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EFFICACY AND SAFETY OUTCOMES OF RANDOMIZED CONTROLLED OPEN LABEL TRIALS INVESTIGATING COMBINATION OF BIOWIN AND BIOWN IN COVID-19 PATIENTS

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ABSTRACT

COVID-19 is the second pandemic of the twenty-first century, with over a hundred million infections and over two million deaths too far. It's a new Coronaviridae strain called Severe Acute Respiratory Distress Syndrome Coronavirus-2 (SARS-CoV-2). It's the 7th known coronavirus to cause sickness in humans, following the Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Distress Syndrome Coronavirus-1 (SARS-CoV-1) (SARS). Most COVID-19 patients, particularly the elderly and immune compromised, experience flu-like symptoms such as a dry cough and a headache. Because current COVID-19 treatment choices are limited, especially for this vulnerable elderly group. Pneumonia, acute respiratory distress syndrome, septic shock, and cardiovascular symptoms are the most prevalent consequences. SARS-CoV-2 is spread mostly through respiratory droplets, which are released into the air when an infected person coughs or sneezes, or in the form of fomites on surfaces. Hand cleanliness, social distance, and personal protective equipment (such as masks) remain the most effective safeguards. Patient management includes supportive care and alternative measures, with a focus on maintaining respiratory functionas main criteria. Therapy with biowin and biown and its combination appear to be most promising and effective in COVID 19 patients. Additionally, accelerated vaccination efforts have taken place internationally, with several promising vaccinations being mass deployed. The nutraceutical supplementation in combating the COVID-19 has gained substantial attention, however to date little is known about the real-life consequences of impairment in this unique patient population. The aim of this study is to evaluate the safety, efficacy and quality of life (QOL) of deficits experienced by patients with COVID-19 infection. The study design is of prospective and a sample size of 50 with inclusion criteria of 18 to 58 years subjected were included in the study. A longitudinal web-based nationwide questionnaire survey of adults with COVID-19 was conducted to assess the qualityof life of patients. Impact on QOL was substantial with 96% of subjects reporting at least one of the defined deficits, and over 75% reporting various assessed parameters showing the impact on their quality of life. Many COVID-19 infected people are asymptomatic or experience moderate symptoms and recover without medical intervention. However, older people and those with comorbid hypertension, diabetes, obesity, or heart disease are at higher risk of mortality. We propose that normalcy could be restored using a combinational supplementation of Biowin and Biown in COVID19 patients. Therefore, it can be concluded the neutraceutical supplement therapy is the best option by improving the respiratory function and ultimately promoting survival in COVID-19 patients that develop severe forms of this devastating disease.

KEYWORDS: COVID-19; Coronavirus; Global & Public Health; Infectious Diseases; Pandemic.

INTRODUCTION

Millions of individuals throughout the world have been afflicted by the novel Corona virus disease outbreak. As of 09/Apr/2021, the WHO estimated that 133,552,774 confirmed cases of covid-19 illness had been documented over the world, with 2,894,295 deaths. Since January 2020, India has reported 13,060,542 confirmed Covid-19 cases, with 167,642 deaths.[1,3, 5,7] Health-care workers (HCWs), the elderly, and persons with co-morbidities are among those at increased risk.[4]

The corona virus pandemic is rapidly expanding and intensifying in all parts of the world, despite the availability of vaccines. Corona viruses are single-stranded RNA viruses that belong to the order Nirovirales, the family corona viridae, and the subfamily

corona virinae. Based on its genetic makeup, the corona virinae subfamily is further classified into three groups: alpha, beta, and gamma corona viruses. In RNA viruses, the corona virus has the biggest genome.[8,10] COVID-19 is caused by a new coronavirus that belongs to the beta coronavirus family and is closely related to the strains that cause SARS-CoV-2 and MERS (Severe Acute Respiratory Coronavirus Disease and Middle East Respiratory Syndrome). Spike, membrane, envelope, nucleocapsid protein, and viral RNA are the four structural parts that make up the new coronavirus virion structure. The receptor binding regions of the spike protein are frequently mutated. Corona virus is spread via respiratory droplets.[11] The virus is expected to adhere to the nasal epithelial lining and reproduce once breathed. The Angiotensin Converting Enzyme -2 [ACE-2] receptor is thought to be important for the virus's binding and penetration into the host cell. Endocytosis or membrane fusion is a characteristic of the virus's entry or penetration into the host cell. Once inside the host cell, the viral RNA binds to the host DNA and begins the replication process. Biosynthesis is another term for this. The following step is maturation, which involves the creation and discharge of viral particles. This virus mostly affects the respiratory system, and the severity of the illness varies from person to person.[12] Natural ingredients such as Curcuma longa and Allium sativum, as well as additions typically utilised in Indian cookery, are employed in the exploratory items. Curcumin, a plant product, has been shown to have a wide spectrum of antiviral action against a variety of viruses.[13,18] Garlic has previously been shown to have antiviral effect by preventing viral entrance into host cells and inhibiting RNA polymerase and reverse transcriptase.[14-17,19,20] As a result, a mixture of Curcuma longa and Allium sativum, as well as other additives, could be utilised to treat Covid 19 sufferers.

MATERIALS AND METHDS

This is a randomized, single centric, single arm, open label study to evaluate the efficacy and safety of BIOWIN/BIOWN in Covid-19 patients. This study aims to confirm the antivirus effectiveness of BIOWIN/BIOWN on coronavirus i.e., COVID 19 and to explore its potential use in the combating to the COVID 19 pandemics, wellbeing and quality of life.[21]

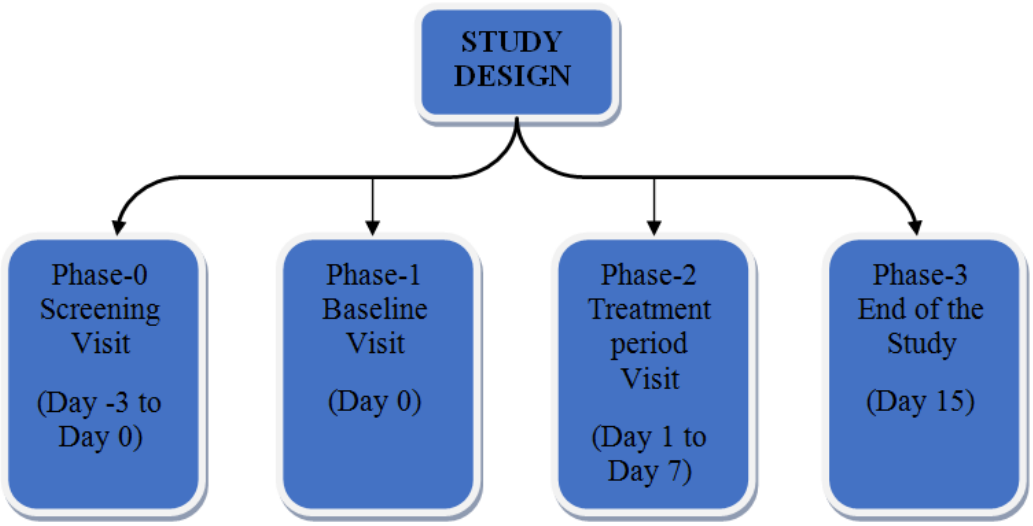

Figure 1: Study Design of Biowin study in Phase wise manner.

Study Design

During Phase 0 the subjects will undergo an evaluation to determine eligibility to participate in this study based on the assessment of the investigator during the study design (Figure 1). At Visit 0, for all subjects informed consent is obtained, demographics and medical history will be obtained. General physical examination including measurement of pulse, respiratory rate, temperature, blood pressure, weight and height and systemic examination of major systems namely cardiovascular system (CVS), central nervous system (CNS), gastrointestinal (GI) and respiratory system (RS) will be performed. Any gynecology related complaints will be recorded in the CRF. Covid 19 positive tests will be confirmed from RTPCR method. After the screening visit the subjects in Phase 1 study the baseline characteristics including physical examination and systemic examination of major systems namely cardiovascular system (CVS), central nervous system (CNS), gastrointestinal (GI) and respiratory system (RS).Any gynaecology related complaint will be recorded in the CRF. Anthropometric measurements - Height, weight, BMI & waist measurement will be recorded. Height will be measured using a measuring tape with a sliding head plate, a base plate and connecting rods marked with a measuring scale. Subjects will be asked to remove their shoes. One measurement will be taken, with the subject stretching to the maximum height and the head positioned in the head plate. The reading will be recorded to the nearest millimeter and results will be noted in source and case report form (CRF).

Weight will be measured using a calibrated weighing machine with a digital display. Subjects will be asked to remove their shoes and any bulky clothing. A single measurement will be recorded to the nearest 100g and results will be noted in source and case report form (CRF).

A total of 51 subjects, who satisfy the inclusion criteria, will be enrolled in the study. In order to define overweight or obesity, a measurement is required that allows for differences in weight due to height. A widely accepted measure of weight for height, the body mass index (BMI), defined as weight in kilograms divided by the square of the height in metres (kg/m2), will be used.

BMI = Weight (Kg) / Height (M) × Height (M)

BMI will be calculated for all the subjects for whom both a valid height and weight measurement will be recorded and results will be noted in source and case report form (CRF). Waist circumference measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest, using a stretch-resistant tape that provides a constant 100 g tension. The subjects will be asked to stand with feet close together, arms at the side and body weight evenly distributed. The subject should be relaxed, and the measurements should be taken at the end of a normal expiration. Each measurement should be repeated twice; if the measurements are within 1 cm of one another, the average should be calculated. If the difference between the two measurements exceeds 1 cm, the two measurements should be repeated. Results will be noted in source and case report form (CRF). Finally the midarm circumference is measured at the mid-point between acromion (top of shoulder) & olecranon (point of elbow).

Efficacy Assessments: The assessment of efficacy parameters were done using the following outcomes of the study.

1. Treatment satisfaction score
2. Treatment preference
3. Quality of life scores

Safety & Tolerability Assessments: They were assessed using various Clinical examination and vital signs. The AEs/SAEs if any arises it will be then recorded and documented. During the treatment period i.e., Phase 2- (Day 1- Day 7) the Subjects will be randomized and issued the test products for the entire study duration. Subjects will be instructed not to take vitamin or mineral supplements during the study.During this treatment period Subjects will be assessed on scheduled Day 7±4 days by covid tests.

The End of Study Visit or Final Visit i.e., (Day 15 ± 3 days) Phase 3 will be performed on Day 15±3 days after the Phase 2. The subjects will undergo efficacy and safety assessments at the site.

Inclusion Criteria

1. Ability to provide written and or e-consent (signed informed consent / consent given through Text message, WhatsApp or e-Mail are accepted (ICMR Guideline).
2. Participants of either gender of age between ≥18 to ≤60 years.
3. Subjects able to communicate effectively.
4. Documented COVID-19 infection observed by positive RTPCR for SARS-CoV-2 on the day of screening.
5. Adults having an asymptomatic mild form of COVID-19 infection.
6. Expressed interest and availability to fulfill the study requirements.
7. Good general health as determined by the discretion of investigator (vital signs (heart rate ≥60 to≤100 bpm; blood pressure systolic ≥80 mm Hg and ≤180 mm Hg; diastolic ≥ 50 mm Hg and ≤100 mm Hg), medical history, and physical examination).
8. For a female participant of child-bearing potential, planning to avoid becoming pregnant (use of an effective method of contraception or abstinence) from the time of study enrolment until the end of study.
9. Male subjects of reproductive potential: Use of condoms to ensure effective contraception with the female partner till the end of study.
10. Ability to schedule and attend visits for the duration of the study.
11. In the judgment of the Principal Investigator, able to comply with protocol requirements.

Exclusion Criteria

1. Contraindications or Hypersensitivity to study product.
2. History or presence of any medical condition or disease according to the discretion of the Investigator.
3. Subjects having history of asthma.
4. Subjects having history of cardiovascular diseases.
5. Subjects having history of diabetes (Type I or Type II) except other than the subject having the pre-diabetes condition with the fasting blood glucose between 100 to 125 mg/dl or random blood glucose > 140-199 mg/dl. 6.Subjects having BP above 180/100 or below 80/50 mmHg
6. Subjects having hyperthyroid/ hypothyroid disease.
7. Subjects with HIV Positive.
8. Subjects having history of high alcohol intake (2 standard drinks per day).
9. Subjects having history of psychiatric disorder that may impair the ability of subjects to provide written informed consent.
10. Any other condition that, in the opinion of the investigator, would adversely affect the subject's ability to complete the study or its measures.
11. Subjects participated in any clinical study within thirty (30) days prior to screening.

13. The administration of the investigational medicinal product is administered in the following manner:
14. One capsule of BIOWIN three times per day for 7 days after food with 150 ml of water. BIOWN - 8ml Liquid once daily for 7 days. Nothing has to be taken for half an hour after taking the capsules.

Composition of Investigational Product

The composition of the capsule and liquid is in the following ratio.

INGREDIENTS	QUANTITY
Curcuma Longa	200 mg
Allium Sativum	225 mg
Additives	+

Sample Size: A total of 50 subjects (assuming 80% power, level of significance 5%, superiority margin 5%, standard deviation 5% and dropout rate 10%) are required to evaluate the efficacy and safety of BIOWIN and BIOWN.

Statistical Analysis

Descriptive statistics such as n, mean, standard deviation, minimum and maximum will be used for summarizing the continuous variables. Frequencies and percentages will be computed for categorical data. Percentages will be calculated based on non-missing observations. Univariate correlations at baseline between values will be done. Non-parametric tests like Mann Whitney-U test or Wilcoxon signed rank test will be used to compare the changes between groups between Visit 0 and after Day 7 (Visit 1) of treatment. The statistical test will be done at 5% levelof significance (p>0.05).

RESULTS AND DISCUSSION

Demographics

A total of 50 subjects were participated in the study, of which 37 (72.55%) were male and 14 (27.45%) were female subjects (Figure 2). Baseline characteristics summarize the age and BMI of the subjects and depicted in Table 1. The mean age of subjects was found to be 41.41± 10.53. The mean BMI of subjects was 24.74± 1.47 and the minimum and maximum recorded BMI was 21.80 and 27.50. The mean height of subjects was 164.98±7.94 years. The mean waist of subjects was 88.16± 8.13 mean midarm of subjects was found to be 29.07± 2.55 (Figure 3).

The purpose of this study was to evaluate the safety, tolerability and efficacy of BIOWIN/BIOWN in Asymptomatic – Symptomatic mild Covid 19 patients. About 50 subjects fulfilled the eligibility criteria and were enrolled in the study and all 50 subjects completed the study till Day 15±2 and were evaluated for safety, tolerability and change in the quality of life. The primary objective was to evaluate the efficacy of BIOWIN/BIOWN in Covid 19 patients and the secondary objectives were: 1. To assess the safety and tolerability of BIOWIN/BIOWN in Covid 19 patients 2. To identify the change in quality of life by using health related quality of life questionnaire (HRQOL-SF-36). By the end of the study period, efficacy, safety and tolerability was established and no adverse events were reported during the study period. • The quality of life is reviewed using QOL Questionnaire and comparison for each question is presented in the tables.

Table 1: Summary of Demographics and Baseline Characteristics of Subjects during screening and baseline visit 1.The values are depicted in Mean± S.D (n=50).

Variable	Values		Total Number of Participants
	Screening Visit	Visit-1	
Age (yrs)	41.41±10.53	41.41±10.53	N=50
Gender			
Male	37(72.55%)	37(72.55%)	
Female	14(27.45%)	14(27.45%)	
Weight(kgs)	67.88±6.94	67.78±6.97	
Height(cms)	164.98±7.94	164.98±7.94	
BMI (Kg/m2)	24.74±1.47	24.74±1.47	
Waist (cms)	88.16±8.13	88.16±8.13	
Midarms (cms)	29.07±2.55	29.07±2.55	

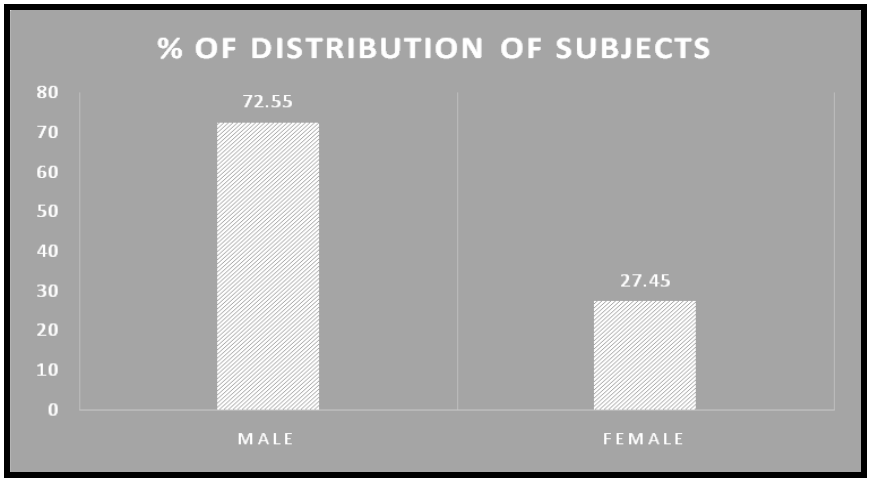

Figure 2: Gender Distribution of subjects recruited in the BIOWIN –BIOWN study.

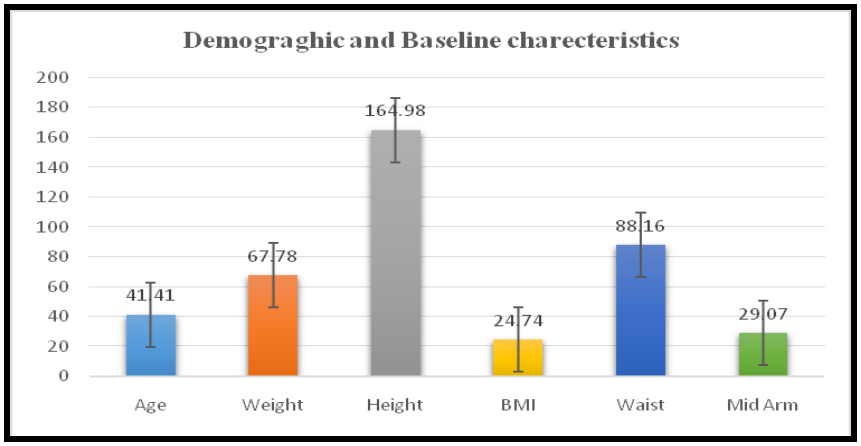

Figure 3: Demographics and Baseline characteristics of the subjects. Values expressed in Mean±S.D. (n=51)

Table 2: Summary of Vital parameters screened and assessed during the complete study duration. The values expresses as Mean± S.D (n=50)

Variable	Values (Mean± S.D)				
Vital Parameters	**Screening Visit**	**Visit-1**	**Visit-2**	**Visit-3**	**Visit-4**
Temperature (^{o}F)	98.81±1.32	98.98±0.28	98.98±0.21	98.40±0.70	95.99±2.57
Systolic Blood Pressure (mmHg)	127.70±6.20	127.45±6.37	127.56±6.43	125.22±6.57	126.12±4.82
Diastolic Blood Pressure (mmHg)	77.34±5.04	77.67±4.92	77.31±5.07	75.78±6.37	84.73±4.80
Respiratory Rate (br.pm)	17.18±1.29	17.20±1.29	17.18±1.30	16.16.±1.01	17.64±1.29
Pulse Rate (bpm)	81.16±3.94	80.90±4.12	80.71±4.15	78.63±4.49	82.24±4.71

The parameter are monitored and recoded the details of Temperature, Blood pressure, respiratory rate and pulse rate are recorded in screening visit and baseline visit. The mean temperature recorded in screening visit was found to be 98.81±1.32^{o}F. The mean systolic blood pressure recorded in screening visit was found to be 127.70±6.20mm of Hg. The mean Diastolic blood pressure showed in screening visit was 77.34±5.04mm of Hg. The mean respiratory rate recorded in screening visit was 17.18±1.29 breaths per minute. The mean pulse rate recorded in screening visit was 81.16±3.94. During visit 1-4 were the data was recorded and submitted to the concerned authorities for validation (Table 2, Figure 4).

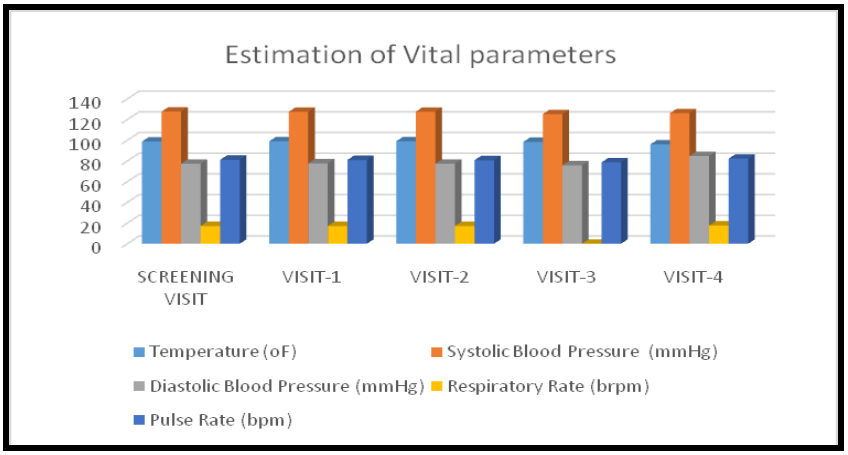

Figure 4: Estimation of vital Parameters of COVID19 patients visit wise (n=50).

CONCLUSION

COVID-19 has caught the globe off guard, and unlike other recent health catastrophes, it has disrupted the daily lives of people from all areas of life. An astounding number of RCTs were planned early in the COVID-19 pandemic to examine the clinical efficacy and safety of several antiviral medicines in the treatment of COVID-19 patients. The outcome areas covered in these clinical trials were extremely diverse, including both clinical and non-clinical measures of quality of life. The pandemic scenario requires researchers to register, plan, and implement a variety of measures for countering and preventing COVID 19's rapid spread. In terms of efficacy and safety, the current study indicates the need for modifications in the design of ongoing and future clinical trials. On an international level, the WHO continues to organise and promote evidence-based information and awareness. National efforts, critical employees, and entire communities are collaborating with the aforementioned bodies, as well as one another, to bring an end to the global health problem. Finally, developing safe and effective treatments is necessary to reduce the burden placed on patients, providers, and health-care systems around the world caused by COVID-19 patients by adopting natural supplements and other alternative therapies for the community's benefit. This study showed the product Biowin/Biown is safe and efficacious in treating Covid-19 patients.

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