Alternative Pricing Models for Remdesivir and Other Potential Treatments for COVID-19

Public Comments

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Peter Bach, Memorial Sloan Kettering Cancer Center

Dear ICER,

I'd like to submit the following public comment to address some of the issues and the evidence that has emerged since you published your initial review of Remdesivir for Covid-19 infection. https://icer-review.org/announcements/alternative_pricing_models_for_remdesivir/ Your analysis at the time was based primarily on the NIAID top line results released at a press conference, and since that time considerably more information regarding the data on Remdesivir has been published. I believe several elements from the richer data now available are relevant to your models and encourage you to review them to see to what extent they might influence your modeling. In some cases it is hard to get precise estimates in the domains I highlight, but the direction and magnitude of the implications seem important.

Your initial model relied on an HR of 0.70 for mortality benefit based on the NIAID press release. This mortality benefit should be looked at with more detail now that additional data are available on several fronts.

Whether or not it is documented sufficiently to model it is one question. The NIAID sponsored trial itself did not reject the null hypothesis on mortality. The only other two comparative trials that included a control arm – the RCT from Wuhan that had a placebo and blinding, and the moderate trial run by GILD that was open label and included a usual care arm, each failed to find any evidence of a mortality benefit of Remdesivir. In each case this may reflect type 2 error, it is rare to assume type 2 error when in fact every comparative analysis failed to reject the null.

Were you to model a mortality benefit, I propose one or two modifications to the HR. If you are to stay within the NIAID result, you should use the risk group stratified HR of 0.74, not the overall 0.70, as the 0.74 reflects a weighted reallocation to compensate for uneven randomization by risk group where baseline risk of death varied widely. If you are to incorporate the other studies, I propose adding the data from the Wuhan trial using a meta-analytic technique that will generate an HR I anticipate that would be nearer to 1.0. I believe the two studies can be combined – the risk profiles of subjects and mortality rates in control arms suggest that the study subjects were sufficiently comparable that you will glean more insight in a pooled analysis than in focusing on one but not the other even though both are now published.

There is also now a trial in moderate patients where the mortality rate is far lower than in the severe group. While NS on mortality benefit, the mortality rate overall was around 1% in GILD's moderate trial, which makes the NNT far greater. You should consider trying to generate a pooled estimate of benefit across the moderate and severe population weighted for the relative size of each. I would anticipate most hospitalized patients are in the severe group, but not all and a
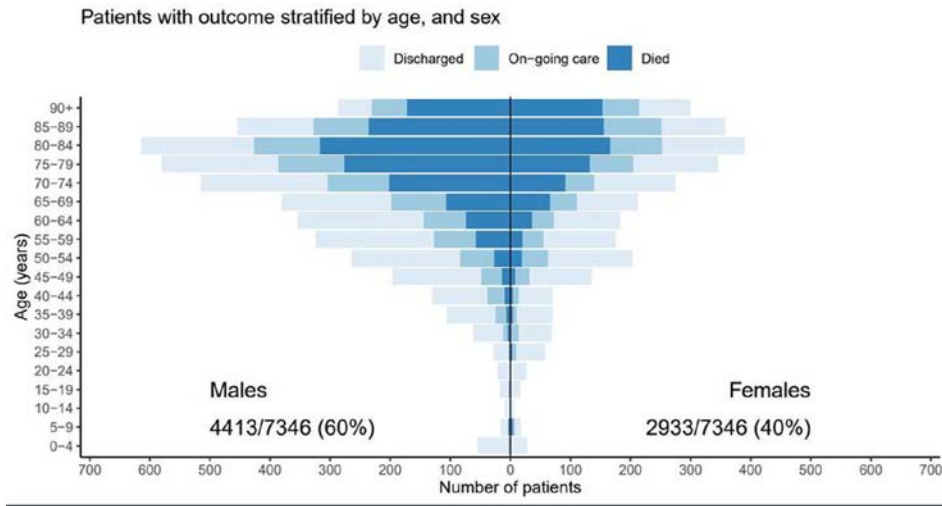
weighted average would result in a higher NNT than in your original estimate. I think it is reasonable to assume an eventual indication will be across both risk groups as the data in the moderate patients also is c/w shorter disease course. Whether or not there is a shortage right now that will limit treated population, the purpose of your analysis is to benchmark the price for a run rate scenario, and as I understand it, GILD has committed to making adequate supply to treat all who need it.

Your initial model seemed to assume that the distribution of demographic characteristics among treated patients would be the same as those among patients who died and thus who could have their death prevented by Rem. This assumption has implications particularly in the calculation of QALY gains per death averted. While it was not that clear when you published your analysis, additional data about Covid-19 outcomes make it clear that the mortality risk from the infection skews both older and male. The implication for your modeling is that the average age of a treated person and gender distribution will be younger and more female relative to the average age and gender distribution of those who die and thus those whose death might be prevented by Rem. Here is a graphic from UK cohort study showing these relations that can be found here: https://www.medrxiv.org/content/10.1101/2020.04.23.20076042v1 This pattern is consistent across all the cohort and RCT's I have seen re: Covid-19 outcomes.

The results from GILD's open label Rem trial in moderate disease show no mortality benefit that is statistically significant. But to my eye the pooled mortality at 14 days across arms is around 1% (6 deaths across all 3 arms, 600 total subjects or thereabouts). While we see no benefit, if you just use the NIAID hazard ratio for death, and I think the one that is most trustworthy is the one that is stratified by severity at baseline and is 0.74, then crudely at least the mortality reduction will be something like 0.74*1% or about 0.26%, giving an NNT to prevent a death of around 400. Your prior analysis was based on an NNT of about 30 or so, yielding the value based price of $4,500. I have previously raised my thoughts about that and the age/sex/risk factor predilections of this disease reducing the QALY gain associated with those prevented deaths, and also that a better NNT estimate would include pooling with the Wuhan data. But here if you take the results on its face the NNT rises greater than 10x meaning the value based price should fall by that amount.

As for your cost-offset calculations, I don't sense they are right now capturing savings as they should be. Figuring out changes in hospital reimbursement will be extremely difficult, the stratified data from the NIAID trial get very thin with regard to preventing major jumps in DRG category such as from pneumonia to ICU admission. The impact on the more severely ill patients seems minimal too. An alternative to trying to wade through the DRG impact is to apply a standard per diem payment rate and work from there. A reasonable number is $2,500 per day for FFS Medicare, a number you can arrive at by dividing total inpatient acute care hospital payments by number of FFS Medicare beneficiary bed days. The non-Medicare per diem may be slightly higher than this, but it

is blend of widely disparate reimbursement rates for commercial, Medicaid, uncompensated care, and so forth.

Patients with outcome stratified by age, and sex

Discharged   On-going care   Died

Males
4413/7346 (60%)

Females
2933/7346 (40%)

Thanks for considering these thoughts.
Best regards,

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June 5, 2020

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

Re: Alternative Pricing Models for Remdesivir and Other Potential Treatments for COVID-19

Dear Dr. Pearson,

GlaxoSmithKline (GSK) appreciates the opportunity to provide comments on ICER's Pricing Models for remdesivir as a treatment for the coronavirus (COVID-19). As COVID-19 continues to affect communities in the United States and around the world, our hearts go out to those impacted. At GSK we continue to contribute to the fight against COVID-19 using our science, knowledge and portfolio to support development of medicines and vaccines for prevention and treatment of COVID-19. As new treatments become available, we are aware of the interest ICER has in assessing the value of these treatments. However, GSK has concerns about the approach ICER has taken to assess remdesivir. These concerns are as follows.

Cost recovery model.

- This modeling approach has not previously been used by ICER nor was it outlined in the Value Assessment Framework 2020 – 2023 (VAF). We have concerns that this approach fails to assess the value of treatments and provides no reward to innovation. ICER mentioned within their model publication that "sunk costs for research and development have already been recouped in the successful market experience of the manufacturer's other treatments in that area." GSK does not believe that the success of existing treatments should be used to lower the perceived market value or reimbursement of another treatment undergoing

approval. In this situation, remdesivir has made substantial losses to the manufacturer, Gilead. Furthermore, the manufacturer has already vowed to give 1.5 million vials up in the form of compassionate use and deserve to be commended for this effort.

GSK asks ICER to reconsider the use of this approach. In the interests of rewarding innovation in medicine at a time when it is critical, we would ask ICER to put clinical and economic value assessment at the heart of their assessments.

Process under which the cost-effectiveness models were developed.

- **Stakeholder engagement.** Within section 6 of VAF 2020-2023, ICER outlined the process for stakeholder engagement. This process states that ICER will engage with relevant stakeholders throughout the review period to ensure the review addresses the most relevant questions for decisionmakers and to ensure the best available evidence is incorporated in the review. However, GSK is not aware that such stakeholder engagement was undertaken as this has not been discussed within ICER's report.

- **Timelines.** Section 6 of VAF also outlines how ICER anticipates undertaking assessments according to review stages. GSK is aware that this review was undertaken outside of the normal ICER assessment timelines but is not aware if and how the different stages of the review were addressed.

- **Transparency**. ICER's approach is based on Modelling Good Research Practices Task force report on "Model Transparency and Validation" jointly produced by International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision-Making (SMDM)[1]. This process aims to describe model structure and processes, major inputs and sources for data and key assumptions used in the analysis. However, within the report ICER has released, there remain some outstanding questions on these inputs (e.g. it is not clear if the reduction in time to recovery with remdesivir resulted in a hospital cost offset which is an important aspect to model given remdesivir showed a shortened time to recovery with a median of 11 days compared to 15 days for those on the placebo arm[2]).

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The process under which the remdesivir assessment was undertaken is not consistent with the framework ICER previously outlined. Therefore, it is difficult to know how robust and comprehensive this assessment is and additionally, key information is missing from the modelling report. In order to provide a more complete, thorough and transparent assessment, ICER should consider utilizing the VAF 2020-2023 framework in all assessments including those for COVID-19.

Methodology

- **Value based price thresholds (health benefit price benchmark).** Within the VAF, ICER highlighted the health-benefit price benchmark as ranging from $100k - $150k

/ QALY and $100k -$150k / evLYG. However, the thresholds of $50k / QALY have been regarded as the "most policy- relevant consideration," within the remdesivir assessment. ICER does not provide justification for the substantial deviation from the thresholds previously cited. This of course has a direct impact on the potential value of the treatment and requires further consideration and/or explanation.

- **Modelling perspective.** Within VAF section 3.5, ICER set out plans for how a modified societal perspective would be included as co-base case. COVID-19 in particular, has had an unimaginable impact on our society and GSK feels economic modelling within this area should explore the societal impact. Only by providing all the information, to include the societal perspective, can policymakers begin to make informed decisions[3]. Additionally, the current model appears to add lifetime healthcare

[1] Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. Med Decis Making. 2012;32(5):733-743.

[2] Biegel JH, Tomashek KM, Dodd LE. "Remdesivir for the Treatment of Covid-19 – Preliminary Report." NEJM, Online May 22nd, 2020.

[3] Cohen JT, Neumann PJ, Ollendorf DA. 2020. "Valuing And Pricing Remdesivir: Should Drug Makers Get Paid For Helping Us Get Back To Work?" *Health Affairs, Online May 20th, 2020.*

costs to those patients who survive COVID-19 but as discussed does not allow for economic gains such as productivity benefits when patients are able to return to work to be realized. Therefore, we could be undermining the value assessment of remdesivir.

GSK recommends further modelling to include the societal perspective should be undertaken within COVID-19 given the large impact this pandemic is having on society. Further, it was outlined in ICER's VAF that this perspective would be included as a co-base case for assessments moving forward.

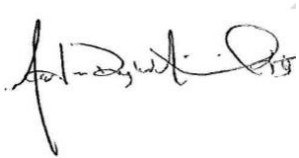### Uncertainty and timing of review

- The current model has been based on the Adaptive COVID-19 Treatment Trial (ACTT-1) (N=1,063)[4]. However, it is not clear if these patients are representative of those most likely to receive treatment in the US. It would seem reasonable to wait for a further data readout of other ongoing trials before we are able to fully assess the value of remdesivir in the most representative population.
- The trial results are still noted as preliminary[4]. It would seem premature to be discussing the value of a medicine when the true value is still unknown and under investigation with additional trials also ongoing.
- Given the manufacturer had agreed prior to EUA to donate 1.5 million vials as compassionate use, it is questionable if the pricing model needed to be completed in such expedited conditions assuming this great deal of uncertainty.

GSK has concerns about the reliability and timing of the model, and its ability to accurately predict the value of remdesivir in COVID-19. It would seem the pricing models have been conducted in a highly uncertain environment in which data is both limited and premature. GSK would recommend that the value assessment be undertaken when the clinical value is much more established. As ICER recognizes it can be both difficult and confusing to "correct" or "update" a value assessment once the initial assessment is in the public domain, particularly in critical times such as those we are facing today.

We are working in an exceptional time, including within the healthcare sector. GSK understands that it may be necessary to operate under a different process. That being stated, we also need to ensure there is scientific rigor, transparency and accuracy in the work we do as well as its ultimate review and interpretation. As the scientific research community within the United States and around the world continues to grapple with and work collaboratively on critical medications to address the COVID-19 pandemic there needs to be similar collaborative efforts in assessing the value of these treatments. These assessment criteria should be clearly outlined and robustly developed in consultation with the relevant parties and experts as has been the case previously (e.g. for VAF). We would ask ICER to reconsider their approach to value assessment of therapies for COVID-19, within the context of our aforementioned points, moving forward.

[4] Biegel JH, Tomashek KM, Dodd LE. "Remdesivir for the Treatment of Covid-19 – Preliminary Report." NEJM, Online May 22nd, 2020.

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

Martin D. Marciniak, PhD

Vice President

US Medical Affairs, Customer Engagement, Value Evidence and Outcomes

Tony Coelho, Partnership to Improve Patient Care

June 10, 2020
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President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson:

As organizations representing older adults, people with disabilities and underlying conditions and their caregivers, we are writing to share concerns about ICER's *Alternative Pricing Models for Remdesivir and Other Potential Treatments for COVID-19*. The current COVID-19 crisis has upended the entire country and our communities are particularly vulnerable, being at heightened risk for severe disease when contracting the virus. In the face of this pandemic, disability rights organizations are fighting for the enforcement of civil rights laws to mitigate health care discrimination in the form of deprivation of healthcare services, like ventilators, in favor of other "healthier" individuals.

Therefore, our members stand to benefit most from innovative treatments for this aggressive virus. Yet, this new value assessment, also intended for use on future treatments for COVID-19, is riddled with methodological flaws due to its hasty development and completely ignores the tremendous amount of stakeholder feedback ICER has received over the last five years on its framework and processes. We are concerned that, if relied upon by policymakers, its implications would be particularly detrimental to caring for older adults and people with disabilities most at risk during this COVID-19 crisis.

No one supports affordability more than the older adults, patients and people with disabilities with a real stake in achieving access to treatments in this pandemic, yet we also know the implications for access that emerge from value assessments that arbitrarily diminish a treatment's value and lead payers to restrict their coverage. We have consistently raised the red flag that ICER's value assessments are methodologically flawed and not fit for the purpose of making decisions related to coverage, reimbursement and incentive programs by policymakers and payers. The latest assessment from ICER validates our concerns.

This cost effectiveness model devalues the lives of older adults. Cost effectiveness analyses using QALYs have long been critiqued for bias against older patients with fewer life years to be gained by treatment, a core rationale for Congress banning use of QALYs in Medicare in 2010. As recently as last year, the National Council on Disability, an independent government agency, issued a report calling for a more comprehensive ban on use of QALYs in our health system due to their implications for violating existing civil rights laws, including the ADA, Section 504, and Section 1557

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of the Affordable Care Act (ACA). ICER ignores this clear precedent and continues to use this discriminatory metric in its value assessment models. The QALY inherently discriminates against older individuals, and this specific model for assessing value of treatments for COVID-19 exacerbates these fundamental flaws as increased age reduces the value of treatment. This model also goes a step further by, in fact, sending the message that there may be more value in people dying since it associates the remaining lifetime of medical costs with saving lives. Stated plainly, this type of modeling conveys the message that there may actually be less value in the saving the life of an older person with chronic conditions than in letting them die.

This cost effectiveness model ignores crucial benefits to patients and society. Many of us have consistently shared with ICER our concerns about advancing models that do not sufficiently incorporate outcomes that matter to patients and their families and societal concerns. In this case, given the toll COVID-19 is taking on our society, non-medical costs are more important than ever. These costs, like lost productivity, do not play a prominent role in ICER's modeling. It also does not recognize the benefit of treatments that may lower the fatality rate enough for society to resume normal activities, nor the stress on our health system's capacity and impact on personnel. We are particularly concerned that despite ICER's 2020 framework indicating that ICER would begin incorporating the societal perspective in the base case of its analyses, ICER chose to omit it from this report even with the huge burden COVID-19 is putting on the nation beyond direct medical costs.

ICER's models are based on flawed assumptions. Moreover, the ICER model uses basic flawed inputs to determine the value of COVID-19 treatments. We question the calculation of symptom days for patients in intensive care, the daily cost for patients on a ventilator which is inconsistent with higher real-world costs, the use of flawed age ranges of patients that would be treated, and a lack of recognition that the treatment being evaluated would not be used on a large scale (only in 12% of patients). These vast flaws lead us to question whether ICER is manipulating the model for the purpose of achieving a lower value.

Therefore, we urge ICER to pause any future development of assessments related to COVID-19 and focus on partnering with stakeholders in the development of rigorous and patient-centered methodologies.

Sincerely,

American Association of People with Disabilities
ACCSES – The Voice of Disability Service Providers
Allergy & Asthma Network
Alliance for Aging Research
Allies for Independence
American Association of Kidney Patients
American Gastroenterological Association
Amyloidosis Support Groups, Inc.
Asthma and Allergy Foundation of America

Association of University Centers on Disabilities
Autistic Self Advocacy Network
Boomer Esiason Foundation
Bridge the Gap – Syngap – Education and Research Foundation
California Access Coalition
Cancer*Care*
Center for Autism and Related Disorders
Center for Public Representation
Cystic Fibrosis Research Inc.
Cure SMA
Cutaneous Lymphoma Foundation
Davis Phinney Foundation
Diabetes Patient Advocacy Coalition
Disability Policy Consortium
Disability Rights California
Easter Seals
Epilepsy Foundation
Epilepsy Foundation New England
Genetic Alliance
Global Liver Institute
Go2Foundation for Lung Cancer
Heart Valve Voice US
ICAN, International Cancer Advocacy Network
International Foundation for Autoimmune & Autoinflammatory Arthritis (AiArthritis)
Life Raft Group
Lupus and Allied Diseases Association, Inc.
Lupus Foundation of America
MLD Foundation
National Alliance for Hispanic Health
National Alliance on Mental Illness
National Diabetes Volunteer Leadership Council
National Infusion Center Association
National Minority Quality Forum
NBIA Disorders Association
New York State Sickle Cell Advocacy Network Inc. (NYS SCAN)
Not Dead Yet
One Rare
Partnership to Fight Chronic Disease (PFCD)
Partnership to Improve Patient Care
Patients Rising Now
Powerful Patient, Inc.
Patient Services, Inc.
PXE International
The Coelho Center for Disability Law, Policy and Innovation
The Sickle Cell Foundation of Georgia, Inc.
Tuberous Sclerosis Alliance
VHL Alliance