RAPID-C19 Oversight Group

Briefing:

serotonin specific reuptake inhibitors (SSRIs) (fluvoxamine, fluoxetine) (generic) [C19-058]

For administrative purposes only:

Version	Section	Date	Initial
0.1	1-5	18/02/2021	[redacted]
0.2	1-5	22/02/2021	[redacted]
0.3	1-5	22/02/2021	[redacted]
1.0	-	23/02/2021	[redacted]

Briefing

1. Key considerations

Question	Response	Section
1. a) Where does fluvoxamine and fluoxetine sit in the treatment pathway?	Prevention / **mild** / **moderate** / severe / critical / rehabilitation [most studies are being conducted in non-hospitalised patents]	
b) Are there other treatments sitting in this place in the pathway?	**Y** / N (refer to the pathway diagram that will accompany the papers at the weekly meetings)	
c) What is the mechanism of action of fluvoxamine and fluoxetine that explains why it is being investigated as a potential treatment for COVID-19, and its particular place in the treatment pathway?	Fluvoxamine and fluoxetine are serotonin specific reuptake inhibitors (SSRIs). Antidepressants may be associated with decreases in plasma levels of inflammatory mediators, including IL-10, TNF-α, CCL-2 and IL-6. In addition, it has been proposed that a potential mechanism for fluvoxamine is immune modulation via σ-1 receptor (S1R) agonism (Hoertel 2021).	
d) Are there other treatments in this class (i.e with the same or similar mechanism of action) that have been considered by the Oversight Group and if so, what are these?	A number of other treatments with activity against IL-6 and TNF-α have been considered by the Oversight Group, in moderate/severe and critically ill patients with COVID-19	
e) Are there other treatments in this class that are currently in clinical trials for COVID-19 and if so, what are they?	There are no other SSRIs being investigated for COVID-19.	
2. Is the evidence base sufficient to allow further action to be taken at this stage? *Sufficient evidence base should take into account the amount of evidence (number of trials and total number of participants) as well as robustness of the trials.*	Y / **N** Results are available for fluvoxamine from one small placebo-controlled RCT and one observational study. There are no published studies for fluoxetine.	5.1 and appendix 1
3. Is there a positive signal of efficacy across the outcomes?	**Y** / N In the published RCT, fluvoxamine showed a significant benefit versus placebo for the primary endpoint of clinical deterioration, however the certainty of effect is low given the	5.1 and appendix 1

	small sample size, short duration of follow up and wide confidence intervals. Results from larger RCTs are required.	
4. Is there a specific population where there could be significant benefit?	Y / N / **Unknown**	
5. Is there a signal of harm (including unfavourable effects and adverse events)?	Y / **N** In the published RCT the proportion of patients with a serious adverse event was lower for fluvoxamine vs. placebo. The number of non-serious adverse events was similar across treatment arms.	5.1 and appendix 1
6. Are there other relevant issues for consideration (e.g. combination therapies, special populations of interest, regulatory issues, potential supply issues, service delivery or technology delivery challenges)?	Y / N / **Unknown** There is no information in the trial registry records for the ongoing studies regarding the new variants of SARS-CoV-2.	
Next steps	Stand down / **monitor** / progress Monitor for results from the larger RCTs expected to report soon.	
Progress: Oversight Group to take action (e.g. commission an evidence summary, begin regulatory discussions). **Monitor**: Oversight Group to reconsider topic at a later date (e.g. after trial results have published). **Stand down**: Oversight Group considers there is not, and is not likely to be, any positive signal that warrants further consideration of this topic.		

2. Treatment

Treatment	Fluvoxamine Fluoxetine
Type	Anti-depressant (SSRIs)
Mechanism of action	Antidepressants may be associated with decreases in plasma levels of inflammatory mediators, including IL-10, TNF-α, CCL-2 and IL-6. In addition it has been proposed that a potential mechanism for fluvoxamine is immune modulation via σ-1 receptor (S1R) agonism (Hoertel 2021)
Administration	Oral
Dose and schedule	Fluvoxamine, 100mg twice or three times daily, orally Fluoxetine, 20mg to 60mg daily, orally
Cost	Fluvoxamine 50mg tablets, 60; £17.53 [a] Fluvoxamine 100mg tablets, 30; £17.70 [a] Fluoxetine 20mg capsule, 30; £1.12 [a]

Existing guidance/information	-
Other relevant information	-
Source: [a] BNF	

3. Regulatory status

Commercial sponsor	Fluvoxamine 100mg tablet: Mylan, AAH Pharmaceuticals Ltd, Alliance Healthcare (Distribution) Ltd, DE Pharmaceuticals, Medihealth (Northern) Ltd, Sigma Pharmaceuticals Plc, Tillomed Laboratories, Wockhardt UK Ltd Fluoxetine 20mg capsule: numerous manufacturers hold marketing authorisations **ACTION (for generics only): NHSE repurposing medicines group to identify commercial sponsors wishing to pursue a license for COVID-19 via the British Generics Manufacturers Association (BGMA)** **ACTION: MHRA to advise on lead regulator (MHRA/EMA) & likely regulatory process that will be followed**
New or repurposed	Repurposed
Branded or generic	Generic
Regulatory status/plans	**COVID-19** Not yet licensed for this indication. Regulatory plans still to be confirmed with sponsors. **Existing indications in the UK** Fluvoxamine is indicated for depressive illness and obsessive compulsive disorder. [a] Fluoxetine is indicated for major depression, obsessive compulsive disorder, bulimia nervosa and menopausal symptoms, particularly hot flushes, in women with breast cancer. [a] **ACTION: NICE & MHRA to [consider the appropriate time to] gather additional information on regulatory plans from identified commercial sponsors**
Source: [a] BNF	

4. Supply activities

Supply	Unknown **ACTION: Once a commercial sponsor is identified, DH Therapeutics Taskforce to [consider the appropriate time to] gather information from companies on supply and scale-up.**

5. Evidence

5.1 Published evidence

The table below highlights the signals from the main published evidence and the strength of these signals, taking into account the magnitude of effect shown and the quality of the evidence. Any published studies not reporting key outcomes of interest or case studies are briefly summarised at the end of the table. Detailed information on all published studies are in appendix 1.

Trial	Result	Assessment of evidence	Certainty of effect*
Mortality			
Lenze 2020 JAMA NCT04342663 US Adult outpatients with confirmed SARS-CoV-2 and symptomatic within 7 days of first dose of trial medicine Fluvoxamine (n=80) Placebo (n=72)	There were no deaths in either group	Double-blind RCT Risk of bias – low (double-blind) however small sample size limit certainty of effect.	Low
Ventilation outcomes			
-	-	-	-
Time to recovery			
-	-	-	-
Clinical deterioration			

Lenze 2020 JAMA NCT04342663 US Adult outpatients with confirmed SARS-CoV-2 and symptomatic within 7 days of first dose of trial medicine Fluvoxamine (n=80) Placebo (n=72)	Primary endpoint: clinical deterioration at day 15 defined by (1) presence of dyspnoea or hospitalisation for shortness of breath or pneumonia and (2) decrease in oxygen saturation (<92%) on room air or supplemental oxygen requirement to maintain oxygen saturation of ≥92%: 0% (0/80) for fluvoxamine vs. 8.3% (6/72) for placebo; absolute difference 8.7% (95% CI 1.8% to 16.4%), p=0.009	Double-blind RCT Risk of bias – low (double-blind), however small sample size, short follow-up time and wide confidence intervals limit certainty of effect.	Low
Adverse events			
Lenze 2020 JAMA NCT04342663 US Adult outpatients with confirmed SARS-CoV-2 and symptomatic within 7 days of first dose of trial medicine Fluvoxamine (n=80) Placebo (n=72)	Serious adverse events occurred in 1.3% (1/80) vs. 6.9% (5/72) of patients Adverse events occurred in 13.8% (11/80) vs. 8.3% (6/72) of patients There were patients in placebo group who had more than one 'other adverse event'. Overall the total number of adverse events (other than serious) was 11 for fluvoxamine and 11 for placebo.	Double-blind RCT Risk of bias – low (double-blind), however small sample size and short follow-up time limit certainty of effect.	Low
****Explanation of the certainty of the effect based on the precision of the estimates and the robustness of the evidence***			
High certainty: Very confident that the true effect lies close to that of the estimate of the effect **Moderate certainty:** Moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low certainty:** Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect			
Summary of other published data/trials			
• A retrospective observational study (Hoertel 2021) conducted in France reported on 7,230 patients admitted to hospitals with COVID-19 of whom 345 (4.8%) received an antidepressant. Intubation or death was reported as follows: no antidepressant 17.3% (1188/6885); any antidepressant 24.3% (84/345); SSRI 23.1% (45/195) and non-SSRI 26% (39/150). Primary multi-variable analyses with inverse probability weighting showed significant associations between any antidepressant use with reduced risk of intubation or death; see appendix 1			

5.2 Ongoing trials

- There are 4 ongoing RCTs of fluvoxamine of phase 2/3 design. Two studies are being conducted in non-hospitalised patients with an expected recruitment of around 3,800 patients and 1 trial, with an estimated enrolment of 400 patients, is in patients admitted to community treatment centres. The 4th study is being conducted in hospitalised patients and has an estimated enrolment of 100 patients
- The non-randomised trial of fluoxetine has an estimated enrolment of 2,000 non-hospitalised patients.
- Two fluvoxamine studies have completed (with published results available for one of these).
- One fluoxetine study was suspended.

5.2.1 Key trials

The table below shows the key trials (in UK and NIHR-prioritised if applicable) that are likely to impact on decision-making (because of robust trial design and reporting of key outcomes):

Fluvoxamine
NCT04668950 (Washington University School of Medicine, RCT of **fluvoxamine**, US) Estimated enrolment: 1100 non-hospitalised patients with mild symptoms of COVID-19 Primary outcome: clinical deterioration Estimated PCD: July 2020
NCT04727424 TOGETHER2 (Cardresearch, RCT of **fluvoxamine**, Brazil) Estimated enrolment: 2724 outpatients with early onset mild symptoms of COVID-19 Primary outcome: emergency visits and observation unit stay >12 hrs; hospitalisation due to COVID-19 progression Estimated PCD: 01/02/2022
NCT04711863 S2020-3124-0001 (Asan medical Center, RCT of **fluvoxamine**, South Korea) Estimated enrolment: 400 patients with mild to moderated COVID-19 in community treatment centres Primary outcome: clinical deterioration Estimated PCD: 31/05/2021
ACTION: NICE to contact principle investigators using standard RAPID C-19 template letter to request more information on earliest anticipated reporting dates if possible, and whether key signals/results can be provided in advance of publication.

Further details of these trials are presented in appendix 2.

5.2.2 Trials with the earliest completion dates

The table below shows the trials due to report soon that are reasonably well designed and powered and/or investigating relevant clinical outcomes of interest:

Design	Size	Location	Primary outcome(s)	Estimated PCD
Fluvoxamine				
RCT NCT04711863	400	South Korea	Clinical deterioration	31/05/2021

RCT NCT04668950	1100	US	Clinical deterioration	July 2021

Further details of these trials are presented in appendix 2.

Appendix 1: Published evidence

A. Systematic reviews/evidence summaries

Reference	Design of study	Population	Results
-	-	-	-
Source: NICE Information Services literature search *Note: Published evidence has been excluded where [XXX, as applicable] (n=X)*			

B. Trials and studies

Reference	Design and location of study	Population	Results
Lenze 2020 JAMA NCT04342663	Double-blind RCT US	Adult outpatients with confirmed SARS-CoV-2 and symptomatic within 7 days of first dose of trial medicine. Fluvoxamine 50mg, then 100mg bd, then 100mg tds up to day 15 (n=80 received fluvoxamine as randomised) Placebo (n=72 received placebo as randomised)	Primary endpoint: clinical deterioration defined by (1) presence of dyspnoea or hospitalisation for shortness of breath or pneumonia and (2) decrease in oxygen saturation (<92%) on room air or supplemental oxygen requirement to maintain oxygen saturation of ≥92%: 0% (0/80) vs. 8.3% (6/72) for the fluvoxamine and placebo groups respectively; absolute difference 8.7% (95% CI: 1.8% to 16.4%), p=0.009 No patients died. SAE occurred in 1.3% (1/80) vs. 6.9% (5/72) of patients AE occurred in 13.8% (11/80) vs. 8.3% (6/72) of patients There were patients in the placebo group who had more than one 'other adverse event'. Overall the total number of adverse events (other than serious) was 11 for fluvoxamine and 11 for placebo. Cochrane living meta-analysis WHO progression score ≥6 day 14 to 28 (all randomised): 0/92 vs. 1/89, RR 0.32, 95% CI 0.01 to 7.82 WHO progression score ≥7 day 14 to 28 (all randomised): 0/92 vs. 1/89, RR 0.32, 95% CI 0.01 to 7.82

Reference	Design and location of study	Population	Results
Hoertel 2021 Molecular Psychiatry [previously available as a preprint]	Retrospective observational multi-centre cohort study 39 hospitals, France 24/1/2020 to 1/4/2020 Antidepressant use defined as receipt of any antidepressant during the first 48 hours of hospital admission and before the end of hospitalisation or intubation or death	7230 patients admitted to hospital with COVID-19 345 (4.8%) received an antidepressant SSRI, n=195 Other, n=150 Mean fluoxetine equivalent dose, 21.6mg	**Primary endpoint: time to intubation or death** No antidepressant 17.3% (1188/6885) **Primary endpoint: composite of intubation or death** Any antidepressant 24.3% (84/345) SSRI 23.1% (45/195) Non-SSRI (39/150) Unadjusted hazard ratio age-stratified estimates of the association between antidepressant use and the endpoint were non-significant (all p>0.05) Primary multi-variable analyses with inverse probability weighting showed significant associations between any antidepressant use with reduced risk of intubation or death: Any antidepressant, HR 0.56, 95% CI 0.43 to 0.73, p<0.001 SSRI antidepressant, HR 0.51, 95% CI 0.36 to 0.72, p<0.001 Non-SSRI antidepressant, HR 0.65, 95% CI 0.45 to 0.93, p=0.018
Source: NICE Information Services literature search (15/02/2021)			
Abbreviations: SAE, serious adverse event. AE, adverse event; RR, risk ratio; HR, hazard ratio; CI, confidence interval; SSRI, serotonin specific reuptake inhibitor			

Appendix 2: Ongoing trials

A. Completed trials

Reference	Sponsor	Design	Location	Population	Primary endpoints	Estimated PCD*
Fluvoxamine						
IRCT20131115015405N4 Up to 300mg daily	Massih Daneshvari Hospital	Phase 2/3 Open-label Randomised Controlled: Fluvoxamine vs no fluvoxamine	Iran	18 years + Hospitalised (ICU) Estimated enrolment: 40	• IL6 level • ESR level • CRP level	Recruitment complete
NCT04342663** 202004023 STOP COVID Fluvoxamine 100mg three times daily for 15 days	Washington University School of Medicine	Phase 2 Double-blind Randomised Controlled: fluvoxamine vs. placebo	US	18 years+ Non-hospitalised Confirmed SARS-CoV-2 Symptomatic Actual enrolment: 152	Time to clinical worsening	Recruitment complete Published (see appendix 1)

Source: National Institute for Health Research Innovation Observatory (scan 11/2/2021)

Abbreviations: IL6, interleukin 6; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ICU, intensive care unit.

*PCD (Primary Completion Date) defined on clinicaltrials.gov as the date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. The "estimated" primary completion date is the date that the researchers think will be the primary completion date for the study.

B. Recruiting

Reference	Sponsor	Design	Location	Population	Primary endpoints	Estimated PCD*
Fluvoxamine						
NCT04711863 S2020-3124-0001	Asan Medical Center	Phase 2 Single-blind Randomised	South Korea	18 to 85 years Confirmed SARS-CoV-2 with mild to moderate symptoms	Clinical deterioration	31/05/2021

Reference	Sponsor	Design	Location	Population	Primary endpoints	Estimated PCD*
50mg once then 100mg twice daily for 10 days Mild/moderate COVID-19		Controlled: Fluvoxamine vs. placebo (ursodeoxycholate)		admitted to community treatment centers Symptom onset ≤7 days Estimated enrolment: 400		
NCT04668950** 202011101 (Stop Covid 2) Early treatment of COVID-19 50mg once then 100mg twice daily for 15 days	Washington University School of Medicine	Phase 3 Triple blind Randomised Controlled: Fluvoxamine vs. placebo	US	18 years+ Non-hospitalised Confirmed SARS-CoV-2 Symptomatic (mild) Risk factor for clinical deterioration Estimated enrolment: 1100	Clinical deterioration	July 2021
NCT04718480** SD-COVID19-01 2020-002299-11 100mg twice daily for 74 days	SigmaDrugs Research Ltd.	Phase 2 Double-blind Randomised Controlled: Fluvoxamine vs. placebo (both plus SoC)	Hungary	18 to 70 years Hospitalised Confirmed SARS-CoV-2 with moderate disease Estimated enrolment: 100	Clinical recovery	August 2021
NCT04727424 TOGETHER_2 100mg on day 1 then 100mg twice daily for 9 days Early onset/mild symptoms	Cardresearch	Phase 3 Quadruple blinded Randomised Controlled: Fluvoxamine vs. metformin vs. ivermectin vs. placebo	Brazil	18 years+ Outpatients Acute flu-like symptoms and confirmed SARS-CoV2 infection or antigen presence At least one risk factor Estimated enrolment: 2724	• Evaluation of emergency visits and observation unit stay >12 hrs • Hospitalisation due to COVID-19 progression	01/02/2022
Fluoxetine						

Reference	Sponsor	Design	Location	Population	Primary endpoints	Estimated PCD*
NCT04377308 FRIDA COVID19 20mg up to 60mg (as tolerated) for 2 weeks to 2 months depending on symptom duration	University of Toledo Health Science Campus	Phase 4 Open-label Non-randomised: fluoxetine or no fluoxetine	US	18 years + Non-hospitalised patients with confirmed COVID-19 with fever, cough and shortness pf breath Estimated enrolment: 2000	• Hospitalisations • Intubation • Death	20/04/2021
Source: National Institute for Health Research Innovation Observatory (scan 11/02/2021)						
Abbreviations: -						
*PCD (Primary Completion Date) defined on clinicaltrials.gov as the date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. The "estimated" primary completion date is the date that the researchers think will be the primary completion date for the study. **Pivotal trials defined as those that are active, phase 2+, randomised with 100+ participants and UK/EU/US/Australia/Canada based.						

C. Suspended/terminated studies

Reference	Sponsor	Design	Location	Population	Primary endpoints	Status
Fluoxetine						
NCT04570449 20mg to 60mg for 8 weeks in increasing and reducing schedule	Milton S. Hershey Medical Center	Phase 1 Quadruple-blind Randomised Controlled: fluoxetine vs. placebo	US	18 years+ Confirmed SARS-CoV-2 <10 days since symptoms; persistent fever, other COVID-19 symptoms Actual enrolment: 0	• rate of hospitalisation • physical symptoms	Withdrawn- study timeline is not feasible
Source: National Institute for Health Research Innovation Observatory (scan 11/2/2021)						
Abbreviations: -						