UNIVERSITY OF MINNESOTA

Infectious Diseases & International Medicine
Department of Medicine

689 23rd Avenue S.E., MRF 4-103
Minneapolis, MN 55455

May 11, 2022

Peter Stein, MD
Director
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993

Ref: pre-EUA 110 Fluvoxamine

Dear Dr. Stein,

I thank you for your team's review of the Fluvoxamine EUA application submitted Dec 21, 2021 and the FDA's "Memorandum Explaining Basis for Declining Request for Emergency Use Authorization of Fluvoxamine Maleate" (attached as appendix).

While this is now less relevant for the United States than when originally submitted in December due to the copious supply of paxlovid, lack of access to effective Covid-19 therapeutics remains an issue both for all those non-"high risk" in the USA as well as in virtually all persons in low- and middle-income countries worldwide who do not have access to paxlovid® or effective monoclonal antibodies. As FDA is aware, for those who are not "high risk" per CDC criteria, they have no access to any EUA therapy.

As per our EUA submission, fluvoxamine when given to those with mild/moderate outpatient Covid-19, reduced the progression to severe COVID-19 experiencing hypoxia and/or need for hospitalization. FDA disagrees that preventing progression to severe COVID-19 is important.

As FDA intends to make the FDA analysis of EUA110 public, I wished to provide feedback to the agency's review on inconsistent logic utilized. I had offered to make such peer review feedback private, but FDA Division of Information Disclosure Policy declined my offer. Thus, this is planned to be posted publicly.

1. **Inconsistent Use of Hospitalization Definition by FDA for Big Pharma vs. generics.**

FDA states in the review that hospitalization and death have been used as the regulatory endpoint for EUAs.

> Page 13-14: "Other products authorized and approved for treatment of mild to moderate COVID-19 in patients at high risk of progression to severe COVID-19 have considered hospitalization and death as the most clinically meaningful endpoints for this population."

And again on Page 15:

> "For reference, in general, clinically meaningful endpoints that have been accepted in support of EUAs for a nonhospitalized population have included "proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28" and "percentage of subjects who were hospitalized or died through Day 29 due to any cause."

As the FDA is aware, "Hospitalization" was defined in the nirmatrelvir and molnupiravir trials in their respective trial protocols as >24 hours of acute care. Specifically,

Pfizer's EPIC-HR Paxlovid: [1]

> "Hospitalization is defined as >24 hours of acute care, in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic."

Merck's MOVE-Out Molnupiravir[2]

> "All-cause hospitalization (≥24 hours of acute care in a hospital or similar acute care facility, including emergency rooms or facilities created to address hospitalization needs during the COVID-19 pandemic)"

Eli Lilly's Bebtelovimab also used "COVID-19 related hospitalization (defined as ≥24 hours of acute care)," per the FDA EUA fact sheet for providers.

This is a very reasonable definition of substantial clinical deterioration for a person who starts as an outpatient with mild to moderate COVID-19. Those who progress to FDA-categorized severe disease or require healthcare utilization, clearly have progressed in their disease. We note that Bebtelovimab did not show any reduction in hospitalization or death at time of EUA issuance.

After publication of the nirmatrelvir and molnupiravir trials, the Lee *et al* individual patient-level meta-analysis was conducted of the fluvoxamine trials utilizing at least 100mg twice daily using the exact same endpoints of >24 hours of acute care being defined as "hospitalization."[3]

In our February 1 EUA communication, we noted that FDA's request for hospitalization-only endpoint data was inconsistent with the treatment of molnupiravir. We warned FDA of your deliberate inconsistency, and FDA has proceeded.

> "This removes >24 hour of acute care in local field hospitals (i.e. MASH style prolonged observation emergency care units) and includes to referral to tertiary referral hospitals only (or death). The TOGETHER trial was designed and statistically powered using a composite endpoint to capture clinical deterioration in the outpatient setting. The composite is similar to the >24 hours of acute care of hospitalization composite endpoint used in the molnupiravir (MOVE-OUT) trial. We note that the disaggregated molnupiravir results have not be publicly provided via the FDA EUA process or disclosed in the NEJM publication."

FDA should evaluate clinical trials using the same endpoint definitions for generic drugs as for big pharma. The deliberate creation of two-tiered system is inappropriate.

2. Individual Patient-level Meta-analysis

As was provided on April 6, 2022, an individual patient-level meta-analysis was conducted with various Bayesian and frequentist models using an intent to treat analysis including all persons who never received fluvoxamine or did not tolerate fluvoxamine due to side effects. This meta-analysis was led by Dr. Todd Lee of McGill University in Canada to precisely match the endpoints used in molnupiravir and paxlovid trials.

The FDA's response included that:

"*the meta-analysis itself had limitations including the fact that the studies evaluated different endpoints, locations varied amongst the trials, the doses of fluvoxamine used were different, the timing of the trials spanned different periods of the pandemic, and the demographics of the patient populations were not uniform. These differences make it challenging to interpret a pooled treatment effect and do not substantially alter the assessment of the individual trials.*"

In response to these points:

- "evaluated different endpoints" – is an erroneous critique. The individual patient level meta-analysis created a uniform endpoint of "Hospitalization" defined as >24 hours of acute care that exactly matched the EPIC-HR paxlovid and MOVE-OUT molnupiravir trials. This is a false statement by FDA.
- "doses of fluvoxamine used were different," – all but 40 participants of the 2,196 participants included in the meta-analysis received 100mg BID or placebo

  As provided in our EUA application (page 12), we noted that the STOP-COVID trial which utilized 100mg up to three times daily, only 50% (n=40) reached that 3-times daily dose, and 45% (n=36) received 100mg twice daily.
- "timing of the trials spanned different periods of the Pandemic" – this is a strength, increasing generalizability.
- "demographics of the patient populations were not uniform" – this increases the generalizability.

From the Lee TC et al. JAMA Open Network 2022, the frequentist risk ratio of 0.75 (95% CI, 0.58-0.97). Excluding the n=40 who received 300mg/day without any events, the meta-analysis would yield fluvoxamine 8.4% (88/1053) vs 11% (121/1103) with an absolute risk reduction of 2.6% (95%CI, 0.1% to 5.1%; P=0.042) for acute care >24 hours (i.e. "hospitalization"). However, "hospitalization" alone is an increasingly improbable endpoint on which to power a clinical trial in 2022.

3. Appropriate Clinical Endpoints

The EUA application noted the 36% reduction in progression to severe Covid-19 as per FDA's definition of severe Covid-19 (Relative Risk = 0.64; 95%CI, 0.50 to 0.84). The FDA ignores progression to severe disease as a valid clinical trial endpoint, yet used prevention of progression to severe disease in vaccine trials.

As published from a follow up letter to the editor query, the TogetherTrial noted:[4]

"all but one patient who met our primary endpoint had at least one US Food and Drug Administration criterion for severe COVID-19, defined as (1) SpO_2 93% or less on room air; (2) PaO_2/FiO_2 less than 300 mm Hg; (3) a respiratory rate more than 30 breaths per min or lung infiltrates more than 50% by chest CT scan. The further one control patient was hospitalised due to proximal deep vein thrombosis. Updating our results using the US Food and Drug Administration definition concludes with a similar RR as the definition we had used (RR 0·67 [95% CI 0·52–0·86], number needed to treat 18 (86/741 *vs* 130/756)."

FDA similarly criticizes the StopCovid trial choice of trial endpoints for effectively using the prevention of progression to FDA-categorized severe Covid-19 (although not worded by

authors as such, due to the timing of FDA releasing endpoint guidance after the trial was complete):

> "**Though disease progression is an important concept, 'clinical deterioration' as defined in the trial has not been established as a clinically meaningful endpoint, and no other endpoints were analyzed."**

In reference to StopCovid trial,[5] this trial used a primary endpoint of hypoxia <92% or hospitalization AND coupled with respiratory symptoms. This aligns with the FDA categorization of severe Covid-19 disease and was extensively used in vaccine trials as an endpoint for severe COVID-19.[6]

If the FDA has more clear guidance for clinical trialists for them to not use FDA-defined definitions, then FDA should be clearer with its guidance documents. The StopCovid trial was conducted from April 10, 2020, to August 5, 2020. Now in May 2022, the FDA states the StopCovid trial choice of primary endpoint that FDA's belated stated in Sept 2020 (after the trial was completed) used definitions of severe Covid-19 disease that was inappropriate – even though the definition was slightly more strict than the Sept 2020 FDA definition of <94% hypoxia.[6]

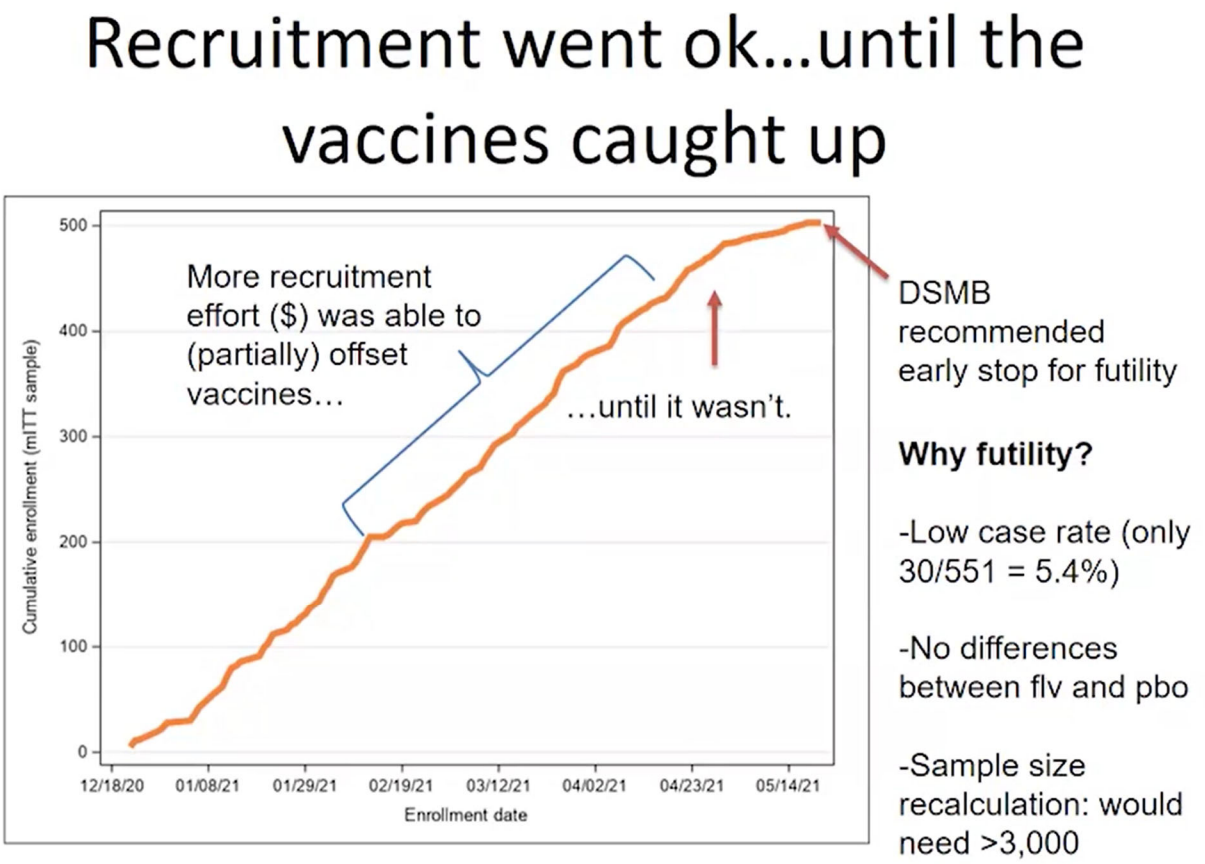
More guidance on the choice of clinical endpoints for outpatient trials in 2022 would be useful. FDA may wish to consult with practicing physicians and patients as to what is "clinically meaningful." Most people would consider it a clinical benefit if a medicine could prevent clinical deterioration to severe Covid-19 with hypoxia to the degree of needing and seeking further healthcare in ERs or hospitals.

4. StopCovid2 Trial Characterization.

StopCovid-2 trial was halted for futility due to the inability to enroll participants in May 2021 at the nadir of the US pandemic, pre-delta. At that time, the event rate of progression to severe Covid-19 was lower than expected (5.4%), and thus the trial was woefully underpowered as originally designed. This necessitated a larger sample size that was unattainable within a reasonable timeframe (based on the rate of ongoing subject recruitment) and the budget resources available. Two applications were made for US government support, which were declined. The general view is this is an underpowered, non-informative trial; however, the StopCovid2 results are included in the individual patient-level meta-analysis.

The FDA has characterized this trial differently. As I was present during discussions, I find the FDA characterization inaccurate.

As per NIH Collaboratory Grand rounds on August 20, 2021:
https://rethinkingclinicaltrials.org/news/august-20-2021-fluvoxamine-for-early-treatment-of-covid-19-the-stop-covid-clinical-trials-eric-lenze-md/ at 15 minutes:



5. ***Logic Issues on Dose Response / Optimal Dose.*** The FDA appears to partially justify the rejection of adding an EUA label to an existing FDA-approved medicine with a known safety track record based on the lack of efficacy at 50mg twice daily for why the effective 100mg twice daily dose is ineffective. This logic is bizarre. Secondly, the FDA also criticizes the lack of clarity on the optimal dosing. FDA quotations are:

   - *"absence of treatment benefit observed in the COVID-OUT trial"* which utilized 50mg twice daily.

   and

   - *"there is a lack of clarity around the optimal dosing regimen for fluvoxamine."*

As per my January 12, 2022 communication, the "Covid-Out trial helps identify that 100mg twice daily is the minimum effective dose." The FDA is using the failure of 50mg twice daily data to justify why 100mg twice daily is ineffective. That logic is poor. This is a different lower dose.

However, I would note that the FDA has not seen the full Covid-out data, which is exceedingly interesting.

Summary:

I provide a response to FDA's prior critique, raising key points of:

- The deliberate use by FDA of using different definitions for "hospitalization" for big pharma vs. low-cost generic drugs. This is troubling. FDA has provided the written documentation of the FDA's two-tiered system. I agree with the definition of hospitalization used in paxlovid, molnupiravir, and bebtelovimab trials of "acute care for >24 hours."
- I concur that fluvoxamine has a very modest efficacy which is about the same efficacy as molnupiravir. The molnupiravir data are similarly weak, and the UK Panoramic trial will provide more definitive evidence.
- As a clinical trialist, there remains a need for greater two-way communication between FDA and the research community. FDA's current guidance for trial endpoints for outpatient early treatment of Covid-19 pretends as if it is circa 2020. A medication is beneficial for many reasons, including shortening duration of illness or preventing progression to severe Covid-19. Progression to hospitalization/death is substantially lower in vaccinated populations and/or those with prior infection. This is no longer a realistic trial primary endpoint. The Paxlovid EPIC-SR trial demonstrates this point to be true. FDA guidance should provide actual guidance in 2022 and beyond.
- There are no FDA-approved or EUA authorized medicines which have shown benefit in vaccinated populations or who are not "high risk." There remains a clinical need of effective medications and possible options. More horse memes by the FDA are not helpful for those of us who are serious clinical trialists. My modest contribution to the pandemic includes four published trials to date and four others completed.[7-10]

Warmly,

David R Boulware 10-May-2022

David R. Boulware MD, MPH, CTropMed, FIDSA
Professor of Medicine
Infectious Diseases & International Medicine
Department of Medicine
University of Minnesota

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