FDA U.S. FOOD & DRUG ADMINISTRATION

Memorandum Explaining Basis for Declining Request for Emergency Use Authorization of Fluvoxamine Maleate

On December 21, 2021, the United States Food and Drug Administration (FDA) received a submission from Dr. David R Boulware requesting emergency use authorization (EUA) of fluvoxamine maleate for the "outpatient treatment of adults 24 years and older with positive test results of SARS-CoV-2 viral testing to prevent progression to severe COVID-19 and/or hospitalization".

The statutory criteria for issuing an EUA are set forth in Section 564(c) of the Federal Food, Drug and Cosmetic Act (FD&C Act). Specifically, the FDA must determine, among other things, that "based on the totality of scientific information available to [FDA], including data from adequate and well-controlled clinical trials, if available," it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by the chemical, biological, radiological, or nuclear agent; that the known and potential benefits, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of the product; and that there are no adequate, approved, and available alternatives.

FDA scientific review staff have reviewed available information derived from clinical trials investigating the use of fluvoxamine for the treatment of COVID-19. A summary of the review includes the following:

- The request is primarily based on results from the TOGETHER trial, a randomized, double-blind, placebo-controlled platform trial in high-risk, symptomatic adult outpatients in Brazil. The primary endpoint was a composite of 1) emergency room visits due to the clinical worsening of COVID-19 (defined as remaining under observation for greater than 6 hours) and 2) hospitalization due to progression of COVID-19 (defined as worsening of viral pneumonia and/or complications), up to 28 days after randomization. While the study met its primary endpoint, the results were primarily driven by a reduction in the emergency department visits lasting greater than 6 hours, and there are uncertainties about the assessment of this endpoint and whether the 6-hour timepoint represents a clinically meaningful threshold.
- The treatment benefit of fluvoxamine was not persuasive when focusing on clinically meaningful outcomes such as proportion of patients experiencing hospitalizations or hospitalizations and deaths.
- The STOP COVID and real-world data studies had design limitations, including small size, single center, endpoint selection, and lack of randomization.

1

- Two additional trials, STOP COVID 2 (a trial that was several times larger than the STOP COVID trial) and COVID-OUT failed to demonstrate a benefit with fluvoxamine in adults with mild COVID-19 in the outpatient setting, and both were terminated early for futility.

Based on the review of available scientific evidence, the FDA has determined that the data are insufficient to conclude that fluvoxamine may be effective in the treatment of nonhospitalized patients with COVID-19 to prevent progression to severe disease and/or hospitalization.

Therefore, FDA has determined that the criteria for issuance of an EUA are not met and is declining to issue an EUA covering fluvoxamine for the treatment of COVID-19 at this time.

Proposed Use and Dosing of the Product Under the EUA

Currently, fluvoxamine is FDA-approved for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD) in children 8-17 years of age and adults.

The EUA request proposes that fluvoxamine be authorized for emergency use for the outpatient treatment of persons > 24 years of age with positive test results of SARS-CoV-2 viral testing to prevent progression to severe COVID-19 and/or hospitalization.

The proposed dosing regimen is as follows:
- Fluvoxamine 50 mg administered orally once daily x 1 day
- Fluvoxamine 100 mg administered orally twice daily starting on the second day through a recommended duration of 10-15 days of illness.

Product Information

Fluvoxamine maleate is a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to the chemical series, the 2-aminoethyl oxime ethers of aralkylketones. It is chemically unrelated to other SSRIs and clomipramine. It is chemically designated as 5-methoxy-4′-(trifluoromethyl) valerophenone (E)-O-(2-aminoethyl) oxime maleate (1:1) and has the molecular formula $C_{15}H_{21}O_2N_2 F_3 \cdot C_4H_4O_4$. Its molecular weight is 434.4. It is a white to off-white, odorless, crystalline powder which is sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether.

Regarding the approved OCD indication, it is thought to inhibit CNS neuron serotonin uptake with minimal effect on reuptake of norepinephrine or dopamine nor binding to alpha-adrenergic, histamine or cholinergic receptors.

The rationale for the use of fluvoxamine in COVID-19 is based on murine sepsis and lipopolysaccharide (LPS) challenge models in which fluvoxamine was found to bind to the sigma-1 receptor on immune cells, acting as an agonist, thereby reducing the production of inflammatory cytokines.[1] No *in vivo* animal models of viral infection evaluating fluvoxamine treatment were conducted. An *in vitro* study appeared to show fluvoxamine reduced the expression of inflammatory genes in human endothelial cells and macrophages.[2] However, these were preliminary data and further studies are needed to characterize the cellular and molecular mechanisms of fluvoxamine on inflammatory pathways. In addition to an anti-inflammatory mechanism of action, fluvoxamine has been theorized to mediate or regulate viral infections through lysosomotropic properties, but additional data are needed to evaluate this potential effect.[3,4]

In summary, there are limited *in vitro* and *in vivo* data to support the proposed mechanism of action (MOA) of fluvoxamine for the treatment of COVID-19. The proposed anti-inflammatory mechanism has not been well-characterized nor is fluvoxamine generally considered an anti-inflammatory drug. There is no evidence to date that an anti-inflammatory therapeutic would be beneficial at an early stage of infection when COVID-19 disease severity is mild and that anti-inflammatory therapies are currently recommended only for hospitalized individuals requiring supplemental oxygen.

Background Information on the Disease/Condition and Available Therapeutic Alternatives

There are many types of human coronaviruses including some that commonly cause mild upper-respiratory tract illness. The 2019 novel coronavirus, first identified in Wuhan, China, and now identified as SARS-CoV-2, causes the disease COVID-19. COVID-19 has the potential to be a serious and life-threatening illness which can result in pneumonia, respiratory failure, multi-organ failure, and death.

On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. According to the WHO, approximately 487 million confirmed cases of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) have been reported as of April 1, 2022, including an estimated 6.1 million deaths.[5] In the US, according to the

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[1] Rosen DA, Seki SM, Fernandez-Castaneda A, et al. Modulation of the sigma-1 receptor-IRE1 pathway is beneficial in preclinical models of inflammation and sepsis. Sci Transl Med. 2019;11(478). Available at: https://www ncbi nlm nih.gov/pubmed/30728287.

[2] Rafiee L, Hajhashemi V, Javanmard SH. Fluvoxamine inhibits some inflammatory genes expression in LPS/stimulated human endothelial cells, U937 macrophages, and carrageenan-induced paw edema in rat. Iran J Basic Med Sci. 2016;19(9):977-984. Available at: https://www ncbi nlm nih.gov/pubmed/27803785.

[3] Sukhatme VP, Reiersen AM, Vayttaden SJ, Sukhatme VV. Fluvoxamine: a review of its mechanism of action and its role in COVID-19. Front Pharmacol 2021; 12: 652688.

[4] Homolak J, Kodvanj I. Widely available lysosome targeting agents should be considered as potential therapy for COVID-19. Int J Antimicrob Agents. 2020;56(2):106044.

[5] https://covid19.who.int/

Center for Disease Control and Prevention (CDC), as of April 4, 2022, approximately 80.0 million cases of COVID-19 have been reported with 978,852 deaths.[6]

SARS-CoV-2 variants have emerged over time and continue to emerge. According to the CDC's national surveillance report for the period of October 10, 2021, to October 16, 2021, the most common Variant of Concern in the United States was the Delta (B.1.617.2) variant. On November 24, 2021, a new variant of SARS-CoV-2, B.1.1.529, was reported to the WHO. On November 26, 2021, the WHO designated this variant as Omicron and classified it as a Variant of Concern. The first confirmed U.S. case of Omicron was identified on December 1, 2021. Currently, the combined national proportion of lineages designated as Omicron is estimated to be 100%. SARS-CoV-2 variants of concern have primarily been characterized as having certain changes in the viral spike protein that could impact virus transmissibility or susceptibility to antibody-based therapeutics or vaccine-induced immune responses.

Patients with symptomatic SARS-CoV-2 infection, or COVID-19, can experience a wide range of clinical manifestations. Mild illness is defined by the presence of symptoms without shortness of breath, dyspnea, or abnormal chest imaging. Moderate illness is defined as the presence of symptoms and evidence of lower respiratory tract disease by clinical examination or chest imaging accompanied by oxygen saturation ≥94% on room air. Severe and critical illness are defined as worsening pulmonary status requiring hospitalization, supplemental oxygen, non-invasive ventilation, high-flow oxygen devices, invasive mechanical ventilation, or ECMO. COVID-19 may result in hypoxemia, respiratory failure, multi-organ failure, and death.[7,8]

The progression of SARS-CoV-2 infection to severe COVID-19 can occur in adults of any age, but the risk increases with age. Per the CDC, approximately 75% of COVID-19 deaths occur in adults aged 65 years and older, and more than 90% of COVID-19 deaths occur in adults aged 50 years and older. Irrespective of age, certain underlying comorbidities or conditions, including but not limited to cancer, chronic kidney disease, chronic lung disease, obesity, diabetes, pregnancy, and immunocompromised states, increase the risk for progression to severe COVID-19.[9] Furthermore, COVID-19 vaccines currently approved in the US continue to provide protection against severe disease, including hospitalizations and death.[10]

As outlined in the NIH COVID-19 Treatment Guidelines, several therapeutic options are now available for the treatment of nonhospitalized adults with mild to moderate COVID-19

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[6] https://covid.cdc.gov/covid-data-tracker/#datatracker-home
[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-developing-drugs-and-biological-products-treatment-or-prevention
[8] https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/
[9] Centers for Disease Control and Prevention. Science Brief: Evidence Used to Update the List of Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19. https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/underlying-evidence-table.html. Accessed March 29, 2022.
[10] https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html

4

who are at high risk of disease progression.[11] For patients not requiring hospitalization or supplemental oxygen, the preferred therapies are ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir. Alternative therapies for use when neither of the preferred therapies are available, feasible, or clinically appropriate include bebtelovimab and molnupiravir. The available therapies are each discussed in more detail below.

There is an approved drug for nonhospitalized patients with COVID-19. Remdesivir (Veklury®) is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor currently approved for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct SARS-CoV-2 viral testing, and who are: 1) hospitalized, or 2) are not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

Paxlovid™ is an oral therapy authorized under EUA for the treatment of mild-to-moderate COVID-19 in adult 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. It includes nirmatrelvir, a SARS-CoV-2 main protease (Mpro, also referred to as 3CLpro or nsp5 protease) inhibitor and ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. Data on the *in vitro* antiviral activity of nirmatrelvir against SARS-CoV-2 has demonstrated that its antiviral activity is retained against the Omicron variant. The clinical data supporting the EUA was derived from a phase 2/3, randomized, double-blind, placebo-controlled trial in 2,246 adult outpatients with mild-to-moderate COVID-19, who were at high-risk for progression to severe disease. The primary endpoint was proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 in the mITT population, who received treatment within 3 days of symptom onset and without COVID-19 therapeutic mAb treatment at baseline. The event rates were 27/387 (7.0%) in the placebo group, and 3/393 (0.8%) in the Paxlovid group. Paxlovid showed a statistically significant absolute reduction of 6.3% (95% CI: -9.0% to -3.6%; $p < 0.0001$), or 89.1% relative reduction compared to placebo.[12]

In the United States, anti-SARS CoV-2 monoclonal antibodies have been authorized under EUA for the treatment of mild-to-moderate COVID-19 in certain high-risk outpatients. Currently, only bebtelovimab is authorized 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 who are at high risk for progressing to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. Due to the high frequency of Omicron and its

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[11] https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/

[12] Paxlovid EUA Fact Sheet: https://www.fda.gov/media/155050/download

5

subvariant BA.2, several other anti-SARS CoV-2 monoclonal antibody therapies are not currently authorized for use in any U.S. region under the EUA for treatment or post-exposure prevention of COVID-19, until further notice by the Agency.

Lagevrio (molnupiravir), a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis, is an oral therapy also authorized for emergency use under EUA. Lagevrio is authorized for treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, who are at high risk for progression to severe COVID-19, including hospitalization or death and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies remains authorized for the treatment of COVID-19 in specific patient populations, specifically those with immunosuppressive disease or receiving immunosuppressive treatment, in inpatient or outpatient settings.

The products described above that have been authorized or approved for the treatment of COVID-19 in an outpatient setting have been largely restricted to antibodies targeted against specific proteins of the SARS-CoV-2 virus or those with evidence supporting an anti-viral mechanism of action (MOA). While there are anti-inflammatory products authorized for the treatment of COVID-19, they have only shown to be beneficial when used at more advanced stages of the disease; consequently, the NIH COVID-19 Treatment Guidelines Panel recommends against the use of dexamethasone or other systemic steroids in the absence of another indication.

Other products are authorized for the prevention of COVID-19 or the treatment of hospitalized patients with COVID-19; however, this is beyond the scope of this review which is focused on the nonhospitalized COVID-19 population.

Related Regulatory Submissions

Fluvoxamine maleate (Fluvox) was approved for the treatment of OCD in 1994 under NDA 022235. It is currently available in generic form under multiple abbreviated new drug applications (ANDAs). The Requester of this EUA has submitted a letter of authorization (LoA) from Apotex Inc. to incorporate reference information from ANDA 075902 into any IND submitted by the University of Minnesota Medical School and to permit the FDA to review any information contained within ANDA 075902 if referenced in a clinical trial.

In addition to the clinical studies submitted in support of this EUA request, fluvoxamine is also being evaluated in two platform trials: COVID-OUT: Early Outpatient Treatment for SARS-CoV-2 Infection (COVID-19) and ACTIV-6 (Accelerating COVID-19 Therapeutic Interventions and Vaccines) and was evaluated in a separate third trial, STOP COVID 2. The Requester is the principal investigator of the COVID-OUT trial under the investigational new drug (IND) application 152439. COVID-OUT is a randomized, double-

6

blind, placebo-controlled, six-arm study in outpatients aged 30-85 years with confirmed SARS-CoV-2 infection and symptoms fewer than 7 days. Active treatment arms include metformin, ivermectin, and fluvoxamine 50mg twice daily. SEE ATTACHED ADDENDUM

[13]

Additionally, fluvoxamine has been included as one of the arms in the ACTIV-6 trial, a master protocol designed to evaluate the efficacy of multiple repurposed FDA-approved medications in patients with mild to moderate COVID-19 infections under IND 155481.[14] No information was submitted on the status of the fluvoxamine arm in ACTIV-6. STOP COVID 2 is a randomized, double-blind, controlled trial, similar in design to STOP COVID. The study population included high-risk, unvaccinated subjects ≥ 30 years of age with a positive SARS-CoV-2 test and ≤ 6 days of symptoms. The study was not conducted under IND but was terminated early due to futility.[15] The study results have not published except as part of a meta-analysis.[16]

Summary of Clinical Data

Initially, three sources of data were submitted in support of this EUA request in the form of two published peer-reviewed manuscripts of double-blind, placebo-controlled randomized clinical trials, the TOGETHER trial and the STOP COVID trial, and a real world data (RWD), open label, prospective study conducted by the investigator as described in Table 1. None of these trials were conducted under an IND and, therefore, did not receive FDA review or feedback. In addition, on April 6, 2022, the Requester submitted a published manuscript that included a systematic review for all registered[17] and completed clinical trials for the treatment of outpatients with COVID-19 that compared fluvoxamine to placebo or standard of care and a meta-analysis of three identified randomized clinical trials. The three trials included the TOGETHER and STOP COVID trials along with the STOP COVID 2 trial, which was neither conducted under an IND nor previously published.[18] To ensure the EUA review considered all available data, the FDA searched for additional sources of information from randomized controlled trials and meta-analyses evaluating fluvoxamine in nonhospitalized patients with COVID-19. A summary of additional data sources is provided in Table 2.

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[13] Information made available to the Agency via email communication from the IND Sponsor and EUA requester Dr. Boulware on March 8, 2022

[14] https://clinicaltrials.gov/ct2/show/NCT04885530

[15] https://clinicaltrials.gov/ct2/show/NCT04668950

[16] Lee TC, Vigod S, Bortolussi-Courval É, Hanula R, Boulware DR, Lenze EJ, Reiersen AM, McDonald EG. Fluvoxamine for Outpatient Management of COVID-19 to Prevent Hospitalization: A Systematic Review and Meta analysis. JAMA Netw Open. 2022 Apr 1;5(4):e226269. doi: 10.1001/jamanetworkopen.2022.6269. PMID: 35385087.

[17] The search included trials registered in the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov

[18] Lee TC, Vigod S, Bortolussi-Courval É, Hanula R, Boulware DR, Lenze EJ, Reiersen AM, McDonald EG. Fluvoxamine for Outpatient Management of COVID-19 to Prevent Hospitalization: A Systematic Review and Meta analysis. JAMA Netw Open. 2022 Apr 1;5(4):e226269. doi: 10.1001/jamanetworkopen.2022.6269. PMID: 35385087.

Table 1.Clinical Trial Manuscripts Submitted to EUA 110

Study Name, Number, and Dates	Reference	Type of Study	Population (N)	Study Design and Type of Control	Test Product(s); Dosing Regimens; Dosage Forms; Routes of Administration; Duration	Study Status
TOGETHER NCT 04727424 randomization to fluvoxamine arm 1/20/2021-8/5/2021	Reis G, et. al.[19]	Efficacy, Safety	N = 1497 Nonhospitalized adults with COVID-19	Phase 3, adaptive, randomized, double-blind, placebo-controlled, platform trial	Fluvoxamine 100 mg PO BID x 10d Placebo PO BID x 10d	Ongoing*
STOP COVID NCT 04342663 4/2020-12/2020	Lenze EJ, et. al.[20]	Efficacy, Safety	N = 152 Nonhospitalized adults with COVID-19	Phase 2, randomized, double-blind, placebo-controlled trial	Fluvoxamine 50 mg PO x 1, 100 mg PO BID x 2d, 100 mg TID x 12d Placebo PO x 15d	Completed
RWD trial 11/2020-12/2020	Seftel, D, et. al[21]	Efficacy, Safety	N = 113 Nonhospitalized adults with COVID-19	Open label, non-randomized, prospective	Fluvoxamine 50 mg or 100 mg PO x 1d, 50 mg PO BID x 14d	Completed

*fluvoxamine arm complete; BID = twice daily; d = day; PK = pharmacokinetics; PO = by mouth; RWD = real world data; TID = three times daily

[19] Reis G, Dos Santos Moreira-Silva EA, Silva DCM, Thabane L, Milagres AC, Ferreira TS, Dos Santos CVQ, de Souza Campos VH, Nogueira AMR, de Almeida A, Callegari ED, de Figueiredo Neto AD, Savassi LCM, Simplicio MIC, Ribeiro LB, Oliveira R, Harari O, Forrest JI, Ruton H, Sprague S, McKay P, Glushchenko AV, Rayner CR, Lenze EJ, Reiersen AM, Guyatt GH, Mills EJ. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: The together randomised, platform clinical trial. Lancet Glob Health. 2022;10:e42-e51. PMCID: 8550952.

[20] Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE, Miller JP, Yang L, Yingling M, Avidan MS, Reiersen AM. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: A randomized clinical trial. JAMA. 2020;324:2292-300. PMCID: 7662481.

[21] David Seftel, David R Boulware, Prospective Cohort of Fluvoxamine for Early Treatment of Coronavirus Disease 19, Open Forum Infectious Diseases, Volume 8, Issue 2, February 2021, ofab050, https://doi.org/10.1093/ofid/ofab050

8

Table 2. Additional Sources of Data Evaluated in the Review of EUA 110

Study Name, Number, and Dates	IND, NDA, or Literature Reference	Type of Study	Population (N)	Study Design and Type of Control	Test Product(s); Dosing Regimens; Dosage Forms; Routes of Administration; Duration	Status
STOP COVID 2 NCT 04668950 12/2020-9/2021	ClinicalTrials.gov[22]	Efficacy, Safety	N = 683 Nonhospitalized adults with COVID-19	Phase 3, randomized, double-blind, placebo-controlled trial	Fluvoxamine 50 mg PO x 1, 100 mg PO BID x 15d Placebo PO x 15d	Completed*
ACTIV-6 NCT 04885530 5/2021-ongoing	IND 155481 ClinicalTrials.gov[23]	Efficacy, Safety	N = 15000+ (N=1200 per study drug appendix) Nonhospitalized adults with COVID-19	Phase 3, randomized, double-blind, placebo-controlled trial	Fluvoxamine 50 mg PO BID x 10d Placebo PO BID x 10d	Ongoing
COVID-OUT NCT 04510194 8/2020-ongoing	Requester provided[24]	Efficacy, Safety	N = 1350 Nonhospitalized adults with COVID-19	Phase 3, randomized, double-blind, placebo-controlled trial	Fluvoxamine 50 mg PO x 1, 50 mg PO BID x 14d Placebo PO x 14d	Ongoing*
Fluvoxamine for Outpatient Management of COVID-19 to Prevent Hospitalization	Lee, TC, et. al.[25]	Meta-analysis	N = 2196 Nonhospitalized adults with COVID-19	STOP COVID 1, STOP COVID 2, TOGETHER	Fluvoxamine various doses Versus placebo	Published

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[22] https://clinicaltrials.gov/ct2/show/NCT04668950

[23] https://clinicaltrials.gov/ct2/show/NCT04885530

[24] [24] Information made available to the Agency via email communication from the IND Sponsor and EUA requester Dr. Boulware on March 8, 2022

[25] Lee TC, Vigod S, Bortolussi-Courval É, Hanula R, Boulware DR, Lenze EJ, Reiersen AM, McDonald EG. Fluvoxamine for Outpatient Management of COVID-19 to Prevent Hospitalization: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022 Apr 1;5(4):e226269. doi: 10.1001/jamanetworkopen.2022.6269. PMID: 35385087.

Study Name, Number, and Dates	IND, NDA, or Literature Reference	Type of Study	Population (N)	Study Design and Type of Control	Test Product(s); Dosing Regimens; Dosage Forms; Routes of Administration; Duration	Status
Efficacy and safety of three new oral antiviral treatment for COVID-19: a meta-analysis	Wen W, et. al.[26]	Meta-analysis	N = 4788 Nonhospitalized adults with COVID-19	Eight studies including TOGETHER, STOP COVID, and the RWD trial	Fluvoxamine at various doses Ritonavir-boosted nirmatrelvir Molnupiravir versus placebo	Published
Fluvoxamine in Nonhospitalized Patients with Acute COVID-19 Infection and the Lack of Efficacy in Reducing Rates of Hospitalization, Mechanical Ventilation, and Mortality in Placebo-Controlled Trials: A Systematic Review and Meta-Analysis	Bhuta, S, et. al.[27]	Meta-analysis	N = 1762 Nonhospitalized adults with COVID-19	TOGETHER, STOP COVID RWD trials	Fluvoxamine at various doses versus placebo	Published

*fluvoxamine arm stopped for futility; +sample size refers to total across all treatment arms; BID = twice daily; d = day; PK = pharmacokinetics; PO = by mouth; RWD = real world data

[26] Wen W, Chen C, Tang J, Wang C, Zhou M, Cheng Y, Zhou X, Wu Q, Zhang X, Feng Z, Wang M, Mao Q. Efficacy and safety of three new oral antiviral treatment (molnupiravir, fluvoxamine and Paxlovid) for COVID-19 : a meta-analysis. Ann Med. 2022 Dec;54(1):516-523. doi: 10.1080/07853890.2022.2034936. PMID: 35118917; PMCID: PMC8820829.

[27] Bhuta S, Khokher W, Kesireddy N, Iftikhar S, Beran A, Mhanna M, Patel NJ, Patel M, Burmeister C, Assaly R. Fluvoxamine in Nonhospitalized Patients With Acute COVID-19 Infection and the Lack of Efficacy in Reducing Rates of Hospitalization, Mechanical Ventilation, and Mortality in Placebo-Controlled Trials: A Systematic Review and Meta-Analysis. Am J Ther. 2022 Mar 31. doi: 10.1097/MJT.0000000000001496. Epub ahead of print. PMID: 35383578.

10

Human Clinical Efficacy

The main source of clinical efficacy data to support this EUA request comes from the TOGETHER trial, given the small sample sizes and design limitations of STOP COVID and the RWD trials, absence of treatment benefit observed in the COVID-OUT trial, and lack of available data from the STOP COVID 2 trial. Results from the TOGETHER, STOP COVID and RWD trials are discussed below. Preliminary data from the COVID-OUT trial, which were made available to the Agency in the form of a draft manuscript, and a recently published meta-analysis are also included in the review of this EUA request.

TOGETHER Trial

Trial Design

The TOGETHER trial is a multi-center, randomized, placebo-controlled, adaptive platform clinical trial evaluating multiple interventions for the treatment of COVID-19 infection and related complications. Participants with a confirmed diagnosis of SARS-CoV-2 infection and symptom onset within seven days were randomized in equal allocation among the treatment arms, which included hydroxychloroquine, lopinavir/ritonavir, ivermectin, metformin extended release, doxazosin, pegylated interferon lambda, as well as fluvoxamine 100 mg twice daily for 10 days or placebo. The fluvoxamine comparison included 1,497 high-risk symptomatic adults across 11 clinical sites in Brazil confirmed positive for SARS-CoV-2 with a pre-specified risk factor for progression to severe disease. There were 741 subjects allocated to receive fluvoxamine and 756 allocated to receive a placebo. Different placebos were employed in order to best match the administration method, dosing, and duration of the intervention assigned to an individual. There was no standard of care (SOC) defined in the protocol. An independent data safety monitoring committee (DSMC) provided trial oversight.

Eligibility Criteria

Inclusion/exclusion criteria specified that subjects had to have at least one of the following risk factors for progression to severe disease: diabetes; systemic arterial hypertension requiring at least one oral medication for treatment; known cardiovascular disease (heart failure, congenital heart disease, valve disease, coronary artery disease, cardiomyopathies being treated, clinically manifested heart disease and with clinical repercussion); symptomatic lung disease or treatment for such (emphysema, fibrosing diseases); symptomatic asthma requiring chronic use of agents to control symptoms; smoking; obesity, defined as body-mass index greater than 30 kg/m² (weight and height information provided by the patient); having had a transplant; stage IV chronic kidney disease or on dialysis; immunosuppression or use of corticosteroid therapy (equivalent to at least 10 mg of prednisone per day) or immunosuppressive therapy; history of cancer in the last 6 months or undergoing current cancer treatment or aged 50 years or older; and unvaccinated status. During the study, the protocol was amended to allow enrollment of vaccinated patients.

Endpoints

Per the website protocol, the primary endpoint was a composite of 1) emergency room visits due to the clinical worsening of COVID-19 (defined as remaining under observation for greater than 6 hours) and 2) hospitalization due to progression of COVID-19 (defined as worsening of viral pneumonia and/or complications), up to 28 days after randomization.[28] The description of the primary endpoint in the manuscript slightly differed as it was the proportion of patients hospitalized, which was defined as either retention in a COVID-19 emergency setting for greater than 6 hours or transfer to tertiary hospital due to COVID-19, up to 28 days after randomization. The 6-hour cutoff was based on an assumed emergency setting evaluation times and referred only to periods of time recommended for observation by a clinician and did not include waiting times. To support an EUA, the FDA recommends proportion of hospitalizations and/or deaths through a pre-defined timepoint as the primary endpoint for trials designed to demonstrate efficacy on progression to severe disease in a nonhospitalized patient, high-risk population.[29,30] However, as the trial was not conducted under an IND, FDA was unable to provide feedback on trial design and selection of endpoints.

Key secondary endpoints evaluated 1) viral clearance at Days 3 and 7, 2) time to clinical improvement, defined as the first day on which the participant reports a score of 0 on the WHO clinical worsening scale (see Appendices), 3) self-reported number of days with respiratory symptoms, 4) time to hospitalization from any cause or due to COVID-19 progression, 5) all-cause mortality and time to death from any cause, 6) the numerical value on the WHO clinical worsening scale, 7) quality of life scale (PROMIS-10 scale), 8) Telephone Interview for Cognitive Status (TICS) memory assessment scale (a standardized test of cognitive functioning that was developed for remote use) at Day 28, 9) days in hospital and on a ventilator, 10) adverse events, 11) adverse reactions, and 12) adherence to fluvoxamine. All secondary outcomes apart from viral clearance were assessed up to 28 days following randomization. The statistical analysis plan did not include a multiplicity control procedure to control the family-wise type I error rate across the secondary endpoints.

Analysis Populations

The following analysis populations were used for efficacy analyses:
- Intent-to-treat (ITT) Population included all randomized patients.
- Per-protocol (PP) Population included randomized patients who adhered to more than 80% of the assigned therapy.
- Modified intention to treat (mITT) was defined in a *post hoc* manner as randomized patients who had received treatment for at least 24 h before a primary outcome

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[28] https://osf.io/eg37x
[29] Development of Monoclonal Antibody Products Targeting SARS-CoV-2, Including Addressing the Impact of Emerging Variants, During the COVID-19 Public Health Emergency: Guidance for Industry
[30] COVID-19: Developing Drugs and Biological Products for Treatment or Prevention: Guidance for Industry

Results

Demographics and Baseline Characteristics

Enrollment into the fluvoxamine group began on January 20, 2021. By August 5, 2021, 1,497 subjects were randomly assigned to receive fluvoxamine (n=741) or placebo (n=756) and further stratified by age (<50 years or ≥50 years). The median age was 50 years (range 18-102) and 862 (58%) were women. The majority of subjects self-identified as mixed race (1428; 95%), followed by white (12; 1%), unknown (47; 3%), and black or African heritage (10; 1%). Although pre-defined risk factors were generally well-balanced between treatment arms, there were more subjects with uncontrolled hypertension (106 vs 88; 14% vs 12%) and Type 2 diabetes (104 vs 92; 14% vs 12%) in the fluvoxamine versus the placebo group, respectively. The mean number of days with symptoms before randomization was 3.8 days (SD 1.87). Given the timing of the study, most subjects were unvaccinated with 86/1497 (6%) of subjects reporting at least one dose of a COVID-19 vaccine at the end of the trial.

Primary Efficacy Analysis

In the ITT population, there were 180 subjects in the fluvoxamine group and 251 patients in the placebo group who accessed care in an emergency setting for the treatment of COVID-19 through Day 28. The Requester reports that for the ITT population, fluvoxamine reduced the 28-day rate of retention in a COVID-19 emergency setting for greater than 6 hours or transfer to tertiary hospital due to COVID-19 compared with placebo as shown in Table 3. The results for the modified ITT (mITT) and per protocol (PP) populations were also reported; however, the analyses in the mITT populations include only patients who had received treatment for at least 24 hours before a primary outcome, and the analyses in the PP population include only patients who adhered to more than 80% of the assigned therapy. Restricting the analyses to subgroups of patients defined by post-randomization outcomes, such as the timing of treatment receipt or adherence to assigned therapy, can lead to biased comparisons between treatment arms and limit the interpretability of these results.

Table 3. Percentage of Subjects Meeting the Primary Endpoint by Analysis Population

Analysis Population	Definition	Fluvoxamine	Placebo	Relative Risk (95% BCI*)
ITT	All randomized	10.7% (79/741)	15.7% (119/756)	0.68 (0.52-0.88)
mITT	Received ≥ 24 hours of study drug	10.5% (78/740)	15.3% (115/752)	0.69 (0.53-0.90)
PP	Received 80% of study drug prior to deterioration	3.6% (20/548)	11.0% (68/618)	0.34 (0.21-0.54)

Source: Original submission provided by the Requester on December 21, 2021.
*BCI = Bayesian Credible Interval

Given the uncertain clinical meaningfulness of the 6-hour emergency setting component of the primary endpoint, further analysis of the proportion of subjects who experienced hospitalization or death by Day 15, 29, and 60 in the fluvoxamine group compared to the placebo group was provided on February 1, 2022, by the Requester in response to an information request (IR). 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

13

considered hospitalization and death as the most clinically meaningful endpoints for this population.[31] In these ITT analyses, while hospitalization or death appeared to be reported more frequently in the placebo group than in the fluvoxamine group, the 95% confidence intervals indicate the amount of statistical uncertainty in the comparisons is too great to determine whether fluvoxamine has an effect on hospitalization or death. In each of the comparisons, the 95% confidence interval for the treatment effect covered the null value of 1 as summarized in Table 4. Additionally, the amount of missing data at each timepoint was not provided.

Table 4. Hospitalization[1] or Death at Days 15, 29, and 60 in the TOGETHER Trial

Outcome	Fluvoxamine N = 741	Placebo N = 756	Relative Risk (95% CI*)
Hospitalization/Death at Day 15; n (%)	74 (10.0%)	96 (12.7%)	0.79 (0.59, 1.05)
Hospitalization/Death at Day 29; n (%)	75 (10.1%)	98 (13.0%)	0.78 (0.59, 1.04)
Hospitalization/Death at Day 60; n (%)	75 (10.1%)	98 (13.0%)	0.78 (0.59, 1.04)

Source: Response to IR dated, January 28, 2022, provided by the Requester on February 1, 2022.
[1]Hospitalization is defined as either retention in a COVID-19 emergency setting for greater than 6 hours or transfer to tertiary hospital due to COVID-19.
*CI = Confidence Interval

Although not sufficiently powered to demonstrate statistical significance on mortality, the Requester reported mortality rates through Day 28 in the ITT population of 2.3% and 3.3% in the fluvoxamine and placebo groups, respectively (RR 0.7, 95% CI 0.38-1.26). When hospitalization was evaluated independently of mortality, the rate was 10.1% and 12.8% in the fluvoxamine and placebo groups, respectively (RR 0.79, 95% CI 0.59-1.05).

Secondary Efficacy Analysis
According to the manuscript, there were no statistically significant differences reported between fluvoxamine and placebo for any secondary endpoints, each evaluated through Day 28 except for viral clearance. The reported results were for viral clearance at Day 7 (odd ratio [OR] 0.67; 95% CI 0.42-1.06) and hospitalizations due to COVID (OR: 0.77; 95% CI 0.55-1.05), all-cause hospitalizations (OR: 0.76; 95% CI 0.58-1.04), time to hospitalization in days (hazard ratio [HR]: 0.79; 95% CI 0.58-1.06), number of days in hospital (ratio of means: 1.23; 95% CI 0.99-1.53), mortality (OR: 0.69; 95% CI 0.36-1.27), time to death (HR: 0.80; 95% CI 0.43-1.51), and number of days on mechanical ventilation (ratio of means: 1.03; 95% CI 0.64-1.67). Additionally, the manuscript reported results for time to recovery (p=0.79), and the PROMIS Global Physical (p=0.55) and Mental Scale (p=0.32); however, point estimates and confidence intervals were not provided. Based on the information available in the manuscript, it is unclear if the aforementioned analyses were entirely derived from the ITT population.

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[31] https://www.fda.gov/media/146173/download

Key Review Issues from the TOGETHER trial

While the primary endpoint results suggest that further clinical trials of fluvoxamine may be warranted, the scientific evidence from this study was not sufficient to support the potential effectiveness of fluvoxamine for the treatment of nonhospitalized patients with COVID-19. As per the protocol, the primary endpoint was a composite of emergency room visits for COVID-19 requiring observation for greater than 6 hours and hospitalization due to progression of COVID-19, up to 28 days after randomization. This efficacy endpoint has not been used to support regulatory decisions for interventions in nonhospitalized patients who are at high risk for hospitalization and death due to COVID-19. 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." In this trial, the primary endpoint result was driven by a reduction in the emergency department visits lasting greater than 6 hours. The treatment benefit of fluvoxamine was not persuasive when focusing on the proportion of patients experiencing hospitalizations alone or hospitalizations and deaths. In authorizing products for outpatient use under an EUA, the Agency has generally required robust data demonstrating an effect on hospitalizations and/or death because of the number of variables impacting emergency department visits and length of stay. Acknowledging that retention in an emergency setting for 6 hours or longer was intended to serve as a proxy for hospitalization in this study, it is uncertain how accurately the study captured recommended retention time for observation, who determined the length of observation, and whether the 6-hour timepoint represents a clinically meaningful threshold. The diminished treatment effect when evaluating hospitalizations and deaths raises questions about the strength of the efficacy data and whether being retained in the emergency setting for ≥ 6 hours may be equated to requiring hospitalization in the United States.

Given that the efficacy results are driven by retention in an emergency setting rather than hospitalizations, an additional factor considered is the clinical setting, since the study was conducted entirely in one region of Brazil. It is difficult to determine if these efficacy results from a study conducted entirely in one geographic location would be generalizable to a US population in the current setting of available therapies.

The Requester relies heavily on the PP analyses that suggest a treatment effect on mortality among those who reported at least 80 percent adherence to the study medication. There was one death (<1%) in the fluvoxamine group and 12 (2%) in the placebo group for the PP population (RR 0.15; 95% CI 0.02; 0.57). However, the validity of this finding is uncertain because patients who did not meet the 80% adherence threshold were excluded from the PP analysis. Analyses evaluating subgroups of patients defined by post-randomization outcomes, such as adherence, leading to biased comparisons between treatment arms. Notably, more individuals in the fluvoxamine group than placebo group were nonadherent (84 participants stopped fluvoxamine and 64 participants stopped placebo owing to issues of tolerability). The mortality comparison within the ITT population, which maintains randomized comparisons, did not identify statistically significant differences. In this analysis from the Requestor, there were 17

15

deaths (2%) in the fluvoxamine group and 25 deaths (3%) in the placebo group (RR 0.7, 95% CI: 0.38, 1.26). Finally, the 80% threshold used to define the PP populations is arbitrary and only 74% of participants in the fluvoxamine arm reached this level of adherence. This may have been due to the side effect profile of fluvoxamine, which may have concomitantly compromised the blinding and impacted subsequent treatment decisions.

STOP COVID Trial

Trial Design

STOP COVID was a double-blind, placebo-controlled, single center, fully remote trial conducted in the United States among 152 nonhospitalized adults diagnosed with COVID-19 within 7 days of symptom onset who were randomized 1:1 to receive either fluvoxamine (100 mg up to 3 times daily for 15 days) or placebo. Supplies included study medication, an oxygen saturation monitor, an automated blood pressure monitor, and a thermometer, and were delivered to the doorstep of subjects who were required to perform their own vital sign monitoring and symptom evaluation. All data, including oxygen saturation, vital signs, medication adherence, and COVID-19 symptoms, were collected via twice-daily electronic surveys that were provided to patients by email with phone calls as backup. Dyspnea was measured using a continuous scale (0 = symptom is not present and 10 = symptom is very severe).

Eligibility Criteria

Adults living in the community with polymerase chain reaction (PCR)-confirmed SARS CoV-2 and symptomatic within 7 days of the first dose of study medication were recruited for the study. Subjects were excluded if they were currently hospitalized, had severe underlying lung disease, were asymptomatic, had exclusionary medical conditions or were immunocompromised, were enrolled in another COVID-19 trial, or were unable to provide informed consent or perform the study procedures.

Endpoints

The primary endpoint was clinical deterioration at Day 15, defined as shortness of breath plus oxygen saturation (SpO2) ≤92% or hospitalization plus SpO2 ≤92%. Regarding the shortness of breath plus SpO2 ≤92% component of this composite endpoint, it is unclear how investigators determined if subjects met criteria based on the information in the protocol and manuscript. However, subjects who developed a decrease in SpO2 < 90% on room air on >2 readings, persistent increase in respiratory rate (RR) to > 30 breaths per minute, persistent increase in heart rate (HR) to > 120 beats per minute, alteration in mentation, or severe worsening in shortness of breath were directed to seek care at the nearest emergency department. Criteria for defining hospitalization events were not provided. Secondary endpoints included episodes of clinical deterioration as rated on a novel 7-point scale developed for this study (see Appendices) and number of days requiring supplemental oxygen, hospitalization, and ventilator support. A pre-specified secondary endpoint evaluating symptomatic severity during the 15 days of the trial using a continuous scale was identified as flawed by the authors and was not pursued further.

16

Notably, the definition of clinical worsening did not incorporate any definitions for sustained recovery, an important component of clinical status.

<u>Analysis Populations</u>

The full analysis set included only subjects who met the eligibility criteria and started taking the study medication.

<u>Results</u>

Demographics and Baseline Characteristics

Of the 1337 patients screened, 834 (62%) were excluded, 322 (24%) declined participation, and 181 (14%) were randomized. Of the 181 patients randomized, 16 could not confirm eligibility at baseline due to staff inability to contact potential participants, 4 had oxygen saturation ≤ 92% at baseline, and 9 withdrew from the study prior to receiving fluvoxamine or placebo, leaving 152 participants that started the study and were included in the analysis. The mean age was 46 years (SD, 13 years), 109 (72%) were female, 106 (70%) were white, and 38 (25%) were black. Baseline conditions were relatively well-balanced. However, there were more subjects with asthma in the fluvoxamine versus placebo group with 17 (21%) and 9 (13%) subjects, respectively. Additionally, 14 (18%) versus 7 (10%) of subjects with a normal body mass index (BMI) were assigned to the fluvoxamine group versus placebo group, respectively.

Primary Efficacy Analysis

In the STOP COVID trial there were zero out of 80 cases of clinical deterioration in the fluvoxamine group compared with 6 of 72 in the placebo group (0 vs 8.3%; 95% CI 1.8-16.4). In the placebo group, clinical deterioration occurred 1 to 7 days after randomization and from 3 to 12 days after the onset of COVID-19 symptoms. Of those meeting the definition of clinical deterioration, all 6 met these criteria by having an SpO2 ≤ 92%. Four (5.6%) of the participants in the placebo group were hospitalized for COVID-19 illness, with the length of stay ranging from 4 to 21 days. One (1.4%) participant in the placebo group required mechanical ventilation for 10 days and no patients died in either group. Further analysis of the proportion of subjects who experienced hospitalization or death by Day 15, 29, and 60 in the fluvoxamine group compared to the placebo group was provided by the Requester. In these ITT analyses, while hospitalization or death appeared to be reported more frequently in the placebo group, the 95% confidence intervals indicate the amount of statistical uncertainty in the comparisons is too great to determine whether fluvoxamine impacts hospitalization or death. In each of the comparisons, the 95% confidence interval for the treatment effect covered the null value of 1 as summarized in Table 5. Additionally, the amount of missing data at each timepoint was not provided. Further, the authors of the manuscript state that the possibility of individuals receiving care at urgent care centers outside the major regional hospital system could not be ruled out in those who were lost to follow-up.

17

Table 5. Hospitalization or Death at Days 15, 29, and 60 in the STOP COVID Trial

Outcome	Fluvoxamine N = 80	Placebo N = 72	Relative Risk (95% CI)
Hospitalization/Death at Day 15; n (%)	1 (1.3%)	5 (6.9%)	0.18 (0.022, 1.50)
Hospitalization/Death at Day 29; n (%)	2 (2.5%)	5 (6.9%)	0.36 (0.07, 1.80)
Hospitalization/Death at Day 60; n (%)	2 (2.5%)	5 (6.9%)	0.36 (0.07, 1.80)

Source: Response to IR dated, January 28, 2022, provided by the Requester on February 1, 2022.
Note, definition of hospitalization not provided.

Of the 152 participants, 18 of 80 in the fluvoxamine group stopped responding to the surveys prior to Day 15 compared with 19 of 72 who were randomized to placebo, and 517 of 3,943 follow-up surveys (13%) were not completed by the trial participants. The manuscript reports that data were censored for participants who stopped responding to surveys prior to Day 15 for reasons described above or because they met the primary endpoint.

Secondary Efficacy Analysis
The investigators did not pursue this analysis further due to lack of differences between the groups in the primary endpoint and observed heterogeneity in severity of baseline symptoms across subjects.

Key Review Issues from the STOP COVID trial

There were deficiencies in the design and conduct of the STOP COVID trial that limit its interpretability and use in support of an EUA request. A major concern is the amount of missing data and reliance on self-reporting. Many participants were lost to follow up, and 24% of participants stopped responding to surveys prior to Day 15. The trial was conducted remotely, placing the burden of reporting symptoms and skill-dependent tasks of measuring vital signs entirely upon the participant. Not only were there very few cases of clinical deterioration observed, but this was also a small study (≤80 participants per arm) conducted within a single geographic area. 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 addition, the authors of the manuscript cite that the observed differences in clinical deterioration may have been a reflection of the comparative baseline distributions of oxygen saturation rather than an effect of treatment, though these data were not provided. Another limiting factor was the short follow-up duration of 15 days, as clinical experience has shown that symptoms can persist and deteriorate after 15 days, rendering this timepoint less informative. As described below in the discussion of the manuscript by Lee et. al., the larger (approximately 3-times larger than the STOP COVID trial) subsequent study, STOP COVID 2, had a similar design and enriched population of high-risk patients, yet failed to confirm the findings of this trial.

18

RWD Trial

The real-world observational study of early SARS-CoV-2 treatment with fluvoxamine was a prospective, open-label design that included 113 subjects offered fluvoxamine on the same day that they tested positive for SARS-CoV-2. A total of 65 people (57.5%) opted for treatment and 48 (42.5%) opted for observation alone. Those who chose to receive fluvoxamine were prescribed a 50- to 100-mg loading dose followed by a 50 mg dose given twice daily for 14 days. Subjects received follow-up at 7 and 14 days. Overall, demographics between the two arms were similar. However, there were key differences including fewer white subjects that opted for fluvoxamine. Additionally, there were fewer patients in the fluvoxamine group that were asymptomatic (38%) at time of initial diagnostic testing than those opting for observation (58%) alone. Amongst all subjects, 30% had 1 or more chronic medical comorbidities. Those opting for fluvoxamine had more frequent diabetes (17% vs 8%) and less treated hypertension (17% vs 35%) than those in the observation group, but overall, there were fewer subjects in the fluvoxamine arm with one of the underlying chronic comorbidities. It is not clear in the manuscript if 'treated hypertension' reflects patients with uncontrolled disease, blood pressure in the normal range, or a combination of both. At 14 days, no patients receiving fluvoxamine had been hospitalized for clinical deterioration and 12.5% (6/48) of patients who declined treatment had been hospitalized (p = 0.005). It is not clear whether the small p-value can be attributed to a true underlying treatment effect of fluvoxamine + usual care compared to usual care alone, for several reasons. In addition to the imbalances between treatment arms as described above, there may be other confounding factors resulting from the lack of randomization in this observational study. Furthermore, the results of the study may be biased due to the open-label nature of study.

Key Review Issues from the RWD Trial

The open-label, non-randomized design of the study significantly limits the interpretability of the results and ability to draw any conclusions regarding a causal effect of fluvoxamine on hospitalization rates.

COVID-OUT[32]

COVID-OUT is a randomized, double-blind, placebo-controlled trial in outpatients aged 30-85 years evaluating metformin, ivermectin, or fluvoxamine within 3 days of confirmed SARS-CoV-2 infection. The primary endpoint was progression to severe COVID-19, defined as hypoxia <=93% or healthcare utilization for COVID-19 (emergency department use, hospitalization, or death) through Day 14. Although preliminary, data obtained from the Requester did not demonstrate a statistically significant effect on progression to severe COVID-19 disease with fluvoxamine treatment, administered as 50 mg twice daily for 14 days, compared to placebo. (b) (4)

There was

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[32] Data from draft manuscript for COVID-OUT trial provided by the Requester to the Agency in email communication dated March 8, 2022

19

no observed reduction in emergency room visits or hospitalizations; no deaths occurred in the fluvoxamine arm of the study.

Meta-Analysis[33]

The authors of this meta-analysis, of whom the Requester is included, extracted hospitalization outcome data in each treatment group from the TOGETHER, STOP COVID, and STOP COVID 2 trials. For the TOGETHER trial, outcome data on emergency department visits lasting more than 24 hours from the TOGETHER trial were used, rather than those for the ≥ 6 hour retention time, as a proxy for hospital admission. The meta-analysis included a total of 2,196 analyzed patients, and it should be noted that due to the relative sample sizes of the studies, the TOGETHER trial is heavily weighted in the results. The authors performed the meta-analysis with three different approaches: a Bayesian analysis using a weakly neutral prior, a Bayesian analysis using a moderately optimistic prior, and a frequentist analysis. The estimated pooled RR of hospitalization between fluvoxamine and placebo for the three analyses were 0.78 (95% Bayesian Credible Interval (BCI), 0.58-1.08), 0.73 (95% BCI, 0.53-1.01), and 0.75 (95% BCI, 0.58-0.97), respectively.

Despite this alternate analysis of hospitalization rates, defined by hospitalization or ED visits lasting ≥ 24 hours for the TOGETHER trial, the meta-analysis was still hindered by the same limitations inherent to the individual studies. The authors note that only three trials were available for inclusion and the TOGETHER trial contributed between 66% and 88% of the analytic weight. Data reported by the authors of the meta-analysis for STOP COVID 2 showed no difference between the fluvoxamine and placebo arms (11/272 vs 12/ 275, RR 0.93 [95% CI 0.42-2.06]). No data were provided from the STOP COVID 2 trial by the Requestor and the fluvoxamine arm was terminated in this study early due to an absence of treatment effect on any outcomes as stated in the manuscript. Furthermore, 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.

Efficacy Conclusions

In summary, based on the totality of scientific evidence available, including data submitted to the EUA request and published studies, the Agency cannot reasonably conclude that fluvoxamine may be effective for the treatment of COVID-19. Due to various limitations in the STOP COVID and RWD trials (e.g., small size, single center, endpoint selection, lack of randomization), the primary data supporting this EUA request are derived from the TOGETHER trial. As noted above, while the study met its primary endpoint, the results were primarily driven by the emergency setting component of the

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[33] Lee TC, Vigod S, Bortolussi-Courval É, Hanula R, Boulware DR, Lenze EJ, Reiersen AM, McDonald EG. Fluvoxamine for Outpatient Management of COVID-19 to Prevent Hospitalization: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022 Apr 1;5(4):e226269. doi: 10.1001/jamanetworkopen.2022.6269. PMID: 35385087.

composite endpoint, a finding with uncertain clinical significance. The treatment benefit of fluvoxamine was less persuasive when focusing on hospitalizations alone or hospitalizations and deaths in both TOGETHER and STOP COVID (see Table 4 and Table 5). While other meaningful endpoints from the TOGETHER trial such as time-to-death, all-cause mortality, and time-to-recovery, showed favorable trends, the authors reported that there were no significant differences between fluvoxamine and placebo.

In contrast to the TOGETHER study which met its primary endpoint, and the small STOP COVID trial, two other trials, STOP COVID 2 and COVID-OUT failed to demonstrate a benefit with fluvoxamine in adults with mild COVID-19 in the outpatient setting, and both were terminated early for futility. COVID-OUT evaluated a lower dose of fluvoxamine (50 mg BID), which could potentially explain the lack of efficacy. However, STOP COVID 2 had a similar design as STOP COVID with a larger sample size (N=553) and enriched population of high-risk patients, yet failed to confirm the findings of the smaller trial.

Given the absence of a persuasive benefit on hospitalizations and mortality, it is also unclear if the results from the TOGETHER trial would extend to other outpatient populations with COVID-19 (e.g., fully vaccinated patients); a significant point given the study was conducted and concluded prior to widespread availability of vaccines and the global prevalence of the Omicron sub-variants, which affect risk of progression to severe disease and thus hospitalization and mortality rates.

Adding to the uncertainty, the mechanism of action of fluvoxamine in COVID-19 has not been well-characterized. The rationale for use of fluvoxamine to treat mild COVID-19 disease is based on preliminary data from animal and in vitro studies that suggest a potential anti-inflammatory mode of action. However, fluvoxamine is not generally considered an anti-inflammatory drug, nor has it been widely used for such purposes in clinical practice. Further, there is no evidence to date that an anti-inflammatory mechanism would be beneficial at an early stage of infection when COVID-19 disease severity is mild. The exact setting in which hyperinflammatory responses drive disease pathology is still under investigation and therapies used as anti-inflammatories are currently recommended only for hospitalized individuals requiring supplemental oxygen and have not proved to be beneficial to those suffering from COVID-19 in the outpatient setting.[34]

The potential anti-inflammatory properties of fluvoxamine are based on its agonism of the sigma-1 receptor. Sigma-1 receptor is an inhibitor of endoplasmic reticulum-driven inflammation and theorized to be a potential therapeutic target in septic shock. The preclinical models used for septic shock to generate these data are useful in developing hypotheses for MOAs, but do not adequately replicate human sepsis nor directly translate to clinical findings. While the pharmacologically active dose of 20 mg/kg delivered

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[34] https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/

21

intraperitoneally in the mouse LPS/sepsis model [35] was comparable to the proposed oral clinical dose of 50 mg twice daily based on body surface area, despite different dosing routes, this comparison should be interpreted with caution as exposure data (e.g., AUC, Cmax) to establish more reliable exposure margins are lacking.

Although the Requester does not propose the use of fluvoxamine as an anti-viral, the theoretical anti-viral properties are mentioned in the manuscripts submitted in support of the EUA request. The basis is that fluvoxamine may be protonated in the lysosome, which could potentially prevent β-coronaviruses, like SARS-CoV-2, from using lysosomal trafficking to escape from infected cells and reinfect others.[36,37,38] No testing in in vivo animal models of viral infection have been conducted to support this hypothesis; thus the potential for fluvoxamine to mediate host-virus interactions to regulate viral infection of host cells through lysosomotropic properties and regulation of endoplasmic reticulum stress remains speculative. While additional mechanistic data are needed, it is unlikely that fluvoxamine possesses a high degree of activity against SARS-CoV-2. As described in Section V, there are currently available therapies with well-characterized anti-viral mechanisms including paxlovid, remdesivir, and molnupiravir, each of which has demonstrated significant reductions in hospitalization and death in randomized clinical trials.

Finally, there is a lack of clarity around the optimal dosing regimen for fluvoxamine. Clinical studies have evaluated different doses, dosing regimens, and treatment durations as tolerability is an apparent issue with increasing doses and low doses (such as in the COVID-OUT study) have failed to demonstrate a benefit.

Human Clinical Safety

Methods

The Requester provided journal articles that contained incidence tables for AEs by grade and body system classification from the TOGETHER trial and overall AEs for the STOP COVID trial. No original datasets or subject narratives were included. The Requester proposes an unapproved use of an approved product with the labeled dose and route for fluvoxamine's approved uses and therefore claims the risk is equivalent or reduced in the

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[35] Rosen DA, Seki SM, Fernandez-Castaneda A, et al. Modulation of the sigma-1 receptor-IRE1 pathway is beneficial in preclinical models of inflammation and sepsis. Sci Transl Med. 2019;11(478). Available at: https://www ncbi nlm nih.gov/pubmed/30728287.

[36] Sukhatme VP, Reiersen AM, Vayttaden SJ, Sukhatme VV. Fluvoxamine: a review of its mechanism of action and its role in COVID-19. Front Pharmacol 2021; 12: 652688.

[37] Ghosh S, Dellibovi-Ragheb TA, Kerviel A, Pak E, Qiu Q, Fisher M, Takvorian PM, Bleck C, Hsu VW, Fehr AR, Perlman S, Achar SR, Straus MR, Whittaker GR, de Haan CAM, Kehrl J, Altan-Bonnet G, Altan-Bonnet N. β-Coronaviruses Use Lysosomes for Egress Instead of the Biosynthetic Secretory Pathway. Cell. 2020 Dec 10;183(6):1520-1535.e14. doi: 10.1016/j.cell.2020.10.039.

[38] Homolak J, Kodvanj I. Widely available lysosome targeting agents should be considered as potential therapy for COVID-19. Int J Antimicrob Agents. 2020;56(2):106044.

intended population as the OCD population due to the shorter duration of treatment. Of note, the approved product label carries a boxed warning for suicidality.[39]

Exposure

The safety database for the indication of COVID-19 consists of 1,497 adults from the TOGETHER trial, 751 of whom received at least one dose of fluvoxamine and 619 of whom reported >80% adherence. Additionally, AEs were reported for 152 adults in the STOP COVID trial, 80 of whom received at least one dose of fluvoxamine.

Fatal Adverse Events

There were 17 and 25 deaths in the TOGETHER trial between the fluvoxamine and placebo groups, respectively. There was one death reported in the RWD study in a subject who declined treatment with fluvoxamine. No deaths were reported in the STOP COVID trial.

Additional Safety Findings

There were reportedly no significant differences in number of treatment emergent adverse events observed among patients in the fluvoxamine and placebo groups. However, 84 participants stopped fluvoxamine and 64 participants stopped placebo owing to issues of tolerability in the TOGETHER trial. Although the specific descriptions of adverse reactions leading to treatment discontinuation were not provided for the TOGETHER trial, the Requester provided the adverse reactions that led to discontinuation in the controlled clinical trials for the indication of OCD. These included nausea (9%), insomnia (4%), somnolence (4%), headache (3%), asthenia (2%), vomiting (2%), nervousness (2%), agitation (2%), and dizziness (2%). In the STOP COVID trial, there was 1 serious adverse event (SAE) and 11 other AEs, whereas the placebo group had 6 SAEs and 12 AEs. Pneumonia and gastrointestinal symptoms occurred more often in the placebo group compared with those who received fluvoxamine. Results from the RWD study reported no SAEs or AEs that led to early discontinuation within the group receiving fluvoxamine.

Safety Conclusion

The majority of common AEs reported in the trial are consistent with events expected in a population with COVID-19 and/or known AEs to occur with fluvoxamine based on the safety database generated for the indication of OCD. While the safety database generated for the indication of COVID-19 is small, fluvoxamine is an approved product with extensive postmarketing experience. Therefore, failing to make an adequate characterization of the risks and benefits of fluvoxamine for its proposed use is primarily due to insufficient scientific evidence on the potential effectiveness of fluvoxamine for the proposed patient population rather than any remaining uncertainties around the adequacy of the safety database.

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[39] https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021519lbl.pdf

Risk-Benefit Assessment and Conclusions for Emergency Use

Due to limitations in the available clinical study results for fluvoxamine in the proposed patient population, lack of compelling *in vitro* and *in vivo* data to support the proposed MOA of fluvoxamine for the treatment of mild COVID-19 disease, and context of increasingly available therapies with well-characterized MOAs and consistent efficacy results in nonhospitalized patients, the FDA cannot reasonably conclude that fluvoxamine may be effective for the treatment of COVID-19. As such, FDA has determined that the criteria for issuance of an EUA are not met at this time. While the FDA has concluded that the existing clinical data are insufficient to support the issuance of an EUA, these data suggest that further clinical investigation may be warranted.

Appendices

WHO Clinical Worsening Scale as Administered in the TOGETHER Trial

WHO Clinical Worsening Scale

WHO clinical worsening scale performed?	o Yes o No (explain)
Date of assessment	DD-MMM-YYYY
WHO clinical worsening scale (please select one option)	o No Clinical or virological evidence of infection o No limitation of activities o Limitation of activities o Hospitalized, No oxygen therapy o Hospitalized, oxygen by mask of nasal prongs o Hospitalized, non-invasive ventilation or high flow oxygen o Hospitalized, Intubation and mechanical ventilation o Hospitalized, Ventilation + Additional organ support – Pressors, RRT, ECMO o Death

Clinical status on 7-point scale used in the STOP COVID Trial

Clinical deterioration, No (%)
0=None
1=O_2 sat <92% but no supplemental O_2
2=Above + supplemental O_2 needed
3=Above + hospitalization needed
4=Above + ventilator needed (<3 days)
5=Above + ventilator needed (≥3 days)
6=Death
Total participants with values >0

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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04/28/2022 12:36:16 PM

PETER P STEIN
04/29/2022 11:41:13 AM

EMERGENCY USE AUTHORIZATION REVIEW
US FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF IMMUNOLOGY AND INFLAMMATION
DIVISION OF PULMONOLOGY, ALLERGY, AND CRITICAL CARE
ADDENDUM

EUA: 000110
Product: Fluvoxamine Maleate
Sponsor: David R Boulware MD, MPH, CTropMed, FIDSA
Intended Population: Outpatient treatment of adults 24 years and older with positive test results of SARS-CoV-2 viral testing to prevent progression to severe COVID-19 and/or hospitalization

This addendum is for corrections to the summary EUA review for fluvoxamine for the outpatient treatment of COVID-19 dated April 29, 2022.

The redacted sentence on page 7 is replaced with the following: "Although the study is ongoing, recent updates from the COVID-OUT trial indicate that the fluvoxamine arm did not show superiority over placebo and has now been stopped for futility."

The corrections do not alter the conclusion of the review.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STACY J CHIN
05/03/2022 10:00:22 PM

PETER P STEIN
05/06/2022 09:52:18 AM