource utilization, we suggest ICER utilize real world evidence in the US setting. These may include, but not limited to, data on natural history, mortality, health care resource utilization (HCRU) data (e.g. hospitalization, readmission, length of stay) by disease severity and by age group.

- We recommend that long-term outcomes such as hospital readmission, that can be quantified, should be included in the cost effectiveness model. Recent studies found that 6.4% to 15% of patients who were hospitalized with COVID-19 are readmitted within 2 months of discharge, and nearly 30% are readmitted within 6 months of discharge[1,2,3].
- The impact from long COVID should be described qualitatively. We recommend that it should not be evaluated in the CE at this time due to the absence of well-defined definition of PASC and limited evidence.

3. Potential Other Benefits and Contextual Considerations (societal benefit)

- We agree that it is important to describe and quantify broader/societal value of COVID treatment for patients, caregivers, and society. The societal cost of COVID-19 can be substantially higher than direct health-care costs. For any broader value of COVID-19 treatments and other benefits that cannot be incorporated into the cost effectiveness model, ICER should consider describing its impact qualitatively.

Recommendations:

- We recommend including variables that could be quantified as broader consequences of COVID-19 into the cost effectiveness model such as productivity loss, unpaid caregiver time, and costs/number of health care practitioners per COVID hospitalized cases[4,5,6].
- Due to rapid evolvement of literature, we recommend that ICER incorporates new literature/evidence, in particular when relating to broader elements of value and contextual considerations when ICER updates its CE model.

4. Scope of Comparative Value Analyses (Model)

- All the 3 references used for developing the CE model in the draft Scoping document are based on inpatient treatments only. These references may not be sufficient to construct the outpatient therapeutics model.
- Primary and secondary outcomes as well as the definitions of outcomes (e.g. time of symptom resolutions, symptom severity) are different or inconsistent across clinical trials. It could be challenging to incorporate some endpoints and adjust for heterogeneity from different trials in the CE analysis and network meta-analysis.

Recommendations:

- For the outpatient CE model, ICER should consider developing a decision tree for the acute phase followed by a lifetime Markov model to best capture initial acute stay and the lifetime aspects of the model[7]. It is important that the model captures the natural history of COVID-19 based on the specified period of pandemic by incorporating evidence from randomized controlled trials as well as real world studies.
- ICER should account for the variability of COVID's impact by age as published evidence

suggests HCRU (i.e. highest level of care setting following hospitalization) and mortality outcomes differ across age groups[8]. We suggest this information should come from real world utilization evidence from large US settings.

- Costs associated with treatment administration by different therapeutics should be captured in the model. These costs may include, but not limited to, outpatient administration costs, and costs of health care personnel.
- In terms of differences in outcomes across trials, the observed differences should be considered and adjusted (only if feasible) when conducting any comparison between treatments to ensure appropriate interpretations of model and assessment conclusion to avoid over or underestimating the benefits of treatments. The model should take account and adjust for variability in geography and epidemiology of COVID-19. Limitations associated with comparing treatments with different patient population characteristics should be explicitly described.

Thank you again for this opportunity to provide comments. We look forward to continuing this engagement throughout the evaluation period. If you have questions, please feel free to contact me.

Sincerely,

Ritesh Kumar

Ritesh Kumar, PhD
Executive Director, Outcomes Research
Center for Observational and Real-world Evidence (CORE)
2000 Galloping Hill Road, Kenilworth, NJ 07033
Email: ritesh_kumar@merck.com
Tel: +1 (908) 740-5889

References

1. Banerjee J, Canamar CP, Voyageur C, Tangpraphaphorn S, Lemus A, Coffey C Jr, Wald-Dickler N, Holtom P, Shoenberger J, Bowdish M, Yee HF, Spellberg B. Mortality and Readmission Rates Among Patients With COVID-19 After Discharge From Acute Care Setting With Supplemental Oxygen. JAMA Netw Open. 2021 Apr 1;4(4):e213990. doi: 10.1001/jamanetworkopen.2021.3990. PMID: 33792728; PMCID: PMC8017465.

2. Ayoubkhani D, Khunti K, Nafilyan V, Maddox T, Humberstone B, Diamond I, Banerjee A. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. BMJ. 2021 Mar 31;372:n693. doi: 10.1136/bmj.n693.

3. Chopra V, Flanders SA, O'Malley M, Malani AN, Prescott HC. Sixty-Day Outcomes Among Patients Hospitalized With COVID-19. Ann Intern Med. 2021 Apr;174(4):576-578. doi: 10.7326/M20-5661. Epub 2020 Nov 11. PMID: 33175566; PMCID: PMC7707210.

4. A Year Into the Pandemic, Long COVID Is Still Burdening Patients—and Their Caregivers. Available at: https://time.com/5946101/long-covid-caregivers/

5. Maltezou HC, Giannouchos TV, Pavli A, Tsonou P, Dedoukou X, Tseroni M, Papadima K, Hatzigeorgiou D, Sipsas NV, Souliotis K. Costs associated with COVID-19 in healthcare personnel in Greece: a cost-of-illness analysis. J Hosp Infect. 2021 Aug;114:126-133. doi: 10.1016/j.jhin.2021.04.018. Epub 2021 Apr 22. PMID: 33894306; PMCID: PMC8061082.

6. Jin H, Wang H, Li X, Zheng W, Ye S, Zhang S, Zhou J, Pennington M. Economic burden of COVID-19, China, January-March, 2020: a cost-of-illness study. Bull World Health Organ. 2021 Feb 1;99(2):112-124. doi: 10.2471/BLT.20.267112. Epub 2020 Nov 30. PMID: 33551505; PMCID: PMC7856360.

7. Sheinson D, Dang J, Shah A, Meng Y, Elsea D, Kowal S. A Cost-Effectiveness Framework for COVID-19 Treatments for Hospitalized Patients in the United STATES. Adv Ther. 2021 Apr;38(4):1811-1831. doi: 10.1007/s12325-021-01654-5. Epub 2021 Feb 27. PMID: 33650025; PMCID: PMC7919620.

8. CDC COVID-NET Interactive: COVID-19-associated Hospitalizations Application Quick Reference Guide Hospitalization Rates by Demographics, Characteristics, and Underlying Medical Conditions. Available at: https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html, accessed on 09/02/2021.

September 15, 2021

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Submitted via email: publiccomments@icer.org

RE: Draft Scoping Document for the Assessment of "Treatments for COVID-19"

Dear ICER Review Team,

On behalf of Pfizer Inc., thank you for the opportunity to comment on the draft scoping document for the assessment of "Treatments for COVID-19." We appreciate ICER's efforts to seek input from a broad range of stakeholders. Pfizer is committed to discovering medicines and vaccines that enhance the health of patients, their families, and society, with the goal of offering breakthroughs that will change patients' lives. We are dedicated to working with all stakeholders to ensure access to these breakthroughs and to identify solutions for creating a more effective, efficient, and equitable health care system for patients.

We offer the following feedback on select sections of the draft scoping document for ICER's consideration.

Early Stakeholder Input
We encourage ICER to reconsider the timing and scope of its proposed review, given the evolving evidence landscape for COVID-19 treatments.

Pfizer's two pivotal clinical studies for PF-07321332/ritonavir are ongoing, with estimated primary completion dates in October 2021, and planned study completion dates in February 2022.[1,2] If successful, a potential U.S. Emergency Use Authorization (EUA) submission for PF-07321332/ritonavir may be filed in Q4 2022.[3]

Clinicaltrials.gov indicates that a pivotal outpatient study of molnupiravir has an estimated primary completion date of November 2021, and an estimated study completion date of May 2022.[4] While some data for monoclonal antibodies are currently available[5,6], Clinicaltrials.gov listings for casirivimab / imdevimab[7] and sotrovimab[8] indicate pivotal studies for these products have estimated completion dates in March 2022 and November 2022, respectively. The FDA has issued EUAs for both casirivimab / imdevimab and sotrovimab.[9]

ICER's current timelines for the COVID-19 review indicate that manufacturer submissions of data will be due in October 2021, to inform a draft report that will be complete in February 2022. Given the unique pathways under which treatments for COVID-19 are currently being developed by manufacturers and evaluated by regulators, we recommend that ICER consider how it may adapt its proposed approach – in terms of timing, products under consideration, outcomes, or other variables – in order to reflect the evolving evidence landscape.

For example, ICER may wish to consider how the availability of data on important secondary endpoints may impact its review. Given the study completion timeframes outlined above, data on all endpoints may not be available during the review for all treatments. The omission of these secondary endpoints from an ICER analysis could have important implications to stakeholder understanding of the clinical and economic value of the therapies under consideration.

Should ICER seek to proceed with the full scope of the review under the current timelines, we recommend ICER reconsider whether oral therapies should be included at this time given the projected lack of available data for these therapies during the review period. We also recommend that ICER seek to carefully frame its results, in reference to the evolving evidence landscape.

Report Aim / Populations

In the "Population" section, ICER highlights that it plans to focus on adults and adolescents with mild-to-moderate newly diagnosed COVID-19 who are at high risk for progression to severe disease or hospitalization. We make the following recommendations with respect to the definition of the study population.

- The "Report Aim" section does not reference the high-risk sub-population; we recommend ICER align language across sections for consistency.
- In its population definition, ICER separates severe disease from hospitalization. The CDC defines "severe disease" as patients who may need hospitalization, intensive care, ventilation, or are risk of death.[10] We recommend that ICER include hospitalization as part of its definition of "severe disease".
- We recommend that ICER clarify its definition of "newly diagnosed" or consider limiting its analysis to patients with confirmed diagnoses.
- We note that while some clinical trials for treatments include both adolescents and adults, others (including Pfizer's current clinical trials for PF-07321332[1,2]) may be limited to those 18 years and older. We recommend ICER clarify demographic populations of interest for each treatment based on clinical trial inclusion and exclusion criteria.

Comparators

We support ICER's proposal to compare each treatment in the review to outpatient "usual care" involving symptomatic treatments, as found in the clinical trials of each product. We agree with ICER's perspective that developing formal quantitative indirect comparisons will be challenging with the limited data that are currently available.

We recommend that ICER avoid informal indirect comparisons across treatments (i.e., league table comparisons), to ensure that stakeholders do not draw incorrect conclusions about the relative safety, efficacy, or value across treatments. Differences in designs across trials (including populations, endpoints, follow-up period, among others) would make such comparisons inappropriate. Further, we note that in studies where heterogeneous populations (i.e., adolescent and adult populations, mild vs mild and moderate patients) were included, lack of a priori subgroup analyses as primary endpoints may compromise statistical confidence in outcomes.

Potential Other Benefits and Contextual Considerations
We recommend that ICER quantitatively consider how the advent of oral therapies will mark a significant change in the COVID-19 treatment paradigm, and how that change will potentially impact both access to treatment and patient outcomes.

The impact of oral therapies may be especially significant in specific populations. A growing body of evidence has suggested that socioeconomic disparities impact risk of COVID-19 infection, access to treatment, and outcomes.[11] In the draft scoping document, ICER highlights "society's goal of reducing health inequities" as an important point of consideration. Given the disproportionate impact of COVID-19 in specific sub-populations, and the associated health care access issues that have historically been observed in the same populations, we recommend that ICER place special emphasis on the advancement of outpatient treatment options which may help reduce disparities in COVID-19 access and outcomes.

Given the continued emergence of SARS-CoV-2 variants and the ongoing global impact of COVID-19, we believe it will be critical to have access to multiple therapeutic options, both now and in the future. We will continue to work diligently in collaboration with regulators to develop antivirals that could potentially reduce the impact of COVID-19 on patients' lives and communities.

We hope that these comments are useful to ICER and look forward to further discussions throughout the review process.

Sincerely,

Gergana Zlateva, PhD
Vice President, Patient & Health Impact, Oncology
Pfizer Inc, 235 East 42 Street, New York, NY 10017

[1] Clinicaltrials.gov. "A Study of PF-07321332/Ritonavir in Non-hospitalized Low-Risk Adult Participants With COVID-19". Available at: https://clinicaltrials.gov/ct2/show/NCT05011513. Accessed on September 15, 2021.

[2] Clinicaltrials.gov. "A Study of PF-07321332/Ritonavir in Nonhospitalized High Risk Adult Participants With COVID-19". Available at https://clinicaltrials.gov/ct2/show/NCT04960202. Accessed on September 15, 2021.

[3] Pfizer, Inc. "Second quarter 2021 earnings teleconference". Available at: https://s21.q4cdn.com/317678438/files/doc_financials/2021/q2/Q2-2021-Earnings-Charts-FINAL.pdf. Accessed on September 13, 2021.

[4] Clinicaltrials.gov. "Efficacy and Safety of Molnupiravir (MK-4482) in Non-Hospitalized Adult Participants With COVID-19 (MK-4482-002)". Available at: https://clinicaltrials.gov/ct2/show/NCT04575597. Accessed September 15, 2021.

[5] GSK. "GSK and Vir Biotechnology announce submission of Emergency Use Authorization request to FDA for VIR-7831 for the early treatment of COVID-19". Available at: https://www.gsk.com/en-gb/media/press-releases/gsk-and-vir-biotechnology-announce-submission-of-emergency-use-authorization-request-to-fda-for-vir-7831-for-the-early-treatment-of-covid-19/. Accessed September 12, 2021.

[6] Regeneron. "Phase 3 PREVENTION trial showed 81% reduced risk of symptomatic SARS-COV-2 infections with subcutaneous administration of REGEN-COV™ (casirivimab with imdevimab)". Available at: https://investor.regeneron.com/news-releases/news-release-details/phase-3-prevention-trial-showed-81-reduced-risk-symptomatic-sars. Accessed September 12, 2021.

[7] Clinicaltrials.gov. "Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Adult and Pediatric Patients With COVID-19". Available at: https://clinicaltrials.gov/ct2/show/NCT04425629. Accessed September 15, 2021.

[8] Clinicaltrials.gov. "Intramuscular VIR-7831 (Sotrovimab) for Mild/Moderate COVID-19". Available at: https://clinicaltrials.gov/ct2/show/NCT04913675. Accessed September 15, 2021.

[9] Food and Drug Administration. "Emergency Use Authorization - Drug and Biological Therapeutic Products". Available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs. Accessed on September 13, 2021.

[10] Centers for Disease Control and Prevention. "People with Certain Medical Conditions". Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Accessed September 8, 2022.

[11] Mackey K, Ayers C, Kondo K et al. Racial and Ethnic Disparities in COVID-19-Related Infections, Hospitalizations, and Deaths: A Systematic Review. Ann Intern Med. 2021;174(3):362-373.

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777 Old Saw Mill River Road
Tarrytown, NY 10591-6707
914.847.7400

September 14th, 2021

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
Two Liberty Square, 9th floor
Boston, MA 02109

Regeneron Pharmaceuticals, Inc. welcomes the opportunity to provide comments to the Institute for Clinical and Economic Review's (ICER) draft scoping document for the proposed value assessment of treatments for COVID-19. While we look forward to providing more specific input on the model structure and parameters upon publication of the proposed model analysis plan, at this early stage we kindly request that the following points be considered for inclusion in the revised scoping document.

- **Recommendation 1: Broaden the data sources used to inform "usual care" hospitalization rates to include real world outcomes of untreated patients.**

  We agree that "usual care" is an appropriate comparator for the interventions listed, but we believe that the focus on clinical trial comparators to inform the specific parameters associated with "usual care" may be too narrow. In the control arms of published randomized clinical trials, including interventions that are not part of the current ICER review, the observed rate of hospitalization or death ranged from 4.1% to 11.1%,[1-5] with a weighted average mean of ~5.1%. However, evidence suggests that the risk of progression from mild/moderate disease to severe outcomes is highly heterogeneous and primarily driven by age.[6] Yet, it is not clear whether some of highest risk patient populations, particularly the elderly or other frail subgroups, are proportionately represented in clinical trials.

  To our knowledge, there are three studies published to date that assess the comparative effectiveness of monoclonal antibody therapy against usual care in real world clinical practice.[7-9] In these studies, the risk of hospitalization among high risk outpatients in the control arm was substantially higher compared to the rates observed in the control arms of clinical trials, ranging from 9.7% to 30%. One likely explanation for this discrepancy is patient age; specifically, the largest of the three real world database analyses with a sample of 5,536 contemporaneous control patients (Webb et al. 2021[9]) had a mean age of 62, with a standard deviation of 15. The corresponding baseline age in the two smaller studies was reported at 63[8] and 64[7], respectively. Randomized clinical trials, in contrast, typically included patients that were substantially younger on average (baseline mean age, in years, reported at 48[4], 49[5], 50[1], 53[2] and 56[3]).

777 Old Saw Mill River Road
Tarrytown, NY 10591-6707
914.847.7400

While clinical trial results are an excellent source to inform a treatment effect, we believe they are inadequate to inform the absolute risk associated with "usual care". Thus, we recommend that ICER broaden the definition of "usual care" beyond the clinical trials to include the identified real-world comparative effectiveness studies noted above. Given the rapidly evolving evidence base in this disease, we further recommend that ICER conduct a systematic review of published evidence to inform real world "usual care" hospitalization rates and, if feasible, periodically update this review throughout the process.

- **Recommendation 2: Consider the large proportion of subcutaneous REGEN-COV™ administrations**
  The draft scoping document lists REGEN-COV as "primarily administered intravenously". This information is now outdated. REGEN-COV recently became available as a subcutaneous formulation under emergency use authorization on June 3rd, 2021. While real world utilization data on the split between the intravenous and the subcutaneous formulation are not presently available, we expect this information to become available over the next coming months.

- **Recommendation 3: List the potential ability of REGEN-COV to limit the course of the pandemic and to alleviate stress on hospital capacity as key contextual considerations**
  There are important contextual considerations that may be difficult to formally include in the cost-effectiveness model in a time to meet all pre-defined timelines, but that are nevertheless worthy of discussion in the scoping document as well as the final report:

    1. In clinical trials, REGEN-COV has been shown to rapidly reduce viral load within days after treatment initiation.[10] In an infectious disease like COVID-19, quickly reducing viral load is significant for everyone interacting with the infected patient, such as household contacts, as reduced viral shedding is likely to reduce transmissions. REGEN-COV and other therapies may therefore play an important role to limit the course of the pandemic on top of existing vaccines. In a recent symposium at the 2021 annual meeting of the American Society for Clinical Pharmacology and Therapeutics, we estimated that the economic value of REGEN-COV could increase by a factor of 2 to 4 if the reduction in transmission risk were to be captured in a dynamic model.[11] Of course, we are aware that the development of a dynamic transmission model is mathematically complex as well as time intensive and it may not be feasible for ICER to develop such a model within the stated timelines. However, we want to point out that not including the likely reduction in new transmissions resulting from lower viral load would make an assessment of

777 Old Saw Mill River Road
Tarrytown, NY 10591-6707
914.847.7400

economic value incomplete and should be listed as a key limitation of the ICER model, as well as a contextual consideration.

2. In clinical trials, various treatments have been shown to reduce the risk of hospitalization or death by approximately 70% relative to usual care.[1-4] This has important implications not just for treatment of eligible patients but may also benefit patients with unrelated conditions. In a pandemic with increasing caseloads, hospital capacity could become overwhelmed with COVID-19 patients, potentially reducing a physician's ability to perform elective and eventually non-elective non-COVID related procedures. The ability of the listed intervention to relieve stress on hospital capacity is an important social value driver and would optimally be included in the cost-effectiveness model. Barring formal inclusion for reasons of complexity, it should be added as a key contextual consideration.

We appreciate the opportunity to comment on the draft scoping document and are looking forward to continuing our engagement with ICER on this important review.

Sincerely,

Andreas Kuznik
Executive Director
Health Economics and Outcomes Research
Regeneron Pharmaceuticals
Tarrytown, NY

777 Old Saw Mill River Road
Tarrytown, NY 10591-6707
914.847.7400

References

1. FDA (US Food and Drug Administration) (2020b). FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF CASIRIVIMAB AND IMDEVIMAB. Emergency Use Authorization. Available online (accessed September 7th, 2021): https://www.fda.gov/media/145611/download
2. FDA (US Food and Drug Administration) (2020b). FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF SOTROVIMAB. Emergency Use Authorization. Available online (accessed September 7th, 2021): https://www.fda.gov/media/149534/download
3. FDA (US Food and Drug Administration) (2020b). FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF BAMLANIVIMAB AND ETESEVIMAB. Emergency Use Authorization. Available online (accessed September 7th, 2021): https://www.fda.gov/media/145802/download
4. Sandulescu O. Therapeutic effect of regdanvimab in patients with mild to moderate COVID-19: Day 28 results from a multicenter, randomized, controlled pivotal trial. 31st European Congress of Clinical Microbiology and Infectious Diseases, online; July 9-12, 2021.
5. Caraco Y, Crofoot GE, Moncada PA, Galustyan AN, Musungaie DB, Payne B, et al. Phase 2 results from a randomized, controlled phase 2/3 study evaluating molnupiravir for treatment of COVID-19 in non-hospitalized adults. 31st European Congress of Clinical Microbiology and Infectious Diseases, online; July 9-12, 2021.
6. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020 Aug;584(7821):430-6.
7. Kumar RN, Wu EL, Stosor V, Moore WJ, Achenbach C, Ison MG, et al. Real-World Experience of Bamlanivimab for COVID-19: A Case-Control Study. Clinical Infectious Diseases: an Official Publication of the Infectious Diseases Society of America. 2021 Apr 13.
8. Piccicacco N, Zeitler K, Montero J, Kumar A, Lakshmi S, Kim K, et al. Effectiveness of SARS-CoV-2 Monoclonal Antibody Infusions in High-Risk Outpatients. InOpen Forum Infectious Diseases 2021 Jun 4.
9. Webb BJ, Buckel W, Vento T, Butler AM, Grisel N, Brown SM, et al. A. Real-World Effectiveness and Tolerability of Monoclonal Antibody Therapy for Ambulatory Patients with Early COVID-19. InOpen Forum Infectious Diseases 2021 Jun 23.
10. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. New England Journal of Medicine. 2021 Jan 21;384(3):238-51.
11. Innovative Pharmacology to Health Economics Approach Using A Multi-Scale COVID-19 Transmission Model. Symposium presented March 12, 2021 at the annual meeting of the American Society for Clinical Pharmacology and Therapeutics. Available online (accessed September 7th, 2021): https://www.eventscribe.net/2021/ASCPT/agenda.asp?startdate=3/12/2021&enddate=3/12/2021&BCFO=M&pfp=FullAgenda&tn=&cpftwo=&custwo=&pta=