Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Research Article

Homeopathy for COVID-19 in primary care: A randomized, double-blind, placebo-controlled trial (COVID-Simile study)

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ABSTRACT

Background: Different homeopathic approaches have been used as supportive care for coronavirus disease 2019 (COVID-19) cases, but none has been tested in a clinical trial.

Objectives: To investigate the effectiveness and safety of the homeopathic medicine, *Natrum muriaticum* LM2, for mild cases of COVID-19.

Design, setting, participants, and interventions: A randomized, double-blind, two-armed, parallel, single-center, placebo-controlled clinical trial was conducted from June 2020 to April 2021 in São-Carlos, Brazil. Participants aged > 18 years, with influenza-like symptoms and positive result from a real-time polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2 were recruited and randomized (1:1) into two groups that received different treatments during a period of at-home-isolation. One group received the homeopathic medicine *Natrum muriaticum*, prepared with the second degree of the fifty-millesimal dynamization (LM2; *Natrum muriaticum* LM2), while the other group received a placebo.

Outcome measures: The primary endpoint was time until recovery from COVID-19 influenza-like symptoms. Secondary measures included a survival analysis of the number and severity of COVID-19 symptoms (influenza-like symptoms plus anosmia and ageusia) from a symptom grading scale that was informed by the participant, hospital admissions, and adverse events. Kaplan-Meier curves were used to estimate time-to-event (survival) measures.

Results: Data from 86 participants were analyzed (homeopathy, n = 42; placebo, n = 44). There was no difference in time to recovery between two groups among participants who were reporting influenza-like symptoms at the beginning of monitoring (homeopathy, n = 41; placebo, n = 41; P = 0.56), nor in a sub-group that had at least 5 moderate to severe influenza-like symptoms at the beginning of monitoring (homeopathy, n = 15; placebo, n = 17; P = 0.06). Secondary outcomes indicated that a 50% reduction in symptom score was achieved significantly earlier in the homeopathy group (homeopathy, n = 24; placebo, n = 25; P = 0.04), among the participants with a basal symptom score $\geq$ 5. Moreover, values of restricted mean survival time indicated that patients receiving homeopathy might have improved 0.9 days faster during the first five days of follow-up (P = 0.022). Hospitalization rates were 2.4% in the homeopathy group and 6.8% in the placebo group (P = 0.62). Participants reported 3 adverse events in the homeopathy group and 6 in the placebo group.

Conclusion: Results showed that *Natrum muriaticum* LM2 was safe to use for COVID-19, but there was no statistically significant difference in the primary endpoints of *Natrum muriaticum* LM2 and placebo for mild COVID-19 cases. Although some secondary measures do not support the null hypothesis, the wide confidence intervals suggest that further studies with larger sample sizes and more symptomatic

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participants are needed to test the effectiveness of homeopathic *Natrum muriaticum* LM2 for COVID-19. *Trial registration:* UMIN Clinical Trials Registry ID: JPRN-UMIN000040602.

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1. Introduction

At the time of this manuscript's preparation, Brazil is the country with the second highest cumulative number of deaths from coronavirus disease 2019 (COVID-19) [1], a pandemic that has overwhelmed the Brazilian Unified Health System [2]. Outpatient management of mild COVID-19 cases is carried out by primary healthcare teams, who provide supportive treatment for patients during at-home-isolation, which lasts a minimum of 10 days from the onset of symptoms until the patient is symptom-free for 3 consecutive days. As monoclonal antibodies that target severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3] are not available or affordable, the country's public health system offers no specific therapy for mild COVID-19 cases that are at risk of clinical progression.

Complementary and integrative medicine (CAM) has been used during the COVID-19 pandemic in 56 countries [4], and research in CAM has been encouraged in Brazil by the National Policy of Integrative and Complementary Practices. One of the guidelines of that policy is to support the development of studies and research that assess and improve the quality of homeopathic care in the Brazilian Unified Health System [5].

Homeopathy is a complex medical system developed by Samuel Hahnemann and is based on the "*similia* principle" [6] of therapeutics. Hahnemann improved the pharmacology and posology of homeopathy until reaching what he considered to be his "most perfected method": repeated (as needed) doses of the "best chosen" homeopathic medicine in liquid form (so that it could be successed before each dose), prepared through the fifty-millesimal dynamization, and used in ascending potencies (when needed), beginning with the lowest degrees [7]. Fifty-millesimal or *Quinquagintamillesimal* (LM or Q) potencies are prepared by trituration of the raw material (in three 1:100 steps), followed by consecutive 1:50,000 (successed) dilutions. Each degree of dynamization corresponds to an approximate dilution of 1:50,000. Therefore, for example, LM1 corresponds to 2×10^{-11}, LM2 to 4×10^{-16} fraction of the raw material.

Different homeopathic approaches have been used in the context of COVID-19 in different countries [8]. However, none of these has been tested in a double-blinded, randomized, placebo-controlled trial. This study aims to investigate the effectiveness and safety of the homeopathic medicine *Natrum muriaticum* LM2 in the treatment of mild cases of COVID-19 in a primary care setting. The rationale for selecting *Natrum muriaticum* LM2 is detailed in the published study protocol [9].

2. Methods

2.1. Trial design

A randomized, double-blind, two-armed (1:1), parallel, single-center, placebo-controlled clinical trial was conducted to test the following hypotheses for mild cases of COVID-19, managed by primary care teams, while undergoing at-home-isolation: H0, the treatment effects of homeopathic *Natrum muriaticum* LM2 are equal to those of placebo (null hypothesis); H1, the treatment effects of homeopathic *Natrum muriaticum* LM2 are not equal to those of placebo (alternative hypothesis).

The following guidelines were adopted for this study (namely, COVID-Simile study): the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [10], the Brazilian National Research Ethics Committee for conducting research during COVID-19 [11], the Consolidated Standards of Reporting Trials (CONSORT) [12], and the Reporting Data on Homeopathic Treatments (RedHot) supplement to CONSORT [13].

2.2. Participants

Women and men aged 18 years or older with influenza-like symptoms, a positive real-time polymerase chain reaction (RT-PCR) test for SARS-CoV-2 [14] and undergoing at-home-isolation were included in this study. The participants received conventional treatment and supervision (telemonitoring and face-to-face appointments when needed) by primary health care teams of São Carlos-São Paulo, Brazil. Willingness to sign an informed consent form and to comply with the study procedures was also required. The exclusion criterion was severe acute respiratory syndrome, a condition that leads to hospitalization by primary care teams. No participant was vaccinated against COVID-19 during the study. COVID-19 vaccines were not available or were not available for the age range of the participants during the study.

2.3. Interventions

Homeopathy: 1 globule of *Natrum muriaticum* LM2 was diluted in 20 mL of 30% alcohol and dispensed in a 30 mL bottle. Placebo: 20 mL of 30% alcohol was dispensed in a 30 mL bottle.

One drop of medicine was taken every 6 hours (4 doses/d) during at-home-isolation, and the participant was instructed to shake the medication flask vigorously ten times before each dose. The posology could be adjusted by telemedicine, with no break in blinding, under the supervision of the principal investigator, and following Hahnemann's principles for the management of acute diseases [7]: participants with more severe symptoms received the study medication every hour, which was stepped down to 1 drop every 2 or 4 hours, as symptoms became moderate or mild, respectively. Even when there was remission of symptoms (and during the study follow-up), the study medication was taken 4 times a day, with the intention of preventing a symptom relapse that could emerge during the natural course of COVID-19 [15].

Natrum muriaticum LM2 and placebo were kindly provided by HN-Cristiano Homeopatia (https://www.homeopatiahncristiano.com.br/), which manufactures LM-potencies in conformity with Hahnemann's standards (standardized LM potencies) [16]. HN-Cristiano is certified by the Sanitary Surveillance of São Paulo and the *Natrum muriaticum* quality certificate number is 270559t.

Three medical doctors (certified homeopaths), with over 25 years of clinical experience, had indicated that *Natrum muriaticum* LM2 was a homeopathically suitable remedy for COVID-19, as detailed in the published study protocol [9].

2.4. Outcome measures

2.4.1. Primary endpoint

The primary endpoint was time to recovery, defined as the number of days elapsed until all COVID-19 influenza-like symptoms were reported to be mild or absent (as used by Butler et al. [17]) during the at-home-isolation period. We chose to monitor 15 influenza-like symptoms, including shortness of breath, cough, tiredness, expectoration, headache, sore throat, chest pain, back pain, body pain, joint pain, muscle aches, lack of appetite, diarrhea, nausea and vomiting, plus anosmia and ageusia, based on a review of the most common clinical symptoms of COVID-19 [18].

2.4.2. Secondary measures

As a complement to the study protocol measures, we included a novel endpoint proposed by Thomas et al. [19] to study COVID-19 in ambulatory patients using Kaplan-Meier curves: the time to reduce symptom number or score by 50%. We believed that it could be a metric that would be more sensitive to the effect size expected from the intervention [20], as most of the mild cases of COVID-19 from our sample would probably present a self-limiting disease during the follow-up period [21].

The measures of the protocol were: (1) recovery time for each monitored symptom; (2) symptom score, i.e., the sum of the scores attributed by the participant to each symptom, using an established symptom grading scale (0 = absent, 1 = mild, 2 = moderate, and 3 = severe) [22]; (3) the number of days of follow-up, and the number of visits to emergency services; (4) the number of hospitalizations; and (5) the presence of adverse events [10].

2.5. Administrative and ethical approvals

The Municipal Health Department of São Carlos approved the COVID-Simile study on April 6, 2020, and the Brazilian National Research Ethics Committee, on May 31, 2020 (report # 4.059.759, Presentation Certificate for Ethical Appreciation number 30638220.0.0000.0008). Administrative and Ethical (report # 4.584.612) approvals were ratified for recruitment adaptations on December 21, 2020, and March 6, 2021, respectively.

2.6. Trial registration

The COVID-Simile study was registered at the University Hospital Medical Information Network (UMIN) Center on June 1, 2020, receiving the UMIN Clinical Trials Registry ID: UMIN000040602 [23].

2.7. Sample size

Considering two independent parallel groups, with 1:1 allocation, an effect size of 0.6, Type 1 error of 5%, and Type 2 error of 20%, the sample size calculated by G*Power 3.1.9.2 Software [24] was 90 participants (45 per group). The effect size is defined by Cohen [25] as the difference in means over the pooled standard deviation, so that $d = 0.6$ corresponds to a moderate effect. Predicting a 10% follow-up loss, 100 participants with COVID-19 were included and randomized to the two treatment arms.

2.8. Centralized randomization, allocation concealment, and blinding

In early June 2020, the study statistician generated a block randomization list, using a 1:1 ratio for both groups (named A and B), a block size of 10, and a web-based tool [26]. He sent the list to the executive coordinator of the Universidade Federal de São Carlos (UFSCar) Health School Unit, who wrote down each randomization result (A or B) on an identification card, placed each card in sequentially numbered, sealed opaque envelopes, and handed them over to the study pharmacist. The administrative director of UFSCar Health School Unit (Prof. Dr. Nelci Adriana Cicuto Ferreira Rocha), at the time, decided the study code, i.e., whether A or B corresponded to homeopathy or placebo, and reported that decision to the study pharmacist.

In mid-June 2020, the study pharmacist opened the envelope number "X" and assigned each participant with the inclusion number "X" to the study group A or B (homeopathy or placebo), according to the identification card (A or B) placed in the envelope and to the study code provided by the administrative director of the UFSCar School Health Unit. Next, the study pharmacist dispensed each medication bottle accordingly, packing and sealing it. He then handed the sealed packages, labeled with the participant's respective inclusion number, to an administrative assistant at the UFSCar School Health Unit (Ms. Costa CRZ), who oversaw the delivery of the medication packages, between June 29, 2020, and April 6, 2021.

The study pharmacist was the only study collaborator who knew the study group (A or B) registered on the card of each envelope, as well as the code, defining whether A or B of the randomization list corresponded to homeopathy or placebo, but he had no knowledge nor control over which participant would receive each study medication. As a result, the clinical investigators, the statistician, the primary care teams, the study collaborators, and the participants remained blinded to the identity of the two treatment groups until the end of the study [27].

2.9. Recruitment

At the time of writing, in the Brazilian Unified Health System, moderate and severe patients were referred to hospitalization, while mild cases were monitored by primary care teams during a period of at-home-isolation.

The recruitment plan could be changed and adapted according to the changes in primary care proceedings. Mild suspected cases of influenza-like illness were initially recruited by primary care teams, pending RT-PCR confirmation of SARS-CoV-2 for inclusion in the study. Since November 2020, when accessing their test result on the Epidemiological Surveillance website (https://servicos.saocarlos.sp.gov.br/notificacaocovid), RT-PCR-positive subjects have been briefly informed that UFSCar professors were conducting a study on homeopathic treatment for COVID-19. They had the option to get further information by following a link on the webpage. An automatic e-mail was sent to the principal investigator when a patient registered interest, and the researchers contacted these patients using WhatsApp. Those who responded and confirmed their interest, after receiving an electronic copy of the informed consent form, were referred to a study researcher from São Paulo/SP, who recorded recruitment data on the study website.

2.10. Delivery of the informed consent form and study medication

The administrative assistant at the UFSCar School Health Unit (Ms. Costa CRZ) entered patient data in the recruitment page of the study website, which automatically generated a sequential inclusion number for each participant. Then, she sent two counterparts of the informed consent form (pre-signed by the principal investigator) and the correspondent medication package (i.e., numbered with the corresponding inclusion number) to the participant's home address through a delivery company, which returned the informed consent form signed by the participant to UFSCar School Health Unit, completing the inclusion process.

2.11. Monitoring and telemedicine

The primary care teams conducted monitoring during the first month of the study, but they became progressively overloaded

with the resumption of routine care, in addition to the care of COVID-19 cases. Therefore, to avoid data loss and to minimize inter-rater variability, from December 4, 2020, until the end of monitoring, a study researcher from São Paulo/SP made phone and WhatsApp calls to participants during their at-home-isolation, updating symptom severity data on the study website. This researcher was a health professional with a specialization in homeopathy and did not live in the city where the study was carried out, minimizing the chance of contact with possible acquaintances.

2.12. Data analysis

A common practice in clinical trials is to check for an imbalance between intervention groups by statistical tests of baseline characteristics. However, various authors have criticized this practice [28]. In quantitative variables, we alternatively used the Wilcoxon rank-sum statistic to measure the imbalance between the intervention groups, as suggested by Ciolino et al. [29]. Similarly, the difference between proportions in each group divided by its standard error was used to measure baseline covariate imbalances in the case of categorical variables. Both statistics can be interpreted as Z scores; that is, they have an asymptotic standard normal distribution under the null assumption of equal distributions between individuals receiving homeopathy or placebo. Therefore, absolute values of measures greater than 1.96 suggest some imbalance between the intervention groups (similar to $P < 0.05$, given the properties of the normal distribution).

The cumulative probability of the occurrence over a period of time was estimated by the Kaplan-Meier method (as a "survival" measure). Nonparametric comparison of survival curves between treatment groups was based on Peto and Peto-modification of the Gehan-Wilcoxon test [30]. The restricted mean survival time (RMST) was estimated to assess the cumulative treatment effects. The RMST is a measure of average survival from time zero to a specified time point and may be estimated as the area under the survival curve up to that point [31]. RMST is presented with its corresponding 95% confidence interval (CI) and P value from a test with the null hypothesis that the difference in the RMST between the two study groups is zero. All survival analyses were done using the "survival" and "survRM2" packages of the R software (version 3.6.2). A per-protocol analysis was performed.

3. Results

3.1. Recruitment, inclusion, and participant's basal data

The primary care teams assessed 74 subjects with influenza-like symptoms: 59 did not meet inclusion criteria (due to a negative result from an RT-PCR test for SARS-Cov-2), and 15 were included. In addition, another 278 e-mails (from potentially interested subjects, with a positive result from an RT-PCR test for SARS-Cov-2) were sent to the principal investigator via the Epidemiological Surveillance website. Those subjects were contacted, but 193 did not want to participate or did not respond to WhatsApp messages. The remaining 85 were included. The first participant was enrolled on June 29, 2020, and the last one on April 6, 2021. Of the 100 randomized participants, 6 did not receive the allocated intervention (3 in each treatment group), and another 6 (3 in each treatment group) did not respond to communications (lost to follow-up). In addition, 2 participants from the homeopathy group discontinued the intervention due to adverse events (detailed below). At the end of the experiment, data from 86 participants were analyzed. The CONSORT flow diagram [32] from assessed subjects to analyzed participants is shown in Fig. 1.

The length of the follow-up period ranged from 3 to 21 days among the participants who received homeopathy (mean 9.8, standard deviation 3.6 days) and from 2 to 27 days among those who received placebo (mean 9.1, standard deviation 4.6 days). The mean number of follow-ups in the homeopathy group was 4.5 (range: 2–7) and 4.6 in the placebo group (range: 2–9).

The measures of imbalance between the two groups showed significantly higher percentages of cardiovascular diseases in the placebo group ($Z = 2.61$), and respiratory diseases in the homeopathy group ($Z = 2.30$), and a longer time interval from the onset of COVID-19 symptoms to intervention in the homeopathy group ($Z = 2.12$). Nevertheless, there was no difference between the groups in the time elapsed from symptom onset to study inclusion, which was 7 days (range 1 to 27 days, interquartile range 6 to 9) among the participants who received homeopathy and 6 days (range 2 to 14 days, interquartile range 5 to 8) among those who received placebo (Wilcoxon test, $Z = –1{,}71$; $P = 0.08$). The baseline characteristics of the study population are summarized in Table 1.

There were 23 individuals in the homeopathy group (23/42 = 54.8%) and 33 in the placebo group (33/44 = 75%) that reported taking other medications during the treatment period, without evidence of differences among the groups (Fisher exact test, P value = 0.07). A list of these medications is presented in Table 2.

3.2. Primary outcome

Survival curves showed no time-to-event differences between the study groups among participants with mild, moderate, and severe symptoms. Panels (a) and (b) of Fig. 2 show Kaplan-Meier curves for the number of days until a patient recovered from the 15 influenza-like symptoms that we monitored were constructed for all participants, as well as a subset of patients who had at least five moderate or severe symptoms at the time they were included in the study. From the time point of inclusion until the monitoring day 0 (first day of medication), influenza-like symptoms had resolved in 4 participants (1 from homeopathy and 3 from the placebo group). Therefore, the comparative analysis of influenza-like symptoms (primary endpoint) was carried out with 41 participants in the homeopathy group and 41 from the placebo group. There was no difference between survival curves ($P = 0.56$ and 0.06, respectively). In panel (b), half of those who took homeopathy recovered within 3 days (95% CI: 2–8), while half of the participants in the placebo group recovered within 6 days (95% CI: 3–10).

The values of RMST for panels (a) and (b) of Fig. 2 are shown in Table 3. The time until recovery was analyzed from inclusion (time zero) to 3 time points: 5, 7 and 10 days after initiation of treatment.

3.3. Secondary outcomes

There was no statistically significant difference between the survival curves of homeopathy and placebo for the number of days required to reduce the symptom number by 50%, considering, respectively, all participants and those with at least 5 moderate or severe symptoms at inclusion ($P = 0.38$ and 0.07, respectively; Fig. 3). The recovery time for each (moderate or severe) COVID-19 symptom could not be calculated, due to the small number of participants with each symptom.

The symptom score covered the 17 monitored symptoms. Panels (a) and (b) of Fig. 4 show the Kaplan-Meier curves for the number of days required to reduce the symptom score by 50%, considering all participants and those with baseline symptom scores greater than or equal to five, respectively. For patients with only mild symptoms (Fig. 4a), there was no difference between groups receiving homeopathy and placebo ($P = 0.86$), whereas in patients

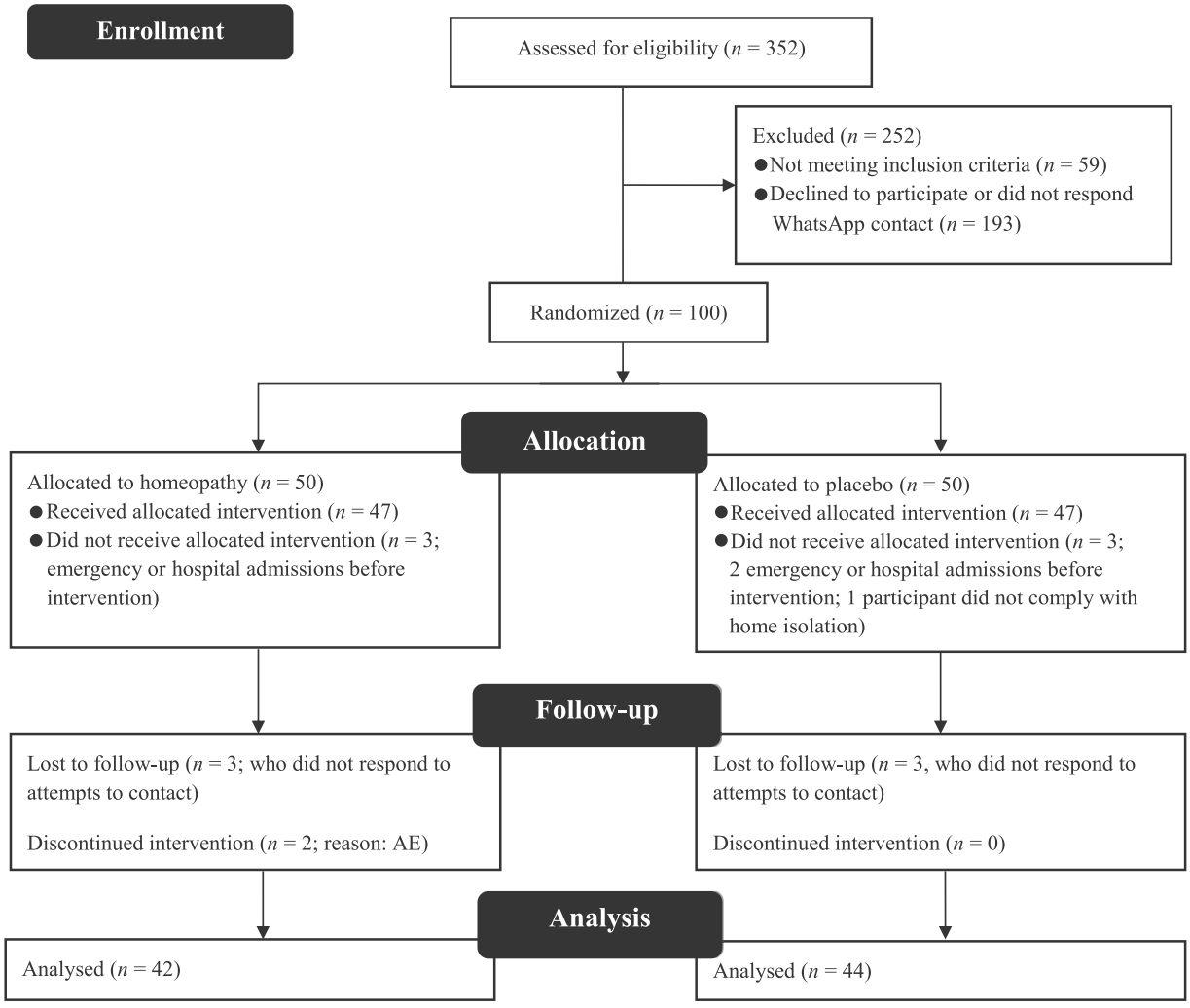

Fig. 1. CONSORT flow diagram. AE: adverse event.

with moderate to severe symptoms (Fig. 4b) a 50% reduction in symptom severity was achieved significantly earlier in the homeopathy group (P = 0.04). Furthermore, half of the participants who took homeopathy achieved a 50% reduction in symptom score within 2.5 days (95% CI: 2–4), while half of those who took placebo reached the same mark within 4 days (95% CI: 3–6).

The values of RMST for panels (a) and (b) of Fig. 4 are shown in Table 4. The time until recovery was analyzed from inclusion (time zero) to 3 time points: 5, 7 and 10 days of follow-up.

Over the course of this study, four participants were admitted to the hospital: one in the homeopathy group and three in the placebo group (2.4% *vs* 6.8% respectively, P = 0.62). All hospitalized participants were male. The hospitalized participant from the homeopathy group was 55 years old and presented class 2 obesity (body mass index [BMI] 38.1 kg/cm^2) as a comorbidity. He had received the study medication 11 days after the onset of his COVID-19 symptoms. In the placebo group, the first participant admitted to a hospital was 33 years old and presented with class 1 obesity (BMI 31.1 kg/cm^2) and arterial hypertension. He had received the study medication six days after the onset of the symptoms. The second hospitalized participant was 40 years old and presented with class 1 obesity (BMI 30.0 kg/cm^2) and arterial hypertension, and had received the study medication 6 days after symptom onset. The last hospitalized participant from the placebo group was 35 years old, was overweight (BMI 28.4 kg/cm^2) and had received the study medication 2 days after the onset of the symptoms.

Regarding adverse events (AE), 2 participants in the homeopathy group discontinued the intervention due to an AE after the first dose (drop): one complained of chest pain and the other of nausea. Among the participants who completed the treatment, six reported transient AEs: five in the placebo group (diarrhea, dizziness, pruritus, hot flashes, and sneezing) and one in the homeopathy group: discouragement, explained by the participant as a "desire to disappear." This AE was reported during two of the three time-points of the follow-up; at the third and last follow-up time-point, the participant reported the remission of that AE, as well as of all COVID-19 symptoms.

4. Discussion

This study was performed in the primary care setting to test whether the homeopathic preparation *Natrum muriaticum* LM2 would be effective as an adjunctive treatment for mild cases of COVID-19 during at-home-isolation. There was no difference in the primary endpoint (time until recovery) between groups receiv-

Table 1
Baseline demographics and clinical characteristics.

Variable	Homeopathy (n = 42)	Placebo (n = 44)	Imbalance measure (Z score)
Age (year, mean ± SD)	37.8 ± 13.5	43.3 ± 17.0	−1.29 [a]
Women (n [%])	28 (66.7%)	28 (63.3%)	0.29 [b]
Employed (n [%])	29 (69.0%)	24 (54.5%)	1.38 [b]
Partnership (n [%])	26 (61.9%)	24 (54.5%)	0.69 [b]
Secondary education (n [%])	19 (45.2%)	24 (54.5%)	−0.86 [b]
Tertiary education (n [%])	18 (42.9%)	11 (25.0%)	1.75 [b]
BMI (kg/m^2, mean ± SD)	28.1 ± 4.4	28.5 ± 7.9	−0.41 [a]
Arterial hypertension (n [%])	7 (16.7%)	14 (31.8%)	−1.63 [b]
Other cardiovascular diseases (n [%])	1 (2.4%)	9 (20.5%)	−2.61 [b]
Diabetes mellitus (n [%])	3 (7.1%)	5 (11.4%)	−0.67 [b]
Chronic respiratory diseases (n [%])	7 (16.7%)	1 (2.2%)	2.30 [b]
Tobacco use (n [%])	3 (7.1%)	4 (9.1%)	−0.33 [b]
Alcohol misuse (n [%])	0 (0%)	2 (4.5%)	−1.40 [b]
Time elapsed from the onset of symptoms to intervention (day, mean ± SD)	9.4 ± 4.1	7.7 ± 2.4	−2.12 [a]
Time elapsed from symptom onset until inclusion (day, median, IQR)	7.0 (1, 27)	6.0 (2, 14)	−1.71
Number of symptoms (mean ± SD) [c]	5.3 ± 2.4	5.3 ± 2.9	−0.09 [a]
Symptom score (mean ± SD)	16.3 ± 6.1	15.1 ± 6.7	−0.79 [a]

BMI: body mass index; SD: standard deviation. IQR: interquartile range; (a): Wilcoxon rank-sum statistic; (b): standardized difference between two proportions; (c): number of mild or severe symptoms, among the 17 symptoms of clinical interest.

Table 2
Concomitant medications recorded in each study group.

Medication	Homeopathy group (n = 42)	Placebo group (n = 44)
Analgesic/antipyretic	10	15
Antiallergic	1	0
Antidepressant	0	1
Antiemetic	1	0
Antitussive	1	0
Azithromycin	4	6
Colchicine	1	0
Corticosteroids	3	7
Mucolytic	0	1
Nonsteroidal anti-inflammatory drugs	2	2
Oseltamivir	0	1
Total	23	33

ing homeopathic medicine and placebo either in the population of patients with mild COVID-19 cases (P = 0.56), or the those with at least 5 moderate or severe symptoms at inclusion (P = 0.06). The median of survival analysis of this group showed that half of the participants recovered within 3 days (95% CI: 2–8) in the homeopathic group, or within 6 days (95% CI: 3–10) in the placebo group. Secondary outcomes indicated that, among more symptomatic participants (baseline symptom score $\geq$ 5), a 50% reduction in symptom severity was achieved significantly earlier in the homeopathy group, when compared with the placebo group (P = 0.04).

It was impossible to estimate hazard ratios to better judge the clinical significance of this difference, because the assumption of proportional risks was not reached between survival curves, and the sample size was insufficient after patients were lost to follow-up. As an alternative, we used the RMST measures from inclusion (time zero) to 3 time points: 5, 7 and 10 days after treatment initiation. Values of RMST shown in Tables 3 and 4 suggest that among the more symptomatic participants, those who received homeopathic *Natrum muriaticum* LM2 might have improved 0.9 day faster during the first five days of treatment, when compared to those who received placebo. That difference was not observed at the other time points, i.e., 7 and 10 days after inclusion, which might be associated with the self-limiting course of the disease, as individuals with mild infection are expected to recover relatively quickly (e.g., within 2 weeks) [33] and the study participants had been symptomatic for a week (on average) at the time of inclusion. Although some secondary measures do not support the null hypothesis, CIs for the respective RMST values are too wide, suggesting that further studies on the efficacy of homeopathic *Natrum muriaticum* LM2 need larger sample sizes than the one used in the present study.

Regarding medication safety, the percentage of hospitalization was about 3 times higher in the placebo group, compared to the homeopathy group, but it was not statistically significant. The baseline clinical characteristics of the participant from the homeopathy group who was hospitalized, included two predictors for COVID-19 severity [34], namely obesity and age over 55. Likewise, two of the three participants from the placebo group who required hospitalization had presented with predictors for severe COVID-19: obesity and arterial hypertension.

All hospitalized participants were followed until discharge, and no deaths occurred in the study population during the follow-up. Participants reported a relatively small number of adverse events in both groups.

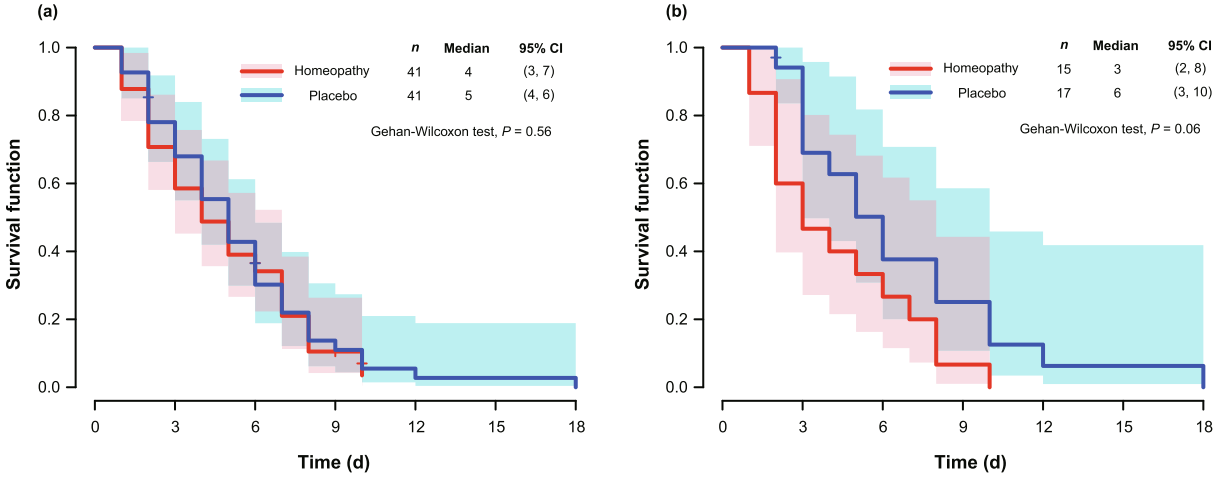

Fig. 2. Primary endpoint: time to recovery from influenza-like symptoms. Data are shown as Kaplan-Meier curves for time until recovery, with 95% confidence intervals (CIs). (a) All participants. (b) Participants with at least 5 moderate or severe symptoms at inclusion.

Table 3
Values of restricted mean survival time (95% confidence intervals) until recovery.

Item	RMST		
	0 to 5 days	0 to 7 days	0 to 10 days
All participants			
Homeopathy	3.7 (3.1–4.1)	4.4 (3.6–5.1)	4.8 (3.9–5.7)
Placebo	3.9 (3.5–4.4)	4.7 (4.0–5.3)	5.1 (4.2–6.0)
Difference	0.2 (−0.3–0.9)	0.3 (−1.2–0.6)	0.3 (−1.5–0.6)
P value	0.376	0.558	0.597
Participants with at least 5 moderate or severe symptoms at inclusion			
Homeopathy	3.2 (2.5–4.1)	3.9 (2.7–5.1)	4.3 (2.8–5.6)
Placebo	4.3 (3.7–4.8)	5.1 (4.2–6.0)	6.0 (4.6–7.4)
Difference	0.9 (< 0.01–1.8)	1.2 (−0.2–2.6)	1.7 (−0.2–3.7)
P value	0.049	0.102	0.076

Data were estimated via the area under the curves of Fig. 2, from inclusion (time zero) up to days 5, 7 or 10 of follow-up. Values of restricted mean survival time (RMST) are presented with their corresponding 95% confidence intervals and *P* values from a test with null hypothesis that the difference in the RMST between the groups is zero. Kaplan-Meier analysis was used to estimate time-to-event measures.

Homeopathy has been used in epidemics, but results are mostly historically described [35], and data were not rigorously tested [36]. In the current COVID-19 pandemic, observational studies have been carried out with homeopathic preparations, such as *Arsenicum album*, *Bryonia alba*, *Gelsemium sempervirens*, *Belladonna*, *Aconitum napellus*, *Eupatorium perfoliatum*, *Wyethia helenioides*, *Pulsatilla nigricans*, *Nux vomica*, *Rhus toxicodendron*, complex *Bryonia alba-China officinalis-Metallum album*, *Phosphorus*, *Sulphur*, and *China officinalis* [37–46]. These studies present relevant data, that should be further tested in clinical trials, but we are not aware of any prior published controlled clinical trial that evaluated homeopathic approaches in the context of COVID-19.

The COVID-Simile Study sought to follow the CONSORT and RedHot guidelines [12,13]. Enrollment was completed in 9 months, after overcoming changes in RT-PCR collection strategies in primary care.

The imbalance assessment between the two groups showed significantly higher percentages of cardiovascular diseases in the placebo group, respiratory diseases in the homeopathy group, and a longer time interval from the onset of symptoms to intervention in the homeopathy group. Theoretically, a higher prevalence of respiratory diseases in the homeopathy group could have biased outcomes in favor of placebo results, as respiratory symptoms were

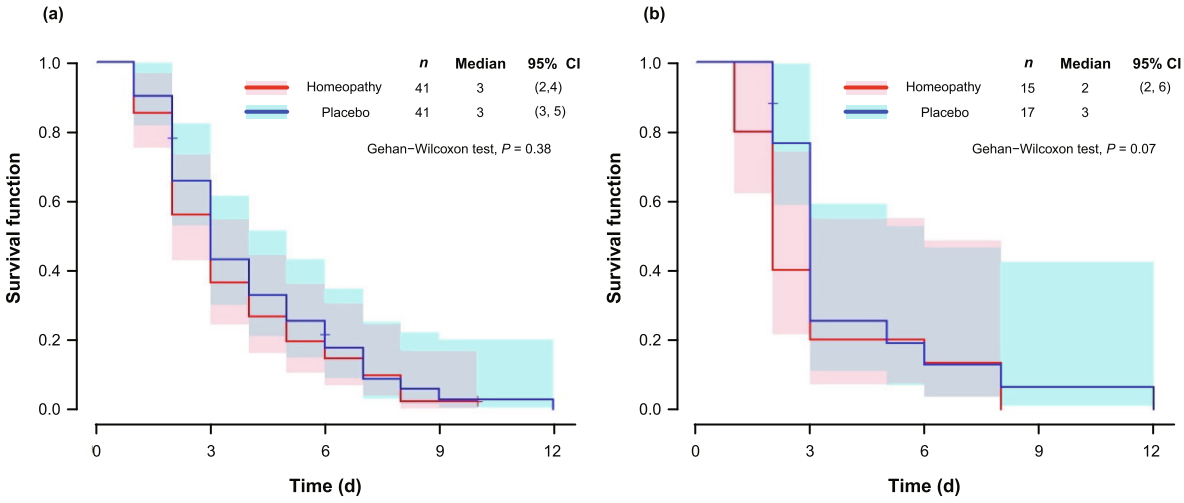

Fig. 3. Kaplan-Meier curves for time to reduce the symptom number by 50%, with 95% confidence intervals (CIs). (a) All participants. (b) Participants with at least 5 moderate or severe symptoms at inclusion.

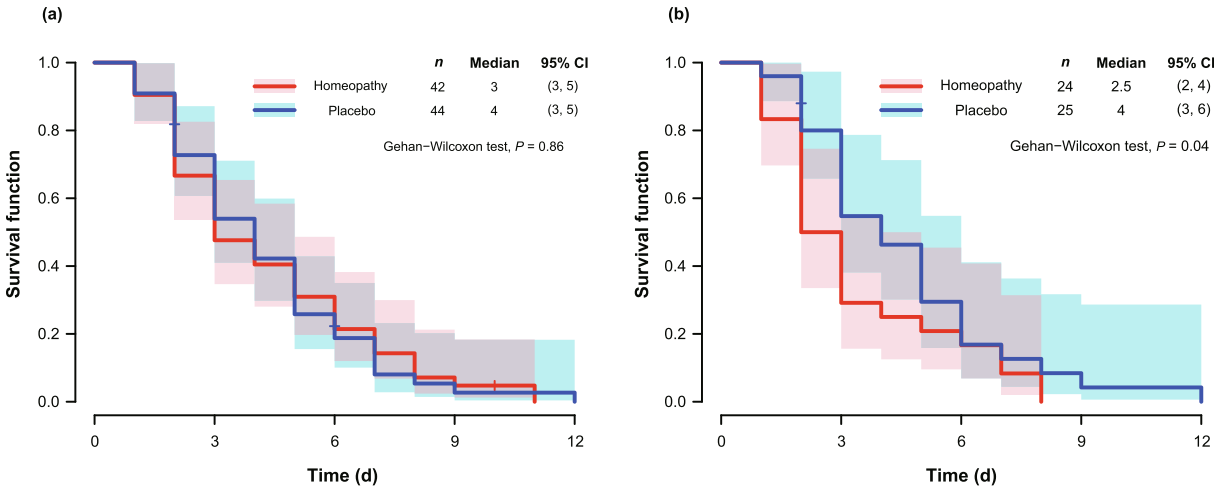

Fig. 4. Kaplan-Meier curves for the number of days required to achieve a 50% reduction in the symptom score, with 95% confidence intervals (CIs). (a) All participants. (b) Participants with a basal symptom score ≥ 5.

Table 4
Values of restricted mean survival time (95% confidence intervals) to reduce symptom score by 50%.

Item	RMST		
	0 to 5 days	0 to 7 days	0 to 10 days
All participants			
Homeopathy	3.5 (3.0–3.9)	3.9 (3.3–4.6)	4.2 (3.4–5.0)
Placebo	3.6 (3.1–4.0)	4.0 (3.4–4.6)	4.2 (3.4–5.0)
Difference	0.1 (−0.4–0.7)	0.1 (−0.7–0.9)	0.0 (−1.0–0.1)
P value	0.638	0.878	0.949
Participants with basal symptom score ≥ 5			
Homeopathy	2.9 (2.3–3.4)	3.3 (2.4–4.1)	3.3 (2.4–4.2)
Placebo	3.8 (3.2–4.3)	4.2 (3.5–5.0)	4.5 (3.5–5.4)
Difference	0.9 (0.1–1.7)	0.9 (−0.1–2.1)	1.2 (−0.12–2.4)
P value	0.022	0.079	0.076

Data were estimated via the area under the curves of Fig. 4, from inclusion (time zero) up to days 5, 7 or 10 of follow-up. Values of restricted mean survival time (RMST) are presented with their corresponding 95% confidence intervals and *P* values from a test with null hypothesis that the difference in the RMST between the groups is zero. Kaplan-Meier analysis was used to estimate time-to-event measures.

assessed at every monitoring. In the same direction, the placebo intervention started earlier than homeopathy. If both were active interventions, that early start could have biased results in favor of the placebo group.

In contrast with those imbalanced clinical characteristics, homeopathy and placebo groups had the same (mean) number of symptoms and similar symptom scores at baseline. Moreover, there were no statistically significant differences in the time elapsed from symptom onset until inclusion, in the length of the follow-up between study groups, or in the number of assessments; this is another sign of clinical balance, as the participants were followed while in at-home-isolation, and the duration of isolation was determined by the time of onset and disappearance of COVID-19 symptoms.

The strengths of the trial include strict concealment and blinding of the randomization under real-world conditions. Paradoxically, real-world conditions were also a limitation. For instance, during the first month of the study, we may have lost some participants to follow-up due to difficulty in communication between enrolled patients and primary care teams. Moreover, the participants were not always available for scheduled follow-up meetings. Real-world variations, combined with the wide range of symptoms in COVID-19 result in greater variability. The greater the variability, the larger the sample size needed for the analyses. Goodman and Berlin [47] argue that the calculation of power after a study is over would be inappropriate, and CIs can play an important role in checking the adequacy of the sample size. Relatively large CIs are a result of small sample sizes. In the present study, the 95% CIs for the median (Figs. 2, 3 and 4) are wide and illustrate the variability in the time to symptom reduction, thus negative outcome measures can result from an insufficient sample size. Therefore, the relatively small sample size of this study is the main limitation to the power of this study.

The COVID-Simile study tested a specific homeopathic methodology, developed by Samuel Hahnemann, to select, prepare, and use a homeopathically suitable remedy to treat a population suffering from an epidemic disease; this approach contrasts with the typical, individualized approach of homeopathy, which would be impractical on a widespread basis [48]. Therapeutics is not a vaccine substitute. We must emphasize in times of vaccine hesitancy [49], since Hahnemann himself was already an advocate of Jenner's (his contemporary) work, stressing the reduction in children mortality after the vaccination against variola [7].

Although many authors have questioned the plausibility of homeopathy for prophylactic and therapeutic purposes [50], efforts have been made to study Hahnemann's ultra-dilutions using current technologies. For example, regarding the homeopathic medicine tested in this study, data from basic research have shown biological activity of *Natrum muriaticum* in a plant model [51], and nanoparticles of sodium and chlorine in LM potencies of *Natrum muriaticum* [52].

Homeopathic treatments should not be prematurely classified as placebos [53]. Instead of "prior disbelief that refuses to conceive the plausibility of homeopathy" [54], clinical studies based on the scientific method should investigate the efficacy of specific homeopathic methods for specific health conditions.

Studies with larger sample size of patients with more symptoms are needed to assess the effectiveness of homeopathic *Natrum muriaticum* LM2 for COVID-19. However, despite the statistical limitations already discussed and the absence of evidence for the effectiveness of *Natrum muriaticum* LM2 for mild disease cases of COVID-19, we believe that this pioneering trial will provide insight for new investigations, and it might be helpful as baseline information for future studies on homeopathic treatment methods for the disease.

5. Conclusion

Results indicated that *Natrum muriaticum LM2* was safe to use to treat COVID-19, but there was no statistically significant difference in the primary endpoint between *Natrum muriaticum* LM2 and placebo for mild COVID-19 cases. Although some secondary measures did not support the null hypothesis, CIs were too wide, suggesting that further studies with larger sample sizes and more symptomatic participants are needed to test the effectiveness of homeopathic *Natrum muriaticum* LM2 for COVID-19.

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Authors' contribution

UCA designed the hypotheses and the experiments; participated in data interpretation and manuscript review and writing; contributed to the scientific discussion of the data and of the manuscript. MSA participated in the experiment design; contributed to the scientific discussion of the data and the manuscript. AEMP performed the experiments and was responsible for data collection. LMH participated in the experiment design and performed the experiments during an open-label phase (see study protocol). ATC participated in the experiment design. JNMD performed the experiments. HFS participated in the experiment design and organized data collection. EZM performed the analysis; participated in data interpretation and manuscript review and writing; contributed to the scientific discussion of the data and the manuscript.

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Declaration of competing interest

The authors declare that they have no competing interests. Cesar AT is co-owner of HN-Cristiano Homeopatia, the pharmacy that has donated the study medication. However, *Natrum muriaticum* has been in use for over 150 years and is not patentable.

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