Final Report:

A randomized, double-blind, placebo-controlled, adaptive-design study to assess the safety and efficacy of daily 200 mg fluvoxamine as add-on therapy to standard of care in moderate to severe COVID-19 patients

(Protocol Number: SD-COVID19-01, EUDRA CT Nº: 2020-002299-11, Sponsor: SigmaDrugs Research Ltd.)

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2. Synopsis

Name of Sponsor:	***SigmaDrugs Research Ltd.***
Study code:	***Protocol No.: SD-COVID19-01; Protocol version: 4.0; Protocol Date: 02 NOV 2021***
Study title:	***A randomized, double-blind, placebo-controlled, adaptive-design study to assess the safety and efficacy of daily 200 mg fluvoxamine as add-on therapy to standard of care in moderate to severe COVID-19 patients***
Study-related main facilities and sites:	**Sponsor:** SigmaDrugs Research Ltd. H-1012 Budapest, Attila út 117. **CRO (medical writing, regulatory affairs, monitoring, medical monitoring):** CPS Cortex Kft. H-1026 Budapest, Sodrás u. 16. **Biometry / data management:** Adware Research Kft. H-8230 Balatonfüred, Völgy u. 41. **Clinical study sites:** Multicenter, 9 sites in Hungary
Phase of development:	Phase II
Study design:	This was a randomized, double-blind, placebo-controlled, adaptive two-stage design, human phase 2 study, with add-on treatment arrangement of fluvoxamine or placebo on top of standard of care (base therapy: the actual proposed therapy of moderate or severe SARS-CoV-2 infected patients according to „Magyar Koronavírus Kézikönyv", including antiviral and immunmodulant therapy and reconvalscent plasma therapy in serious cases as indicated by the investigator).
Study duration:	**Screening period:** up to 48 hours. Preferably, after diagnosing the COVID-19, treatment were to be started on the following day (D1). Subjects stayed in the clinic for up to Day 7, in a mandatory manner. Subjects may have been emitted from hospital after medical review of Day 7 data at the earliest. The **in-house period** was allowed to be prolonged indefinitely, depending on the clinical status of the patient. Day 75 was the closing visit of the treatment period. Month 3 and Month 6 **follow-up** visits tracked potential long-term pulmonary complications of COVID-19 (e.g. pulmonary fibrosis) by native pulmonary CT.
Treatment groups:	All patients received a **base therapy**: the actual proposed therapy of moderate or severe SARS-CoV-2 infected patients according to 'Magyar Koronavírus Kézikönyv' (Hungarian Coronavirus Handbook), including antiviral and immunmodulant therapy and reconvalscent plasma therapy in serious cases indicated by the investigatoras per standard of care. Investigational drug was an **add-on therapy**. Patients were stratified based on one criteria: belonging to the group at high risk for COVID-19 (comorbidities of hypertension, diabetes mellitus, chronic cardiovascular or chronic respiratory diseases) or not.
Study treatment:	**Fluvoxamine:**

	Careful dose escalation, and tapered dose reduction: • Day 1-2: 50 mg bedtime (2 days on this dose level) • Day 3-4: 100 mg bedtime (2 days on this dose level) • Day 5-6: 150 mg bedtime (2 days on this dose level) • Day 7-60: 2 x 100 mg (BID: morning and bedtime) (54 days on this dose level) • Day 61-65: 150 mg bedtime (5 days on this dose level) • Day 66-70: 100 mg bedtime (5 days on this dose level) • Day 71-74: 50 mg bedtime (4 days on this dose level) – N.B. Final reconciliation of the study drug: at Day 75 visit. **Placebo:** Placebo dosing schedule will be the same as with the active ingredient, to fulfill double-blind nature of dose administrations.
Study population:	**Key attributes:** • Hospitalized patients with confirmed SARS-CoV-2 infection by polymerase chain reaction (PCR) or known contact of confirmed case with syndrome consistent with coronavirus disease (COVID-19) with PCR pending. • Moderate or severe cases: meeting at least one of the following criteria: ◦ dyspnoea or tachypnoe (respiratory rate ≥22 / min); ◦ need for oxygen supplementation; ◦ pulmonary murmur with physical examination with oxygen saturation at rest ≤ 93% (without oxygen support); ◦ pulmonary infiltrates on medical imaging Definition of moderate and severe COVID-19 as per “Magyar Koronavírus Kézikönyv”, “Igazolt COVID-19 fertőzött felnőtt betegek rizikóstratifikációja” fejezet (Hungarian Coronavirus Manual, Section “Risk stratification of confirmed adult COVID-19 patients”). Radiological findings – established either by chest X-ray or native chest (pulmonary) CT scan – included multiplex consolidations and milk-glassy haze, often in a bilateral distribution. **Study population amendments to the original enrolment criteria:** • ***Protocol v3.0:*** ◦ Amended inclusion-exclusion criteria: clarification regarding mild-moderate-severe COVID disease state as per Hungarian Coronavirus Handbook ◦ Malignancy exclusion criterion limited to the past 5 years ◦ Age range: 18-80 years • ***Protocol v 4.0*** implemented adaptive changes to the study based on the interim analysis, and also streamlined study flow to be in line with standard COVID care, based on study sites feedback: ◦ Amended inclusion criteria to enrol severe but not critical state patients and to exlcude patients who undervent >10 days of COVID care previously ◦ Setting target patient number to 100.
Criteria for evaluation:	**Efficacy objectives:** • To assess efficacy of fluvoxamine administration in moderate to severe SARS-CoV-2 infected patients on short term healing. • Assessment of efficacy of fluvoxamine administration in moderate to severe SARS-CoV-2 infected patients on healing course. • Assessment of efficacy of fluvoxamine administration in moderate to severe SARS-CoV-2 infected patients on prevention of long-term complications of

	COVID-19, in particular, development of pulmonary fibrosis. **Safety objective:** Assessment of safety of fluvoxamine administration in moderate to severe SARS-CoV-2 infected patients. **Efficacy endpoints:** • [SEC 00] Time to clinical recovery after treatment, defined as days from randomization (Day 1) to ANY THREE items of the following four: ◦ resolution from fever: oral or tympanic (core body) temperature ≤ 37.5 °C, axillary, forehead or wrist (surface body) temperature ≤ 37.0 °C for at least 48 hours without antipyretics ◦ return of respiratory rate to normal (≤ 20 / min) ◦ normalization of SpO2 (≥95% without oxygen support) ◦ cough remission (any reduction in cough-burden Visual Analogue Scale, compared to Day 1 baseline) • [SEC 01] Time to achieve a score of 0-2 (ambulatory state) on the WHO Ordinal Scale for Clinical Improvement • [SEC 02] Characterization of time course of select cytokine levels (TNF-alfa, IL-1 beta, IL-6), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), D-dimer – in subjects randomized to either fluvoxamine or PBO • [SEC 03] Dynamic changes in oxygenation index (SpO2) • [SEC 04] Time course of cough burden • [SEC 05] Time to negative COVID-19 nucleic acid results • [SEC 06] Rate of patients with native chest CT recovery from the acute stage of COVID-19 by Day 45 visit • [SEC 07] Rate of patients requiring oxygen supplementation (WHO Ordinal Scale for Clinical Improvement score = 4, any time during the course of the disease) • [SEC 08] Rate of patients requiring mechanical ventilation (WHO Ordinal Scale for Clinical Improvement score = 5-7, any time during the course of the disease) • [SEC 09] Rate of ICU admission • [SEC 10] 30-day mortality and overall mortality (WHO Ordinal Scale for Clinical Improvement score = 8, at or any time before Day 30; by Month 6 final visit, respectively) • [SEC 11] Long-term efficacy of fluvoxamine in preventing pulmonary pathology (fibrosis), as monitored by native chest CT - Presence / quantification (e.g. percentage) / absence of: ◦ reticular abnormality, ◦ traction bronchiectasis and bronchiolectasias, ◦ honeycombing. • [SEC 12] Rate of patients requiring treatment with antiviral and immunmodulant therapy or reconvalscent plasma against COVID-19 disease • [SEC 13] Time to achieve a score of 0-1 (No limitation of activities) on the WHO Ordinal Scale for Clinical Improvement • [SEC 14] Time to achieve a score of 0 (Uninfected) on the WHO Ordinal Scale for Clinical Improvement **Safety endpoints:**

	• [SAF 01] Change in the total score of PHQ-9 questionnaire from baseline • [SAF 02] Number and frequency of Adverse Events, descriptive statistical parameters of safety laboratory and other safety parameter values.
Statistical methods:	A separate Statistical Analysis Plan was prepared before starting the statistical analysis which includes detailed description of all statistical procedures. Statistical analysis was performed using SAS 9.4. Microsoft MS Word 2010 was used for reporting. Efficacy analyses were performed without formal hypothesis testing, resulting p-values to be interpreted in a descriptive manner. Definition of significance: • During the analysis $p<0.05$ was considered as significant. • The term "borderline significant" was applied to statistical test results which nearly reached the level of significance.
Statistical patient populations:	• 66 patients received treatment and were included in the final analysis. • There were 34 patients in the Fluvoxamine and 32 patients in the Placebo group. • All 66 patients were included in the safety analysis set (SAS) and in the safety analysis. • All 66 patients were included in the ITT dataset (ITT) and in the efficacy analysis. • 49 patients (24 from the Fluvoxamine group and 25 from the Placebo group) were included in the PP dataset. • 55 patients (27 from the Fluvoxamine group and 28 from the Placebo group) were included in the MPP dataset. • 45 patients (25 from the Fluvoxamine group and 20 from the Placebo group) were included in the LTP dataset.
Results:	***Demography:*** 63.6% of the patients were male. The mean age was 53.1 years (SD: 13.8 years). Age ranged from 21 to 78 years. All patients were Caucasian. No significant difference was found between treatment groups regarding age or gender (p=0.2816 and p=0.2262, respectively). ***Efficacy endpoints:*** Statistical results are summarized using the ITT population. PP and MPP populations resulted in similar result, please refer to the statistical details section. • **[SEC 00] Time to clinical improvement:** ◦ This endpoint was initially the primary endpoint of the study. However, during the interim analysis it was revealed that SPO2 and Respiratory rate were measured in many cases while the patients received supplementary oxygen, and fever was not present in most patients. This resulted in almost instantaneous recovery –based on the endpoint - for most patient, therefore these results cannot be considered fully relevant. The endpoint was continued to be observed but demoted to secondary endpoint. ◦ Among the high-risk patients, mean time to recovery was 2.1 days (SD: 1.06 days) in the Fluvoxamine group and 3.1 days (SD: 5.21 days) for the Placebo group. ◦ Among the low-risk patients, mean time to recovery was 2.2 days (SD: 1.48 days) in the Fluvoxamine group and 1.7 days (SD: 0.79 days) for the Placebo group. ◦ Among male patients, mean time to recovery was 2.2 days (SD: 1.45 days) in the Fluvoxamine group and 1.7 days (SD: 0.85 days) for the Placebo

	group. ◦ Among female patients, mean time to recovery was 1.9 days (SD: 0.57 days) in the Fluvoxamine group and 3.2 days (SD: 5.4 days) for the Placebo group. ◦ Treatment groups were compared by the Wilcoxon and the logrank tests but neither test showed significant difference between treatment groups either for the whole ITT population or for the subgroups. • **[SEC 01] Time to achieve a WHO score<=2 (i.e. ambulatory status, mild disease):** ◦ In the ITT population mean Median time to achieve a WHO score<=2 was 12 days in the Fluvoxamine group and 13 days, while the mean time to achieve a WHO score<=2 was 10.5 days (SD: 6.05 days) in the Fluvoxamine group and 13.6 days (SD: 8.31 days) in the Placebo group. ◦ It is worth mentioning that the difference in the 75 percentiles was much larger than in the medians. By Day 13, 75% of the Fluvoxamine group achieved mild disease and could be discharged from the hospital, while this ratio was only 50% in the Placebo group. Both the Wilcoxon and the logrank tests showed significant difference between treatment groups (p=0.0352 and p=0.0320, respectively), however the Cox regression model could not detect significant difference. ◦ This favorable statistical significance pattern for fluvoxamine regime remained in the high-risk patient stratum as well: mean time to achieve a WHO score<=2 was 10.3 days (SD: 5.35 days) in the Fluvoxamine group and 14.2 days (SD: 6.66 days) for the Placebo group. Both the logrank and Wilcoxon tests showed significant difference between treatment groups (p=0.0405 and p=0.0479, respectively). ◦ Striking is the gender difference in this parameter: mean (SD) time for males was 9.7 (5.13) versus 12.3 (5.47) days, favoring the active Fluvoxamin treatment, which was significant using Wilcoxon-test (p=0.0492) and borderline significant with Logrank test (p=0.0537). • **[SEC 02] Inflammatory biomarker and cytokine levels:** Biomarker and cytokine levels did not exhibit clinically and statistically significant alterations upon fluvoxamine treatment. • **[SEC 03] Dynamic changes in oxygenation index (SpO2):** This parameter cannot be analyzed as planned originally, as patients received oxygen supplementation at several time points and therefore changes were not informative. • **[SEC 04] Time course of cough burden** was assessed using descriptive statistical methods and by a mixed model. VAS values decreased during the study in both treatment groups. It must be noted that baseline VAS values were higher in the Placebo group. By Day 7 the mean and median values of the groups were close to each other but there was a remarkable difference in the 75-percentiles values. This phenomenon corroborates the conclusions drawn from the analysis of [SEC01] that those patients who were in the better 50% showed similar results but the more severe patients tended to show better improvement when treated with Fluvoxamine. (p=0.0132) • **[SEC 05] Time to negative COVID-19 nucleic acid results** was 45 days in the fluvoxamine group and 14 days in the placebo group. It must be noted that patients could be discharged from hospital without negative PCR result. PCR testing was performed at visit days and according to standard-of-care and not due to study considerations, therefore time to PCR negativity can be biased. In a few cases PCR negativity was never confirmed as it was no longer clinically

	indicated after the clinical signs have resolved. • **[SEC 06] Rate of patients with native chest CT recovery from the acute stage of COVID-19 by Day 30 visit** was similar in the two treatment groups. • **[SEC 07] Rate of patients requiring oxygen supplementation** was similar in the two treatment arms. Those patients who required oxygen supplementation during the study, required oxygen supplementation already at baseline. • **[SEC 08] Rate of patients requiring mechanical ventilation:** No patients needed mechanical ventilation during the study. • **[SEC 09] Rate of ICU admission:** 1 patient from the Fluvoxamine group was admitted to ICU due to worsening of COVID-19 pneumonia. • **[SEC 10] 30-day mortality and overall mortality:** 2 deaths occurred in the study. In the first 30 days 1 patient died from the Placebo group. • **[SEC 11] Long-term efficacy of fluvoxamine in preventing pulmonary pathology (fibrosis):** There was 1 honeycombing in the Fluvoxamine group. Ratios were similar during the study. • **[SEC 12] Rate of patients treated with antiviral and immunmodulant therapy or reconvalescent plasma against COVID-19 disease**: only 1 patient received reconvalescent plasma therapy, 5 patients received immunmodulant therapy, and almost all (58 of 67 patients) received antiviral therapy in the ITT population. No significant differences were detected by the Fisher's exact tests. • **[SEC 13] Time to achieve a score of 0-1 (No limitation of activities) on the WHO Ordinal Scale for Clinical Improvement:** Median time to achieve a WHO score<=1 was 14 days in the Fluvoxamine group and 21 days in the Placebo group. The mean time to achieve WHO score<=1 was 18.4 days (SD: 11.29 days) in the Fluvoxamine group and 23.1 days (SD: 12.86 days) in the Placebo group. Difference between treatment groups was boarderline significant according to the logrank test (p=0.0660) and significant according to the Wilcoxon tests (p=0.0393, respectively). The analysis was repeated for the high-risk and low-risk subgroups separately. Difference between treatment groups was not significant for the high-risk patients but it was significant for the low-risk patients both according to the logrank and Wilcoxon tests (p=0.0468 and p=0.0444, respectively). • **[SEC 14] Time to achieve a score of 0 (Uninfected) on the WHO Ordinal Scale for Clinical Improvement:** Median time to achieve WHO score=0 was 45 days in the Fluvoxamine group and 59 days in the Placebo group. Mean time to achieve WHO score=0 was 37.4 days (SD: 17.63 days) in the Fluvoxamin group and 44.5 days (SD: 21.55 days) in the Placebo group. Difference between treatment groups was not significant according to either applied test. ***Safety endpoints:*** • **PHQ-9 score:** mean PHQ-9 scores decreased during the study. The maximum increase was 12 points till Day 45 in the Fluvoxamine group and 3 points in the Placebo group. The maximum increase was 5 points till Day 75 in the Fluvoxamine group and 0 points in the Placebo group. Difference between groups was not significant according to the applied mixed model. • **Adverse events:** There was no visible difference between the overall frequency of AEs between the treatment groups. The "Results" section of this Final Report contains a detailed tabulation (SOC and PT) of adverse and serious adverse events, per treatment group, and also a special tabulation for a relevant subset of AEs which are at least possibly related to the IMP.

	• **Serious adverse events:** There were 3 (8.8%) SAEs in the Fluvoxamine group and also 3 (9.4%) SAE cases occurred in the placebo group. • **Deaths:** 2 deaths occurred in the study. In the first 30 days 1 patient died from the Placebo group. 1 patient from the Fluvoxamine group died after Day 30. • **Pregnancies:** no pregnancies occurred during the study.
Summary	Fluvoxamine proved to be a safe and tangible add-on component to standard-of-care COVID therapy. It showed significant improvement versus placebo in several departments, like restitution of physical fitness (WHO activity score) and earlier hospital discharge.