A Randomized, Placebo-controlled Homeopathic Drug-proving of SARS CoV-2 nosode (BiosimCovex) in healthy volunteers

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ABSTRACT
Introduction: Homeopathic Drug-proving is a systematic examination and recording of the symptoms experienced by healthy volunteers after the administration of an investigational medicinal substance. Randomized, placebo-controlled HDP was conducted using BiosimCovex (SARS CoV-2 nosode) in healthy volunteers. Materials and methods: The nosode BiosimCovex was prepared from the oropharyngeal biomaterial of the SARS-CoV-2 virus-positive patient. BiosimCovex 30c was given orally in a randomized, placebo-controlled trial to examine the safety, pathogenetic effects of 30 volunteers (18-65 years of age and both genders) and explore therapeutic application. Volunteers were administered a dose of 6 pills of the nosode once a day for two weeks followed by 30 days observation period. Pre and post-examination physical, vital signs, and laboratory investigations were done with a run-in period of 7 days. Symptoms experienced by the volunteers were recorded and analyzed, and Qualitative and Quantitative indices per volunteer were reported. Trial registered at http://ctri.nic.in (CTRI/2022/06/043392). Results: BiosimCovex nosode exhibited quantitatively distinct symptoms, which can be applied in clinical practice. The number of symptoms reported in the verum arm was 73 (placebo 11). The incidence of the Pathogenetic effect per volunteer in the verum group was 8.1 vs that of the placebo 5.5. The Qualitative Pathogenetic Index was 0.295 in the verum group as compared to the placebo 0.193. The symptoms observed matched with the symptoms produced in an open-label Phase 1 study conducted during the COVID-19 pandemic and also with that of the viral infection. There were no serious/fatal adverse events during the study. Safe use was documented. Conclusion: The BiosimCovex nosode has demonstrated its safety and specific symptoms in a homeopathic drug proving, thus supporting its inclusion in the homeopathic literature.

Keywords: SARS CoV-2, BiosimCovex, nosode, homeopathy, drug proving

INTRODUCTION
Samuel Hahnemann practiced a distinct method called drug-proving, (also known as Homeopathic Pathogenetic Trial, HPT), a systematic examination and recording of the symptoms experienced by healthy volunteers after an administration of an investigational medicinal substance. Identifying and documenting a pathogenetic effect of a substance has been practiced in homeopathy since its inception in
1796. Symptoms and signs at the physical and mental level are carefully recorded in terms of their occurrence, quality, intensity, modalities, and concomitants as per availability. This data on the effects of the medicinal substance is utilized by the prescribers based on symptom-similarity.

Nosodes are well-known homeopathic medicines used for preventive and therapeutic actions [1,2]. The emergence of the SARS CoV-2 virus in late 2019 encouraged the development of Coronavirus nosode (BiosimCovex) [3]. As our initial phase 1 trial with drug proving was an open-label study on ten healthy individuals in June 2020, examining the safety and deriving some drug-proving effects [4,5] we decided to conduct a full-fledged, randomized placebo-controlled HDP for exploring its therapeutic application. Another phase II, feasibility RCT documenting its preventive efficacy in the pandemic in a quarantine facility was also conducted in Mumbai from June 2020 to July 2020 [6]. The objective of this study is to examine and document BiosimCovex’s primary effects, particularly focusing on the symptoms observed in healthy volunteers, to inform its potential application in clinical practice.

MATERIALS AND METHODS

Study Design

The randomized (2:1), double-blind placebo-controlled HDP was conducted at a site in Kolkata, India, Dr. Samit Ghosh Clinic, Kolkata, West Bengal.

The drug was proved in 30c potency on 30 volunteers, out of which 21 were on verum and 9 on a matching placebo. To achieve 30 volunteers, we screened 41 volunteers (13 females, 18 males), one volunteer declined to participate and 10 were excluded (Fig. 1).

The first volunteer was enrolled on 24th June 2022, and the last volunteer’s last visit was completed on 8th November 2022. Written informed consent was obtained from each volunteer before the performance of any study-specific procedures. The study was conducted by the guidelines of ICH-GCP (International Conference of Harmonization - Good Clinical Practice), Homeopathy GCP [7] and the ethical principles outlined in the Declaration of Helsinki 2008 [8] and drug-proving guidelines [9].

Investigations

Pre and post-drug administration investigations included complete blood count, Erythrocyte Sedimentation Rate (ESR), white blood cells, platelets, total and differential leucocyte counts, blood biochemistry, immunology, serology, molecular biology, urine routine analysis, pregnancy test, chest x-ray, and electrocardiogram (ECG).

Study Population

Principal Investigator Dr Samit Ghosh, BHMS, Kolkata, India recruited the volunteers from the investigator’s database and referrals.

Major inclusion criteria

The major inclusion criteria to screen volunteers includes both males and females.
of age 18 – 60 years. Healthy individuals with no apparent disease and normal routine laboratory parameters during screening, intelligent enough to carefully record the facts, subjective and objective symptoms generated by the drug during proving and able to be informed of the nature of the study and willing to give written informed consent.

**Major exclusion criteria**
The major exclusion criteria were any disease or condition that might compromise the hematopoietic, renal, endocrine, pulmonary, central nervous system, cardiovascular, immunological, dermatological, gastro-intestinal or any other body system. COVID-19 RT-PCR-positive individuals. Persons with color blindness. Persons who have undergone surgery in the last two months, planned medical/dental treatment during the proving period including herbal or dietary supplements, procedures, or medications that are likely to interfere with, or substantially alter, responsiveness to the proving substance. Participants were not on any homeopathic remedy in the preceding month and have had no significant change in health status in the last month and participation in another clinical or proving trial during the last 6 months.

The eligible healthy volunteers between 18 to 60 years, both males and females and the participants who were willing to provide written informed consent were recruited for the study in a 2:1 ratio of BiosimCovex to placebo.

The subjects who tested positive for COVID-19 at baseline and volunteers with any disease or condition that might compromise the hematopoietic, renal, endocrine, pulmonary, central nervous system, cardiovascular, immunological, dermatological, gastro-intestinal or any other body system were excluded.

**Ethics and approvals**

The study protocol, amendment, and informed consent forms were reviewed and approved by the Health Point Ethics Committee (CDSCO registration Number: ECR/284/Inst/WB/2013/RR-19). The study registration number at Clinical Trials Registry, India (CTRI) was CTRI/2022/06/043392 [Registered on: 21/06/2022, weblink: https://ctri.nic.in/ClinicalTrials/ptmaindet2.php?EncHid=NzA1MjA=&Enc=&userName=CTRI/2022/06/043392. Biosimilia Private Limited sponsored the investigations and extended the study financial support.

**Study medication**
BiosimCovex was prepared from the oropharyngeal biomaterial of the patient who was positive for the Wuhan strain of SARS CoV-2 virus confirmed by gene-sequencing (Identified SARS CoV-2, NCBI Reference Sequence: NC_045512.2). The torque of 501.27 Nm was imparted during each step of 10 strokes to every potency to standardize the medicine [10]. BiosimCovex was prepared by Biosimilia at Haffkine Institute for Training and Research, Mumbai, India in accordance with Biosafety guidelines. The safety of BiosimCovex was documented by molecular and animal toxicity studies. Acute and repeat dose toxicity studies were conducted in mice, rats, and rabbits as per OECD (Organization for Economic Co-operation and Development) guidelines [11]. RT-PCR of 1c to 6c and 30c potencies were done to document the absence of any viral component in the specific potency from a standardization and safety perspective. The volunteers were given a dose of placebo on day one and were observed for 7 days of the run-in period. On day one of the second week, the volunteers were given study medication (coded as BSC-022 potency 30c) either BiosimCovex or placebo (Lactose pills impregnated with dispensing alcohol) in a blinded manner. A dose of 6 globules (size 30) was administered orally, daily for two weeks.
Randomization
The volunteers satisfying all inclusion and exclusion criteria were randomly assigned to receive either placebo or BSC-022 in 30c potency. The randomization list was prepared using computer-generated random sequence using the seed method.

Blinding and allocation
This was a double-blind study. The investigator, study staff, study volunteers, site monitors, and sponsor remained blinded to the treatment throughout the study. Serially numbered, sealed envelopes were used for the allocation of treatments. Unblinded data analysis was performed by an independent statistician after resolving the data anomalies and database lock.

Study end-points and assessments
The volunteers maintained a diary to record clinical symptoms daily. The diaries had a page for each day where a head-to-foot scheme (Location: Body part) was preprinted allowing the prover to note the symptoms, their duration, sensations, modalities, and concomitants. Self-assessment of symptoms and the investigator’s assessment were documented. The investigator has a degree of BHMS and experience of over 35 years in homeopathic practice, ICH-GCP, and drug proving guidelines-trained. The assessor interviewed the volunteers in person on weekly visits and follow-up visits until 7 weeks. Telephonic communication was advised in case volunteers experienced symptoms. Pre and post-changes in blood investigations were analyzed. The volunteers were clinically examined by a general physician, gastroenterologist, gynecologist, and homeopath, pre and post-study.

Safety assessments
Safety assessments included the monitoring of volunteers for any adverse events, serious adverse events, clinical and laboratory investigation results, blood pressure, physical examination findings, and general well-being.

The RT-PCR tests for diagnosing COVID-19
RT-PCR for COVID-19 was done for all the volunteers at the time of screening and during the trial period if any volunteer experienced any COVID-19-related symptom/s. Rapid antigen tests were done every 15 days for all the volunteers during the study period.

Symptom recording
The symptoms experienced by the volunteers during the study period were recorded and analyzed in a specific format.

- All symptoms were reported with the location, sensation, duration, frequency, and concomitants if any. For example, a dull headache with the heaviness of the head all over the head < 1-4 p.m. is associated with sleepiness. (Volunteers: 1).
- Every symptom described by the volunteers has been graded as + (mild), ++ (moderate), +++ (bothersome), and ++++ (extremely bothersome). This method allowed qualification grading, which helped us quantify the quality of symptoms.
- The symptoms exhibited during the run-in period were eliminated if the volunteer also exhibited the same or similar symptoms after consumption of the study medication.
- The intensity of the symptom is denoted by simple, *italics*, bold, or bold **CAPITAL** letters based on the intensity and duration of the symptoms, and the number of volunteers who experienced it. Final notation at the discretion of the principal investigator.
Similar symptoms experienced by more than one volunteer were recorded in italics or bold text and considered as characteristic.

Indices calculation

**The incidence of Pathogenetic effects (per volunteer)** = \( \frac{\text{Total number of findings claimed in the trial}}{\text{Total number of subjects using the medicine}} \)

1. The incidence of pathogenetic effects per volunteer was defined as the total number of findings claimed in the trial divided by the total number of subjects using the medicine and included in its final pathogenetic description.

2. The Quantitative Pathogenetic Index [12] \( A = \frac{(B/C)}{D} \)

   The following parameters are considered:
   - \( A \) = Quantitative Pathogenetic Index (number of symptoms per volunteer per day)
   - \( B \) = Total number of findings claimed in the trial
   - \( C \) = Total number of volunteers using the medicine and included in its final pathogenetic description
   - \( D \) = Number of days.

3. The Qualitative Pathogenetic Index [12] \( a = \frac{(b/c)}{d} \)

   While undertaking the projects on drug proving, the investigator qualified every symptom by its intensity, as explained above. This allowed the qualification of individual symptoms. The number of symptoms for each grade was divided by the number of volunteers and the number of days. The mean grades (++, +++, and ++++) were compared between the verum and placebo arms (table 1).

   \( a \) = The Qualitative Pathogenetic Index (number of symptoms, of a given intensity, per volunteer per day)

\( b \) = Total number of symptoms of a particular intensity
\( c \) = Number of volunteers who contributed to the symptoms
\( d \) = Number of days.

**RESULTS**

The mean age of the volunteers was 32.1 years (29.89 BiosimCovex and 26.03 Placebo) with negligible difference in gender, 38% female and 62% males in BiosimCovex and 33% female and 66% male in the placebo group. Nine volunteers from the verum group and two volunteers from the placebo exhibited definite symptoms. Symptoms experienced by the volunteers in the run-in period were excluded from the analysis.

In the verum arm, a total of 73 symptoms, and in a placebo group 11 symptoms were recorded. The incidence of the Pathogenetic Effect (PE) per volunteer in the verum arm was 8.1 versus 5.5 in the placebo arm (Fig. 2). The Quantitative Pathogenetic Index of BiosimCovex was 0.193 and that of placebo was 0.112. The Qualitative Pathogenetic Index of BiosimCovex was 0.295 as compared to 0.193 in the placebo arm (Fig. 3). Qualitatively distinct symptoms of grade ++, +++ (moderate to bothersome) were noted in the verum arm (Fig. 4).

Many symptoms observed matched with the symptoms produced in our open-label Phase 1 study [5] conducted during the COVID-19 pandemic and also with that of the COVID-19 infection [13].
As the symptoms reported by the volunteers in the study were mild to bothersome, short-lasting, self-limiting, and did not require medical intervention, they did not qualify as serious adverse events.

In the first parenthesis, the number indicates the total number of volunteers who produced that particular symptom. The second parenthesis indicates the volunteer’s randomization number and the intensity of the symptoms reported. Intensity gradation: Mild (+), moderate (++), bothersome (+++), and extremely bothersome (++++).

For example, **IRRITABILITY** (n=6) (4****, 21**, 22**, 24**, 29**, 30**), denoted that the six volunteers reported the symptom of Irritability. In the second parenthesis, volunteer number 4 reported Irritability****, volunteer 21 reported Irritability**, and so on.

**Fig 2: Qualitative Pathogenetic Index**
**Fig 3: Incidence of Pathogenetic effect per volunteer**
**Fig 4: Qualitative Pathogenetic Index: Symptom Intensity**

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<th>Table 1: Intensity grading (Qualitative Pathogenetic Index)</th>
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**Symptoms in verum arm:**

**Mind:**
• **IRRITABILITY** (n=6) (4****, 21**, 22**, 24**, 29**, 30**+)
  - **Irritability with absent-mindedness, forgetfulness** (4**** on day 9,12,13,16,17,20,23,25,26, 30, 24** on day 8, 10, 12, 14, 16, 17, 18, 20, 21)
  - Irritable < morning and evening (21** on day 8, 9, 11, 13, 15, 17, 18, 20, 22)
  - Irritable, > after sleep (22** on day 8-11, 20-23)
  - Irritable, < slight contradiction (29** on day 8, 12, 16, 18, 22, 23)
  - Irritable, entire day, < morning, > after sleep (30** day 8-10, 13-16, 18, 20, 21, 22)

• **ANGER** (n=4) (1**, 4****, 22**, 29**+)
  - Absent-mindedness, forgetfulness (See under Irritability)
    - **Anger, no inclination to do work** < working, talking and noise, > sleeping and rest (1** on day 10-21 on 2 to 12 hours, 22** on day 8-11 and 20-24 on entire day)
    - **Anger** (4**** on day 9, 12, 13, 16, 17, 20, 23, 25, 26, 30)
    - Anger, < small causes, > after sleep (29** on day 8, 12, 16, 18, 22, 23)

• **ANXIETY** (n=5) (1***, 21**, 24**, 29**, 30**+)
  - Anxiety (1** on 10-21)
  - Anxiety, <morning and evening, > sleep and rest (21** on day 8, 9 to 22, 24 ** on day 9 days, < afternoon (30** on day 8, 9, 10, 13, 14, 15, 16, 20, 21, 22)
  - **Anxiety, < small causes, > after sleep (29** on day 8, 12, 16, 18, 22, 23)

• **Fear of dark with hallucination that someone standing behind and observing (n=1)** (12*** on day 11, 13, 15, 16, 17, 18, 19, 20, 26)

**Dreams:**
- **Falling from the bed** (12*** on day 8, 10), wakes up suddenly (12*** day 15, 16, 17)
- Dream confusion (21** on day 10, 11, 12), dream of feeling lost (21** on day 14, 16, 19, 21)
- Dreams of falling out of bed (22** on day 12, 13, 15)
- Dream confusion, feeling lost, from midnight 2.30 am to 4 am (24** on day 8, 11, 14, 16, 18)
- Dreams of feeling lost from family (30** on day 18, 19, 20, 22)

**Head:**
- **HEADACHE** (N=6) (1**, 8*, 21**, 24***, 29**, 30***)
  - **Throbbing** (n=4) (1**, 24***, 29**, 30***)
    - Throbbing sensation in temples (1** on day 9 on 30 minutes, 29** on day 14 on one day)
    - **Throbbing sensation from left to right** (24*** on day 9, 10, 11)
    - Throbbing sensation <morning (30*** on day 11, 12)
  - **Frontal, temporal** (n=2) (8*, 21**)
    - Frontal region at the left side, <9 am - 12 am (8* on day 5, 6)
    - Frontal headache throbbing sensation right to left, >pressure (21** on day 9, 10, 11, 12)
  - Vertigo: **Body aching with vertigo on 4 days** (4**** on day 8, 11, 12, 18) (→ Generalities)

**Nose:**
- **Watery discharge** (n = 4) (22**, 24**, 29**, 30***)
  - Watery discharge full day (22** on day 17, 18, 24** on day 10, 11, 15)
- Watery discharge, < Morning and evening (29++ on day 13, 14)
- Watery discharge, < in the afternoon (30+++ on day 11, 12)

Abdomen:
- Pain in abdomen (n=2) (12+++ on day 11, 14-19, 22-25, 28, 22+++ on day 13, 14)
- Tightness in abdomen (n=2) (29++ on day 11 on a day, 30++ on day 13, 15, 17, 21)
- Acidity, eructation (n=1) (1++ on days 18, 21)

Stool:
- HARD STOOL, CONSTIPATION (n = 6) (4++, 12++, 22++, 24++, 29++, 30++)
  - Stool staining, constipation, (4+++ on day 8, 10, 11, 22, 23, 25, 30, 24++ on day 8, 13, 14, 16-20, 29++ on day 15 on a day)
  - Black hard stool, constipation (12+++ on day 8, 22-25, 28, 30++ on day 8 on 6 days)
  - Dry hard stool, constipation, > in the evening after taking warm water (22++ on day 14-18, 22-25, 28)

Sleep:
- SLEEP, DISTURBED (n =6) (12+, 21++, 22++, 24++, 29++, 30++)
  - Sleep disturbances (12+ on days 8, 13)
  - Sleepless (21++ on day 12 on 6 days)
  - Sleep delayed, less sleep (22++ on day 18)
  - Disturbance in sleep, <about 2 am- 5 am (24++ days 13, 15)
  - Sleep, delayed (29+++ on day 20)
  - Loss of sleep (30+++ on day 19)

Heart:
- Palpitation in the heart, sensation as if it will stop <Afternoon, evening, >After sleep (n = 1) (29++ on day 9)

Chest:
- CHEST, HEAVINESS and sensation of contraction (n = 6) (12++++, 21++, 22++, 24++, 29++, 30++)
  - Chest pain, left side <morning and evening, (12++ on day 13, 14, 16, 18, 20)
  - Chest heaviness, and sensation of contraction (21++ on day 8, 9, 10, 13, 18, 20, 22, 22+++ on day 9, 12, and 15, 24++ on day 9, 12, 15, 29++ on day 10,17,19,21)
  - Heavy chest contraction for 1-3 hours (30++ on day 8,9,16,20,22,23)

Neck:
- Pain sensation, entire day, > afternoon (n = 1) (1**** on day 12 for a day)

Skin:
- Skin eruption (n = 2) (12++, 22++)
  - Skin eruption, on chin, right side, feels like a cat scratch (12++ on day 11-28)
  - Skin itching and burning, red circular itching eruption, on the right dorsum of the hand (22++ on day 12, 13, 14)

Generalities:
- WEAKNESS AND PAIN (n = 8) (1****, 4****, 12***, 21++, 22++, 24++, 29++, 30++)
  - Whole body painful (1**** on day 12,18)
  - Body aching, with vertigo for 4 days (4**** on day 8, 11, 12, 18)
- **General weakness >after sleep, <morning and evening (12+++ on day 9, 11-28)**
- Weakness and body pain (21++ on day 8 to 22)
- Weakness and body pain (22++ on day 6-11, 15, 16, 19, 20)
- **BODY PAIN AND WEAKNESS, LOW ENERGY LEVEL (24+++ on day 6-18, 29+++ on 7-12,16,18,20,22, 30+++ on day 6-24)**

**Extremities:**
- **Body pain, lower and upper extremities, and joints (n=3) (4++, 12++, 22++)**
  - Whole body painful, lower and upper extremities (4++ on day 9-13,16,20)
  - Whole body and joints, painful (12++ on 8-11, 13, 14, 16, 19-21)
  - Painful, joints, upper and lower extremities (22++ for day 17, 18)

**Symptoms in the placebo arm:**

**Mind:**
- Irritable, angry <morning (n = 1) (3+ for day 18 for a day).

**Head:**
- **Headache (n = 2) (3++, 7+++)**
  - Frontal, Headache Throbbing sensation > pain in morning (3+++ on day 4,5,6,7)
  - Frontal, Headache at afternoon 5 pm to 9 pm (7+++ on day 3, 39, 40, 41, 42, 43)

**Nose:**
- Watery discharge (n = 1) (7+ on day 39, 40, 41, 42).

**Face:**
- **Itching (n=1) (3++ on day 7 for one day)**

**Teeth:**
- Pain in teeth (n = 1) (3+ on day 16, 24)

**Chest:**
- Chest contraction in the evening (n = 1) (3+ on day 11 (1hr), 14(4hr), 16 (4hr), 17(2hr),15 (20min))

**Heart:**
- Sensation as if the heart will stop (n = 1) (3+++ on day 10, 16, 17, 19, 20, 21, 22, 27, 29)

**Throat:**
- Dry cough (n = 1) (3+++ for day 4, 5)

**Abdomen:**
- Whole abdomen pain, griping (n = 1) (3+ for day 11 for 1 day)

**Stool:**
- Constipation hard stool and slightly blackish, <morning 6am >after stool (n = 1) (3+++ on day 10,12, 15,16,17,18,19,20,21)

**Fever:**
- Low grade fever (n = 1) (3+++ for day 5, 6, 7)

**Skin:**
- Redness on the skin (n=1) (7++ for day 5, 6)

**Generalities:**
- Fatigue, whole day, <morning, >evening (n = 1) (3+++ for day 18, 19, 20)
Laboratory analysis: BSC-2022 study
There were no serious or fatal adverse events during the study. The basic biochemistry and liver function tests were not affected by BiosimCovex 30C (Table 4). The P-value results of the t-Test, for all subjects at baseline (pre), compared to end visit (post), were not significantly different, and in the normal reference range. Triglycerides in verum (p=0.032) and T3 in the placebo group (p=0.026) showed significant differences. To obtain the comparative results between the BiosimCovex and placebo groups (Table 5), the difference between pre and post was calculated and then the values were compared by non-parametric method (Mann-Whitney U Test). Significant differences were noted for alkaline phosphatase and T3, however, did not go beyond the normal reference ranges. The subjects were closely monitored and did not show any abnormal or irreversible clinical changes.

All the volunteers were vaccinated at least four months (average) before they joined the study. Volunteers (n=27) out of 30 had positive total (COVID-19 IgG, IgM) antibodies at the baseline. Two volunteers in the BiosimCovex arm had < 1 (negative) (COVID-19 IgG, IgM) antibodies at the baseline, which increased to 1870 (from 0.08) and 1580 (from 0.86) after six weeks of the trial period.

DISCUSSION
An ability of BiosimCovex, a potentized nosode containing SARS CoV-2 organisms to trigger subtle changes in physiology in a way that the volunteers exhibit subjective, mild to moderate, reversible symptoms and signs in this RCT, the HDP, with significant Qualitative and Quantitative Indices (0.295 and 0.193), is scientifically exciting and guiding for prescribing it in practice. BioSimCovex is one of the few new nosodes that have been developed in recent times which may have undergone randomized placebo-controlled drug proving.

Since the phase 1 safety trial [4] was not placebo-controlled, we conducted this controlled HDP, which has shown many symptoms comparable to that of phase 1 (Table 2). The presumed nanomaterials [14] in homeopathic potencies have shown effects comparable with that of the source materials (SARS CoV 2 virus) in this study (Table 3), as well as in other studies such as HIV Nosode [15], Hepatitis C Nosode [16], and Capsaicin [17], drawing attention to the fact that the ultra-dilute format of the potentized medicines retains the ability to alter human physiology.

Homeopathically, the primary effects of the BiosimCovex on healthy volunteers are suggestive of its therapeutic role for the conditions such as acute colds and coughs, bronchitis, COVID-19 illness, fibromyalgia,
<table>
<thead>
<tr>
<th>Sr No.</th>
<th>Location</th>
<th>Symptom (Intensity of symptoms in ascending order: +, ++, ++++, +++++)</th>
<th>Phase 1 – Drug-proving</th>
<th>HPT</th>
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<tbody>
<tr>
<td>1</td>
<td>Head</td>
<td>1. Frontal headache</td>
<td></td>
<td>1. Frontal headache throbbing sensation right to left</td>
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<td></td>
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<td>2. Pain on the right side of the head</td>
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<td>2. Frontal region at left side headache</td>
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<td>3. Headache (Right side)</td>
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<td>3. Throbbing sensation in temples</td>
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<td>4. Frontal and occipital headache</td>
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<td>4. Slightly throbbing sensation from left to right</td>
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<td>5. Heaviness in the head</td>
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<td>5. Headache throbbing sensation</td>
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<td>2</td>
<td>Nose</td>
<td>1. Watery discharge</td>
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<td>1. Watery discharge</td>
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<td></td>
<td>2. Sneezing</td>
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<td>3. Congestion in the right sinus (sinusitis) and brain fog as concomitant symptom</td>
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<tr>
<td>3</td>
<td>Neck and shoulder</td>
<td>1. Pain, radiating from the neck, shoulder</td>
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<td>1. Pain sensation in neck</td>
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<td>2. Effect on the right neck, cannot lift the right hand</td>
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<td>4</td>
<td>Throat</td>
<td>1. Cough, dry</td>
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<td>Chest</td>
<td>1. Heaviness in the chest</td>
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<td>1. Contraction and heaviness</td>
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<td>2. Shortness of breath</td>
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<td>Chest heaviness and contraction</td>
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<td>3. Desire to take a deep breath</td>
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<td>6</td>
<td>Abdomen</td>
<td>1. Tightness in the abdomen</td>
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<td>1. Abdomen pain,</td>
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<td>2. Constipation</td>
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<td>2. Whole abdomen</td>
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<td>4. Acidity, eructation</td>
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<td></td>
<td></td>
<td>5. Hard stools</td>
</tr>
<tr>
<td>7</td>
<td>Sleep</td>
<td>1. Loss of sleep</td>
<td></td>
<td>1. Sleep disturbance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Drowsiness</td>
<td></td>
<td>2. Sleepless</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. Delayed and less sleep</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4. Loss of sleep</td>
</tr>
<tr>
<td>8</td>
<td>Heart</td>
<td>1. Palpitation</td>
<td></td>
<td>1. Palpitation</td>
</tr>
<tr>
<td>9</td>
<td>Mind</td>
<td>1. Anxiety</td>
<td></td>
<td>1. Anxiety</td>
</tr>
</tbody>
</table>
### Table 3: HPT Symptoms comparison with COVID-19 illness symptoms

<table>
<thead>
<tr>
<th>Sr no.</th>
<th>HPT</th>
<th>COVID-19 illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Fever</td>
<td>Fever or chills</td>
</tr>
<tr>
<td>2.</td>
<td>Heaviness in chest and sense of contraction</td>
<td>Cough</td>
</tr>
<tr>
<td>3.</td>
<td>Tiredness</td>
<td>Shortness of breath or difficulty breathing</td>
</tr>
<tr>
<td>4.</td>
<td>Body-ache, pains</td>
<td>Fatigue</td>
</tr>
<tr>
<td>5.</td>
<td>Headache</td>
<td>Muscle or body aches</td>
</tr>
<tr>
<td>6.</td>
<td>Sore throat</td>
<td>Headache</td>
</tr>
<tr>
<td>7.</td>
<td>Running of nose</td>
<td>New loss of taste or smell</td>
</tr>
<tr>
<td>8.</td>
<td>Headache</td>
<td>Sore throat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congestion or runny nose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea or vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diarrhea</td>
</tr>
</tbody>
</table>

### Table 4: Basic laboratory findings during the study course (t-Test, paired two Samples for Means)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>BiosimCovex (B)</th>
<th>Placebo (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Parameters</td>
<td>Pre Mean (SD)</td>
<td>Post Mean (SD)</td>
</tr>
<tr>
<td>Hemoglobin g/dL (13-17) for females (12-15) (N= B:21, P:9)</td>
<td>13.15 (1.82)</td>
<td>13.22 (1.35)</td>
</tr>
<tr>
<td>P value</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>Total leucocyte count (TLC) cells/cu.mm (4000-10000) (N= B:21, P:9)</td>
<td>6961.04 (2563.97)</td>
<td>6753.87 (1759)</td>
</tr>
<tr>
<td>P value</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>ESR (0-20) mm at the end of 1 hour (N= B:21, P:9)</td>
<td>9.70 (10.88)</td>
<td>13.52 (7.75)</td>
</tr>
<tr>
<td>P value</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Glucose, Fasting mg/dL (&lt;100) (N= B:21, P:9)</td>
<td>96.41 (10.39)</td>
<td>92.44 (9.72)</td>
</tr>
<tr>
<td>P value</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol mg/dL &lt;200 (N= B:21, P:9)</td>
<td>161.78 (20.27)</td>
<td>171.31 (31.23)</td>
</tr>
<tr>
<td>P value</td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>
Table 5: Comparative results between the two groups (Mann-Whitney U Test)

<table>
<thead>
<tr>
<th>Blood Parameters</th>
<th>Rank Sum BiosimCovex</th>
<th>Rank Sum Placebo</th>
<th>U</th>
<th>N BiosimCovex</th>
<th>N Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Triglycerides mg/dL (&lt;150) (N= B:21, P:9)</td>
<td>93.33 (28.82)</td>
<td>115.12 (80.41)</td>
<td>107.74 (59.08)</td>
<td>107.39 (89.15)</td>
<td>0.03</td>
<td>0.39</td>
</tr>
<tr>
<td>7 Bilirubin, total mg/dL (0.20-1.20) (N= B:21, P:9)</td>
<td>0.65 (0.23)</td>
<td>0.59 (0.28)</td>
<td>0.55 (0.23)</td>
<td>0.60 (0.24)</td>
<td>0.33</td>
<td>0.31</td>
</tr>
<tr>
<td>8 Alanine Aminotransferase (ALT/SGPT) U/L (9-52) (N= B:21, P:9)</td>
<td>27.13 (18.52)</td>
<td>26.83 (15.72)</td>
<td>23.98 (13.68)</td>
<td>25.20 (14.56)</td>
<td>0.42</td>
<td>0.43</td>
</tr>
<tr>
<td>9 Aspartate Aminotransferase (AST/SGOT) U/L (17-59) (N= B:21, P:9)</td>
<td>37.03 (8.32)</td>
<td>34.08 (9.54)</td>
<td>31.28 (5.39)</td>
<td>30.52 (5.18)</td>
<td>0.16</td>
<td>0.38</td>
</tr>
<tr>
<td>10 Alkaline Phosphatase U/L (38-126) (N= B:21, P:9)</td>
<td>98.12 (27.80)</td>
<td>98.63 (26.93)</td>
<td>101.50 (20.97)</td>
<td>92.48 (21.12)</td>
<td>0.49</td>
<td>0.19</td>
</tr>
<tr>
<td>11 Creatinine mg/dL (0.66-1.25) (N= B:21, P:9)</td>
<td>0.73 (0.19)</td>
<td>0.73 (0.19)</td>
<td>0.70 (0.12)</td>
<td>0.69 (0.14)</td>
<td>0.48</td>
<td>0.43</td>
</tr>
<tr>
<td>12 T3, Total ng/mL (0.7-2.04) (N= B:21, P:9)</td>
<td>1.37 (0.39)</td>
<td>1.28 (0.26)</td>
<td>1.42 (0.25)</td>
<td>1.18 (0.23)</td>
<td>0.13</td>
<td>0.02</td>
</tr>
<tr>
<td>13 T4, Total μg/dL (6.09-12.23) (N= B:21, P:9)</td>
<td>9.29 (2.30)</td>
<td>9.13 (2.14)</td>
<td>9.83 (2.07)</td>
<td>8.94 (1.73)</td>
<td>0.39</td>
<td>0.15</td>
</tr>
<tr>
<td>14 TSH μIU/mL (0.34-5.60) (N= B:21, P:9)</td>
<td>2.34 (2.06)</td>
<td>2.59 (3.70)</td>
<td>1.85 (2.12)</td>
<td>3.12 (4.25)</td>
<td>0.17</td>
<td>0.32</td>
</tr>
<tr>
<td>15 SAR-COV-2 Total Ab (&lt;1.0) (N= B:21, P:8)</td>
<td>170.74 (224.77)</td>
<td>380.03 (515.86)</td>
<td>346.18 (199.91)</td>
<td>367.88 (164.33)</td>
<td>0.06</td>
<td>0.45</td>
</tr>
<tr>
<td>16 CD 45 absolute /c.mm (1115-4009) (N= B:17, P:7)</td>
<td>2444.98 (622.61)</td>
<td>2577.47 (777.45)</td>
<td>2561.75 (850.58)</td>
<td>2901.34 (1138.23)</td>
<td>0.22</td>
<td>0.23</td>
</tr>
<tr>
<td>17 CD 4 LYM absolute count cells/μl (404-1612) (N= B:17, P:7)</td>
<td>894.67 (291.81)</td>
<td>1017.77 (367.64)</td>
<td>922.12 (477.90)</td>
<td>1095 (558.50)</td>
<td>0.11</td>
<td>0.27</td>
</tr>
</tbody>
</table>
arthritis, headaches, anxiety, and sleeplessness. As per the homeopathic method of using nosodes, BiosimCovex could be explored for conditions such as COVID-19, long-covid and the after-effects of COVID-19, besides its proven efficacy as prophylactic [6] against COVID-19 infection.

Phase 1 study with BiosimCovex had shown elevated immune markers such as IL-6 and CD4, suggestive of its prophylactic role full stop [4] BiosimCovex did not show a statistically significant increase in IgG and IgM antibodies in the vaccinated volunteers already having elevated levels of the antibodies at the baseline. This drug proving has shown an increase in COVID-19 IgG and IgM in two volunteers who had it negative at the baseline (p=0.065). CD4 count increase is also observed in this study which is comparable with our previous phase 1 trial finding, however, it was not statistically significant. We have further research findings with phase 2 and phase 3 studies with BiosimCovex. (The manuscripts are under review process.) Nosodes’ role as novel immunomodulators calls for further exploration. The study could not be made multicentric, and unlike, our previous phase 1 study we could not enroll the vaccine naïve
population which may be considered one of the limitations. Protocol deviation for the inability to conduct CD4 tests for 4 volunteers at the screening due to the deterioration of the sera, was documented. Further drug-proving could be done in different geolocations. The prescribing of BiosimCovex becomes possible based on the pathophysiology of the SARS-CoV-2 organisms and the symptomatology exhibited in this study.

CONCLUSION
BiosimCovex nosode developed during a pandemic condition has shown safe use and produced significant symptoms in the homeopathic drug proving helping its inclusion in the homeopathic literature.

ACKNOWLEDGEMENT
Our sincere thanks to the study volunteers, site investigator Dr. Samit Ghosh, Kolkata, and his team. Thanks to the Ethics Committee for the review. Thanks to Dr. Mukesh Srivastava for the statistical review and analysis.

CONFLICT OF INTEREST
The author is a developer of BiosimCovex nosode, having intellectual property rights on it. He had no role in the collection of the data.

REFERENCES


[17] Shah R. Effect of orally administered potentized capsaicin and dihydrocapsaicin in humans: a