TITLE PAGE

Investigational product: FDA-277 (Domperidone)

SARS-CoV-2 infection

Sponsor: Agencia Estatal Consejo Superior de Investigaciones Científicas, M.P (CSIC)

Protocol Title:

A Randomized, Double-Blind, Drug Repositioning Clinical Trial comparative with placebo, to Evaluate the Efficacy and Safety of FDA-277 in Combination with Standard of Care in the Treatment of Infection Caused by SARS-CoV-2, in Patients With early Stage COVID-19 Disease, Receiving Primary Care Treatment

Design: Phase 3 drug repositioning, parallel, double-blind, randomised, comparison with placebo, 28 days of follow-up, 30 mg daily of Domperidone during 7 days of treatment in patients with early stage COVID-19 disease (mild to moderate) at Primary Health Care.

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Confidentiality Statement

Ethical Statement

The study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents.

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1. SYNOPSIS

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Title of Study:

A Randomized, Double-Blind, Drug Repositioning Clinical Trial comparative with placebo, to Evaluate the Efficacy and Safety of FDA-277 in Combination with Standard of Care in the Treatment of Infection Caused by SARS-CoV-2, in Patients With early Stage COVID-19 Disease, Receiving Primary Care Treatment. Code: CSIC-FDA277-2021-01.

Investigators:

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Study centre(s):

1. C.S. Los Yébenes, Madrid, Spain; 2. C.S. Fronteras, Torrejón de Ardoz (Madrid), Spain; 3. C.S. Benita de Ávila, Madrid, Spain; 4. C.S. Baviera, Madrid, Spain; 5. C.S. Los Alperchines, San Fernando de Henares (Madrid), Spain; 6. C.S. General Fanjul, Madrid, Spain; 7. C.S. Daroca, Madrid, Spain; 8. C.S. Reina Victoria, Madrid, Spain; 9. Clínica Monmar, Las Rozas (Madrid), Spain; 10. C.S. Las Rozas, El Abajón, Las Rozas (Madrid) Spain; 11. C.S. Villablanca, Madrid, Spain; 12. C.S. Dos de Mayo, Móstoles (Madrid), Spain

Publication (reference)

Studied period: (date of first enrolment/date of last completed) March 23rd, 2022 /November 3rd, 2022	Phase of development: Phase 3

Objectives:

Primary objective: The primary objective is to evaluate the efficacy of Domperidone combined with standard of care (SOC) on reducing the SARS-CoV-24 viral load from baseline.

Secondary Objective: To evaluate the laboratory efficacy of Domperidone combined with SOC in PCR negative result (SARS-CoV-2 negative from baseline); To evaluate the clinical efficacy Domperidone combined with SOC in reducing the symptoms of COVID-19 disease; To evaluate the efficacy of Domperidone combined with SOC on the need for medical care, hospitalization, oxygen therapy, or mortality through day 28 from baseline; To evaluate the safety of Domperidone administered in patients infected with SARS-CoV-2.

Methodology:

A phase 3, prospective, randomized, double-blind, placebo controlled, parallel-group, multicentre, drug repositioning clinical trial, with allocation ratio 1:1 of study groups Domperidone plus SOC versus placebo plus SOC group.

The random allocation sequence was generated by an independent technician, in random blocks of 4 and 6 treatments to distribute 10 randomization number envelopes by centre. The statistician was blinded to the study group during the study analysis.

The patients must be diagnosed of active SARS-CoV-2 infection confirmed by compatible symptoms and a positive result in the detection tests for active infection (DTAI), rapid antigen detection test or in the PCR for viral RNA detection test.

The stratification of asymptomatic group of patients was discarded due to restrictions for the use of DTAI or PCR test in Spain.

The study setting was consultation in Primary Health Care of 12 centres located in Madrid (Spain).

Two randomised, double-blind study group of patients were included to receive treatment with Domperidone 3 daily doses of 10 mg (30 mg/day) for 7 days, plus SOC treatment versus the placebo plus SOC treatment study group. All the patients were followed up to 28 days. Phone contacts were completed at day 1, 4, 7 and 14 and a visit at day 28. In all the contact with the patient the pulse

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oximetry, heart rate and temperature were determined by the patient with the study material supplied, and questions about the appearance of new symptoms and the symptoms severity was assessed in a ten-point severity scale.

The viral load was determined by detection of three highly conserved regions of specific genes of the SARS-CoV-2 pathogenic viral RNA strain (ORF1ab, N Protein and S Protein), in saliva samples obtained at baseline, day 4, day 7 and day 14 form study treatment initiation. All the study samples were analysed in a central laboratory (ARQUIMEA,Medical, S.L.U.). Viral RNA was obtained using the Chemagic Viral DNA/RNA 300 kit H96 (Perkin Elmer), purification of viral RNA was done using the automated Chemagic 360 Instrument (Perkin Elmer). RT-qPCR was completed with the TaqPath COVID-19 CE-IVD RT-PCR Kit (Thermofisher) and detection of ORF1ab, N Protein and S Protein regions of the SARS-Cov-2 virus were completed in the 7500 Real-Time PCR instrument (Thermofisher) and QuantStudio 5 Real-Time PCR instrument (Thermofisher). The sensitivity of the platform was >99% and specificity of 99.5%.

The primary efficacy endpoint was to compare the reduction in viral load as Basal-4 days difference in SARS-CoV-2 RT-qPCR number of cycles of the Domperidone in combination with SOC group versus the placebo plus SOC group as an assessment of efficacy at 4 days from baseline. A higher number of cycles mean a lower viral load.

The secondary efficacy endpoints in the comparison of the group of patients treated with Domperidone or with placebo were pre-defined as: Comparison of the reduction in viral load (Basal-7 days difference, basal-14 days difference, in SARS-CoV-2 number of Cycles) as an assessment of efficacy at 7 and 14 days from baseline; Comparison of the proportion of patients with negative SARS-CoV-2 PCR result at 4, 7, and 14 days from baseline. Positive values are considered if at least 2 of the 3 genes analysed amplify with cycles below the mean value of 35 (Ct<35); Comparison of the time from baseline to obtain a negative PCR test for SARS-CoV-2; Comparison of the clinical efficacy in reducing the symptoms of COVID-19 disease was assessed: Reduction in severity of each symptom (evaluated by 0 to 10 point numerical rating scale NRS) related to SARS-CoV-2 disease at 4, 7, 14, and 28 days or EOS from baseline; Proportion of patients with clinical improvement, defined as improvement by two or more points on a 0 to 10 NRS; Time to clinical improvement; Proportion of patients in whom each symptom related to SARS-CoV-2 disease disappears at 4, 7, 14, and 28 days from baseline; Proportion of patients with no symptoms at 4, 7, 14 and 28 days from baseline; Time to disappearance of each symptom related to SARS-CoV-2 disease from baseline; Comparison of the need for medical care, hospitalization, oxygen therapy, or mortality through day 28 from baseline: Proportion of patients requiring hospitalization, oxygen therapy, or who develop complications from SARS-CoV-2 disease through Day 28 from baseline; Proportion of patients who die within the 28-day follow-up period and reported mortality within three months of study end; To evaluate the safety of Domperidone in patients with COVID-19.

Number of patients (planned and analysed):
200 planned; 180 enrolled; 173 analysed

Diagnosis and main criteria for inclusion:

The patients must be diagnosed of active SARS-CoV-2 infection confirmed by compatible symptoms (fever, cough, shortness of breath or difficulty breathing, sore throat, body or muscle pain, fatigue, headache, chills, nasal congestion, loss of taste or smell, nausea or vomiting, diarrhoea) and a positive result in the detection tests for active infection (DTAI), rapid antigen detection test or in the PCR for viral RNA detection test.

Inclusion criteria:1) Patient, of either sex, 18 years of age or older; 2) Patient weighing more than 35 Kg; 3) Patient with a diagnosis of active SARS-CoV-2 infection confirmed by Compatible symptoms and a positive result in the detection tests for active infection (DTAI), rapid antigen detection test or in the PCR for viral RNA detection test; 4) Patients presenting with symptoms must present within the last 72 hours with one or more of the following symptoms associated with SASR-Cov-2 infection: fever, cough, shortness of breath or breathing difficulties, sore throat, body or muscle pain, fatigue, headache; 5) In patients with symptoms due to SARS-CoV-2 infection, the severity of symptoms should be mild or moderate; 6) The patient has received sufficient information about the study orally and in writing and has signed the informed consent to participate in the clinical trial.

Exclusion criteria: 1) Patient living with a patient who has previously been enrolled in the study and who continues to be followed up (until Day 28); 2) Patient with severe COVID-19 disease; 3) Patient has any of the following diseases that may be affected or affect the results of the study: Active infectious disease other than SARS-CoV-2 infection requiring systemic therapy; Clinically significant uncontrolled respiratory disease; Prior cardiovascular disease: ischemic heart disease, heart failure, atrial fibrillation; Severe kidney failure; Active or treated malignancy; Immunosuppression due to an illness or the treatment received; Illness requiring surgical intervention within 30 days following the screening for the study; Severe obesity; Other diseases that the physician believes may pose an increased risk to the patient;4) Domperidone contraindications: Patient with hypersensitivity or intolerance to Domperidone or to any of the excipients; Patients with prolactin-secreting pituitary tumor (prolactinoma); Patients in whom stimulation of gastric motility may be dangerous, such as gastrointestinal bleeding, mechanical obstruction, or perforation; Patient with moderate to severe liver failure, with results in liver function tests, aspartate transaminase, alanine transaminase,

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alkaline phosphatase ≥ 5 times the upper limit of normal; Patient with clinically significant abnormalities on the 12-lead electrocardiogram that may have been performed during the study screening period, specifically existing prolongation of cardiac conduction intervals, QTc interval; Patient with underlying heart disease such as congestive heart failure or bradycardia; Patient with significant electrolyte disorders such as hypokalaemia, hyperkalaemia, hypomagnesaemia; Patient under treatment with drugs that prolong the QT interval; Patient under treatment with potent CYP3A4 inhibitor drugs; 5) Pregnant women; 6) Breast-feeding women; 7) A patient with mental impairment that invalidates his/her ability to consent to participate in the study, or that limits his/her ability to comply with the study requirements, or that is expected to be non-cooperative; 8) Patient on treatment with drugs with known antiviral potential; 9) Participation in a clinical trial within the last month.

Test product, product dose and mode of administration, batch number:

Domperidone tablets of 10 mg three times a day (30 mg/day) for 7 days, given before meals (breakfast, lunch, and dinner); Batch number: 210001; Expiry date: November 30th, 2023

Plus Standard of Care for SARS-CoV-2 disease.

Placebo equivalent tablets of 10 mg three times a day (30 mg/day) for 7 days, given before meals (breakfast, lunch, and dinner); Batch number: 210001; Expiry date: November 30th, 2023

Duration of treatment: 7 days.

Reference therapy, dose and mode of administration, batch number:

Standard of care treatment (SOC) for SARS-CoV-2 disease: acetaminophen 500 mg 1-4 times daily, non-steroidal anti-inflammatory drugs, symptomatic treatment, and hydration for mild clinical conditions. Only if suspected bacterial co-infection/superinfection should be prescribed amoxicillin/clavulanic acid 875 mg/125 mg every 8 hour for 7 days; alternatively, levofloxacin 500 mg every 12 hours on the first day and 500 mg every 24 hour for 4 days.

Statistical methods:

The null hypothesis considers no difference between the group of patients treated with Domperidone combined with SOC and the group treated with placebo plus SOC in the reduction in viral load (number of RNA replicates of SARS-CoV-2 virus determined by PCR in saliva samples) from the baseline visit prior to treatment and Day 4 post-treatment. The sample size calculation for the primary study variable was performed for a two-sided analysis of variance, with fixed effects and two levels in the factor evaluated corresponding to treatment or control group. A Type I error is set at a two-sided 0.05 level with a minimal effect with clinical relevance of 2 log10 reduction in viral copy number as the minimal difference between the on-treatment groups. A moderate effect of 0.25 (Cohen's f) was targeted leading to an expected common standard deviation of 4 log10. Given a sample of 200 patients (100 assigned to receive the evaluated treatment and 100 to receive SOC), a power of 94% is obtained to demonstrate the estimated difference. (Sample Power, IBM-SPSS).

The main analysis of the primary endpoint was measured by the Student t test for independent samples. The ANOVA for repeated measurements and a factor (Split-Plot) with Bonferroni adjustment for multiple comparisons was applied to the comparison of viral load between the study groups at baseline, day 4, day 7 and day 14. The primary analysis was adjusted based on justified demographic and effect-modifying variables. Kaplan Meier survival analysis and Log Rank test was applied for the analysis of time to get negative PCR. Type I error is set at a two-sided 0.05 level. The software IBM-SPSS 27.0 was used for the statistical analysis.

Summary - Conclusions

A final sample of 180 patients (173 evaluable) was included in 12 study centres with distribution of 87 patients in the Domperidone + SOC treatment group and 86 patients in the placebo plus SOC treatment group.

A total of 109 patients (63%) were female and 64 males (37%), with mean age of 47.8 years old (SD 1.2), being 154 (89%) Caucasian and 17 Hispanic (9.8%). 27 patients (15.6%) suffered previous COVID-19 disease a mean of 14.2 months (SD 1.7) before the study initiation.

The number of patients with previous complete vaccination for SARS-CoV-2 was 159 (91.9%), with a mean of 6.3 months (SD 0.3) from last vaccination dose.

A total of 166 patients (96%) were included with mild COVID-19 disease, 4 patients (2.4%) had moderate disease and 3 patients (1.7%) were asymptomatic.

Baseline patient's demographic anthropometric and clinical history were homogeneous between the study groups. A mean of 7.3 symptoms (SD 0.29) were present at baseline observing a maximum of 20 symptoms at baseline. No differences in the number or symptoms severity were observed between the study groups at baseline except for dysgeusia that was more frequent in the Domperidone group (2.3% 12 patients) versus the placebo group (0.6%, 3 patients), p=0.023. Also, the otalgia was more severe for the domperidone group (10 points in 2 patients) versus the intensity in the placebo group (6.7 points in 3 patients), p= 0.004. Vital signs, systolic and diastolic blood pressure and respiratory rate, heart rate, oxygen saturation and temperature were also

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homogeneous between the study groups. Viral load at baseline was homogeneous between the study groups for ORF1ab (21.3 Cts, SD 0.4), N Protein (21.5 Cts, SD 0.4) and S Protein (27.5 Cts, SD 0.6). 165 patients (95.4%) completed the 28 days of follow-up, as 8 patients withdrawn the study, 4 in each study group.

Efficacy Results:

For the primary efficacy endpoint, as reduction in viral load (increasement of number of Cycles) from baseline to Day 4 of follow-up, no statistically significant differences were observed for none of the three specific genes of the SARS-CoV-2 pathogenic viral RNA strain with mean difference of 0.4 Cts (95%CI -1-1.9) for ORF1ab (p=0.551), mean difference of 0.5 Cts (95%CI -0.9-1.8) for N Protein (p=0.505) and mean difference of 0.02 Cts (95%CI -1.5-1.5) for S Protein (p=0.981).

For ORF1ab, significant increasement in Cts (reductions in viral load) were observed during the follow up for the total group from baseline to any time-point of the follow-up (p<0.001), but no differences were observed between the study groups at day 4 (p=0.580), Day 7 (p=0.780) and Day 14 (p=0.393). For N Protein, significant increasement in Cts were observed during the follow up for the total group from baseline to any time-point of the follow-up (p<0.001), but no differences were observed between the study groups at day 4 (p=0.501), Day 7 (p=0.800) and Day 14 (p=0.408). For S Protein, significant increasement in Cts were observed during the follow up for the total group from baseline to any time-point of the follow-up (p<0.001), but no differences were observed between the study groups at day 4 (p=0.773), Day 7 (p=0.965) and Day 14 (p=0.727).

A sensitivity analysis was done on the primary efficacy endpoint and in the evolution of the viral load with non-imputation rules applied to the study data, with no differences with the results of the main analysis.

No significant differences were observed between the Domperidone versus placebo study group in the percentage of positive PCR results at Day 4, of 92% vs 89.5% (p=0.583), at Day 7 of 72.4% vs 76.7% (p=0.513) and Day 14 of 32.2% vs 27.9% (p=0.540), neither in the viral load classification (low, medium, high) in the follow-up.

Median to get the negative result was 14 days (12.9-15.1), with no statistical differences between the study groups (0.821).

No significant differences between the study groups were observed in the evolution of the vital signs that significantly improved form day 1 to day 28 (p<0.001) in the oxygen saturation (%), heart rate (p=0.011) and axillary temperature (p<0.001).

No statistical differences were observed between the study groups in the severity of any or the symptoms observed at Day 1, Day 7, Day 14 and Day 28, except for the dysgeusia at Day 4 with 5.3 points in domperidone group vs 9.8 points in the placebo group (p=0.001) and weakness with 5 points in the domperidone group vs 3.1 points in the placebo group (p=0.007).

A total of 33 patients (19.1%) continued with persistent symptoms after the day 28, with no differences between the study groups (p=0.677).

Safety Results:

A total of 23 patients (13.3%) experienced adverse events, 14 patients in the Domperidone group (16.1%) and 9 patients in the placebo group (10.5%), with no statistical differences (p=0.276). The total number of adverse events observed was 28. Of them 85.7% (24) were mild, 10.7% (3) moderate. One not related severe palpitation (3.6%) was observed but considered by the physician as not related to domperidone.

No adverse events were considered related to study drug, 6 possibly related to Domperidone (digestive discomfort, dizziness, dyspepsia, epigastralgia, stinging on the tongue and tachycardia) and nine unknown (asthenia, cholelithiasis, elevated blood pressure, herpes infection, habonose lesions on arms, low oxygen saturation, nausea, palpitations, paresthesia, polytraumatism, presyncope, skin rash and vaginitis), with 13 adverse events not related to the study treatment. Eight adverse events in the placebo group and two adverse events in the domperidone group (digestive discomfort and dyspepsia) lead to discontinuation of the study Drug (p=0,008). No treatment-emergent laboratory abnormalities were observed. No patients needed to be hospitalized due to the COVID-19 disease, neither needing oxygen-therapy.

Conclusion

No significant differences were observed between the study groups in the viral load at Day 4 (ORF1ab, N Protein, S Protein), nor in the secondary efficacy endpoints. In this study cannot be demonstrated arguments in favour of the use of Domperidone for the treatment of mild to moderate SARS-CoV-2 infection.

Date of report
November 15th, 2022