A Randomized, Double-Blind, Placebo-Control Pilot Trial of Xuanfei Baidu Granules (XFBD), a Traditional Chinese Medicine (TCM), in Persons with COVID-19

Short name: XFBD001

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Protocol Chairs:

Peter Kuhn, PhD (Medicine, Biological Sciences and Engineering)

Anne Hamilton, PhD (Preventive Medicine)

Darcy Spicer, MD (Medicine) Medical Monitor

Anna Wu, PhD (Preventive Medicine)

Pharmacist:

Elizabeth Qi, PharmD

Biostatistician:

Cheryl Vigen, PhD.

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

AE	adverse event
ARDS	acute respiratory distress syndrome
CFR	Code of Federal Regulations
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CVD	cardiovascular disease
DRESS	drug reaction with eosinophilia and systemic symptoms
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
EKG	electrocardiogram
GCP	Good Clinical Practice
GI	Gastrointestinal
HTN	hypertension
ICU	Intensive care unit
ICF	informed consent form
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	intravenous
MERS	Middle East Respiratory Syndrome
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus 2
TCM	Traditional Chinese Medicine
XFBD	Xuanfei Baidu Granules
WHO	World Health Organization

SCHEMA

XFBD001

A Randomized Double-Blind Placebo-Control Pilot Trial of Xuanfei Baidu Granules (XFBD), a Traditional Chinese Medicine (TCM), in Persons with COVID-19

DESIGN

Pilot This is a randomized double-blind placebo-control pilot trial to document safety and efficacy endpoint assessments and to determine the feasibility of community recruitment and enrollment of symptomatic adult outpatients with COVID-19.

DURATION 12 weeks. Treatment will be for 14 days with 10 weeks of follow-up.

SAMPLE SIZE

Pilot 60 patients who start study treatment; approximately 30 participants in each of the two treatment arms (A and B). Participants who are randomized and who do not start study treatment will be replaced

POPULATION Symptomatic, outpatient, adults (≥18 years) with SARS-CoV-2 infection

STRATIFICATION Stratification will be by “high” versus “low” risk of progression to severe COVID-19 disease, where “high risk” is defined as a person age ≥60 years or having one of several specified comorbidities.

REGIMEN Participants will be randomized 1:1 individuals. Participants will receive either XFBD (10 g orally twice a day) for 14 days (Arm A) or a placebo twice a day for 14 days (Arm B).

1. HYPOTHESIS AND STUDY OBJECTIVES

1.1. Hypothesis

1.1.1. Xuanfei Baidiu granules (XFBD) will prevent hospitalization and death in persons with symptomatic SARS-CoV-2 infection.

1.2. Primary Objective

:

1.2.1. To document the feasibility of recruitment through community setting by assessment of the number of positive cases identified per week.

1.2.2. To document the proportion of patients who agree to participate as measured by enrollment and randomization.

1.2.3. To document the treatment emergent side effects and safety profile of the XFBD and placebo.

1.2.4. To document the rate of hospitalization or death within 42 days of enrollment in the XFBD and placebo treated groups.

1.3. Secondary Objectives

1.3.1. To document the effect of XFBD on Symptom Severity Score within 28 days of enrollment in the XFBD and placebo treatment.

1.3.2. To document the proportion of patients who are compliant taking greater than 90% of the test substance as measured by self-report

1.3.3. To document the proportion of patients who comply with symptom monitoring.

1.3.4. To document the proportion of patients who comply with repeated clinical testing.

1.3.5. To document the hospital-free days from enrollment to 42 days (number of days patient not in hospital).

1.3.6. To document cumulative incidence of serious adverse events, and adverse events leading to early discontinuation of XFBD or placebo.

1.3.7. To document cumulative incidence of grade 3 and 4 adverse events.

1.3.8. To obtain levels (detectable versus not detectable, and continuous on $\log_{10}$ scale) of SARS-CoV-2 RNA from nasal swabs at approximately days 1, 7 and 14 among a subset.

1.4. Exploratory Objectives

1.4.1. To document the rate of subjects tested as negative for SARS-CoV-2 at day 14.

1.4.2. To document the rate of housemate infection.

1.4.3. To document if XFBD changed the severity and duration of self-reported symptom experience of COVID-19.

2. INTRODUCTION

2.1. Background Threat

A novel pneumonia caused by a previously unknown betacoronavirus emerged in Wuhan, China, in December 2019. The virus is closely related to the severe acute respiratory syndrome coronavirus (SARS CoV), which led to an outbreak in 2003 causing the disease SARS, and has been named SARS-CoV-2. The human disease caused by SARS-CoV-2 is called COVID-19.

During the current SARS-CoV-2 outbreak, the incidence of known cases has rapidly increased such that, on January 5, 2020, there were 59 confirmed cases, 278 cases on January 20, 2118 cases on January 26, and more than 80,000 cases and 2700 deaths by February 25, 2020, according to various international health reporting agencies. As a result, on January 30, 2020, the International Health Regulations Emergency Committee of the World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern. On January 31, 2020, the US Department of Health and Human Services declared a public health emergency in the United States. As of July 14, 2020, there are more than 13 million cases of COVID-19 globally, including over 3.3 million cases in the United States (US), resulting in a total of over 574,000 deaths globally, with over 136,000 deaths in the US. Despite quarantine measures, SARS-CoV-2 continues to spread (1). Outbreak forecasting and modeling suggest that these numbers will continue to rise (2).

Global efforts to evaluate novel antivirals and therapeutic interventions to treat COVID-19 have intensified. There is currently no approved therapeutic agent to treat COVID-19 effectively. Therefore, there is an urgent public health need for the rapid development of novel interventions.

Virology

Coronaviruses (CoVs) are positive-sense, single stranded, enveloped RNA viruses, many of which are commonly found in humans and cause mild symptoms. Over the past two decades, emerging pathogenic CoVs capable of causing life-threatening disease in humans and animals have been identified, namely, SARS-CoV-1 in 2002-2003 and Middle East Respiratory Syndrome coronavirus (MERS-CoV) in 2012.

Disease Course

Once infection occurs, the clinical course is variable. Best current data suggests that fewer than 2.5% of infected persons will show symptoms within 2.2 days (CI, 1.8 to 2.9 days) of exposure, and symptom onset will occur within 11.5 days (CI, 8.2 to 15.6 days) for 97.5% of infected persons" (3) In most (~80%) cases, COVID-19 presents as a mild-to-moderately severe, self-limited acute respiratory illness with fever, cough, and shortness of breath. It remains unclear exactly what the rate of progression of COVID-19 is and what the predictors are for complications, including pneumonia, acute respiratory distress syndrome (ARDS), kidney failure, and death. It is also clear that older age, male sex, and comorbidities, including diabetes and hypertension, increase the risk for worse outcomes (Figure 2.1-1) (4-6). In a recent meta-analysis, the main clinical symptoms were fever (88.5%), cough (68.6%), myalgia or fatigue (35.8%), expectoration (28.2%), and dyspnea (21.9%). Minor symptoms included headache or dizziness (12.1%), diarrhea (4.8%), and nausea and vomiting (3.9%). Laboratory examinations showed that lymphocytopenia (64.5%), increase of C-reactive protein (CRP) (44.3%), increase of lactate dehydrogenase (LDH) (28.3%), and leukocytopenia (29.4%) were more common in those with COVID-19 (7).

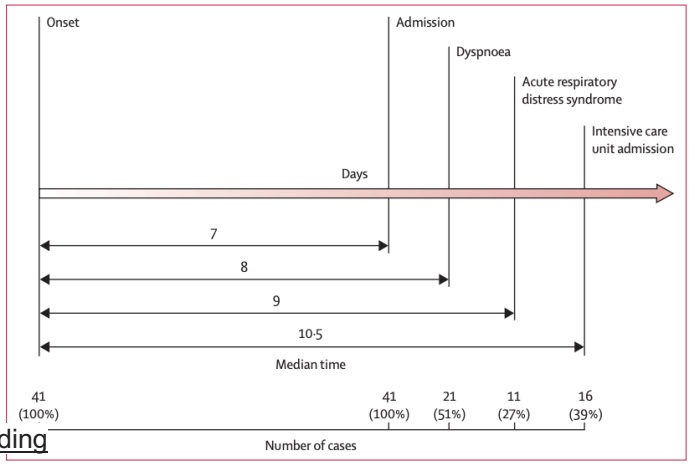


Figure 2.1: Timeline of COVID Disease Progression after Hospitalization.

Onset refers to onset of symptoms.

Shedding

Viral infections jump from host to host through a variety of pathways. CoVs do this through respiratory droplets. Understanding this shedding is important to understanding epidemic spread and how shedding relates to disease progression. The best evidence available now suggests that viral shedding, especially in upper respiratory secretions, is detectable around 2 days before symptoms develop in people and continues throughout the symptomatic phase. This shedding can be quite high during active disease and can continue for up to 37 days, with a quarter of persons still shedding at 3 weeks, as detected by nasopharyngeal swabs (4).

Biomedical Interventions

There are no approved treatments for COVID-19. Some agents have shown activity against other betacoronaviruses, such as lopinavir/ritonavir, chlorpromazine, nitazoxanide, gemcitabine, and dasatinib (9), and two agents have shown *in vitro* activity against the virus, including chloroquine and the adenosine analog remdesivir (10). There is no clinically proven antiviral treatment for SARS-CoV-2 infection, although a clinical trial of remdesivir (11) is underway in China and the US for severe pulmonary disease (12), and anecdotal evidence has been published about Hydroxychloroquine and Azithro (13).

TCM Interventions

From February 16th to 24th, the Huazhong University of Science and Technology team completed 9 autopsies of patients treated with non-invasive ventilation and died from COVID-19. The preprints are available. (14)

The autopsy reports showed that a gray-white viscous liquid appeared in the lung tissue samples, a white foamy mucus was found in the trachea, and a sticky jelly-like mucus was found in the bronchi of the right lung as well as significant and severe fibrinoid exudate in alveolar spaces. The authors suggest that COVID-19 pneumonia mainly results from inflammatory reactions characterized by deep airway and alveolar damage.

With this thick mucus occupying the alveoli, bronchi and pulmonary interstitium, respiratory function is significantly reduced. As a result, the patient's blood oxygen saturation can be reduced to 80% or lower. In comparison to the 95% and above oxygen saturation of healthy individuals, the patient is considered hypoxic.

Patients with hypoxia can be put on oxygen therapy to improve their oxygen saturation. However, if the patient's lungs are unable to complete the oxygen exchange, no amount of concentrated oxygen will improve their blood oxygen saturation. Unlike SARS patients with hyaline membranes in the alveoli, COVID-19 patients had mucous plugs in all the respiratory tracts, terminal bronchioles, and pulmonary alveoli. These mucus plugs in the distal respiratory tracts seemed to have played a part in the failure of sputum suction by bronchoscopy. (15)

After the autopsies, nearly 10,000 patients in *fangcang* (mobile cabin) hospitals specifically built for the COVID-19 outbreaks utilized traditional Chinese medicine with a coverage of 95% of all *fangcang* patients.

According to Chinese national statistics, 91.5% of confirmed diagnosed patients (74,187) were prescribed TCM. There were those who refused or were found unsuitable to use TCM. Hubei province alone accounted for 61,449 (90.6%) of patients who utilized TCM. Clinical observation showed that 90% of mild and moderate cases were successfully relieved of their symptoms and/or prevented progression into severe and critical condition. (16)

Currently, in Wuhan, the hospitalized patients with COVID-19 went from 60,000 two months ago to approximately 5000, and patients with severe illness decreased from 12,000 to approximately 1800. They had a period of 5 days without any increased new cases, critical cases, or deaths. (17)

TCM Background

Traditional Chinese medicine (TCM) takes a holistic approach in treating disease and categorizes health disorders from both its origin and the resulting symptoms. The origin of an illness can be from either cold or heat; the resulting symptoms can be cold-based (i.e. shivering, watery diarrhea, edema, cough with profuse, thin, and clear phlegm, etc.) or heat-based (i.e. fever, dry cough, sore throat, cough with thick, yellow phlegm, dysentery, etc.) The basis of treatment is to eliminate the original cause while treating the resulting symptoms concurrently.

Given the autopsy results and clinical presentation, in TCM theory, SARS-CoV-2 is seen as thriving in cold and damp weather while the disease COVID-19 consists of mostly warm-heat symptoms (i.e. fever, dry cough, heat induced cough with yellow phlegm). The TCM medicinals used in the treatment of COVID-19 mainly consist of heat-clearing and toxin-removing medicinals to reduce fever and clear away bacteria and viruses; cough-suppressing and phlegm-transforming medicinals to thin the phlegm so it is easier to expectorate; and lung-diffusing and pant-calming to soothe the tracheal smooth muscle and relieve symptoms of dyspnea.

The prescriptions for the prevention and treatment of COVID-19 were selected *Shang Han Lun*, or Treatise on Cold Damage Disorders, dated to the end of the Han Dynasty (220 AD). (18) In this treatise, all the diseases originate from cold, but the symptoms could either be cold-based or heat-based. This ancient treatise is a well-known reference for traditional Chinese medicine practitioners. Some of the botanical medicinals in the chosen prescriptions have also been isolated and developed into conventional medicine. (19)

For example, ephedrine can be isolated and extracted from ephedrae herba (麻黄 *mahuang*). Ephedrine is a stimulant that excites the sympathetic nervous system, constricting blood vessels to act as a pressor and bronchodilator. In traditional Chinese medicine, the function of ephedrae herba is recognized similarly and is mostly used to treat bronchial asthma and prevent asthma attacks. (20-22)

Another example is Glycyrrhizae radix et rhizoma (甘草 *gancao*), also known as Chinese liquorice, which is a medicinal and can also be used as a sweetener in food products. The medicinal function includes clearing heat (including the reduction of fever), removing toxins (anti-infection, anti-infective), loosening and transforming phlegm to eliminate, suppressing cough, easing tension, and relieving pain. This medicinal is used in the treatment of sore throat, oral mucosa ulcers, cough, palpitations, and pain.

Generally, the design of a TCM prescription takes into account the source of the illness, the resulting symptoms, the external environment, and the personal constitution of the patient. In the following delineation, this document focuses on the aspects of a broad application TCM in which the prescription is balanced to be less dependent on environmental and individual factors for general application.

Potential Risks of XFBD

XFBD contains ephedra herba, which has levels of ephedrine and pseudoephedrine. Both are known sympathomimetic agents, which can cause an increase in blood pressure and heart rate. The level of ephedrine and pseudoephedrine in each packet is at most 15mg or 30mg per day. In some over-the-counter (OTC) medication, the daily dose of pseudoephedrine can exceed 300 mg, which is 10 times the daily dosage of ephedrine and pseudoephedrine in XFBD.

XFBD also contains armeniacae semen amarum with levels of amygdalin, or laetrile. In TCM prescription theory and analysis, the levels of amygdalin are lower in the XFBD combination than in the plant armeniacae semen amarum alone. The level of armeniacae semen amarum in each packet is at most 80mg per day. Various studies have shown that 80mg is well below the level of toxicities manifesting.

Assessment of Potential Risks and Benefits

There is human clinical data on the XFBD prescription in Wuhan, China, with over 280 patients in clinical trials and approximately 6,000 patients in clinical care. In Wuhan, China, they saw a 50% reduction in progression of disease for patients with mild or moderate COVID-19 disease. (personal correspondence with Dr. Zhang Bo Li, dated Mar 31, 2020) The small risk with the use of the granules, including 30 mg of ephedrine per day, is amply outweighed by the potential for reducing serious consequences COVID-19 progression.

2.2. Rationale

At present, there is no specific antiviral therapy for COVID-19. Few treatment studies have been conducted because most human CoV strains cause self-limited disease, and care is supportive. After SARS-CoV-1 was identified in 2002-2003 and caused a large global outbreak, there was an increased interest in the development of specific therapeutic agents. SARS-CoV-1 patients were treated with corticosteroids, type 1 IFN agents, convalescent plasma, ribavirin, and lopinavir or ritonavir; except for

ribavirin, many of these agents have in vitro pre-clinical data that support their efficacy (42-57).

Given the lack of specific antiviral therapy for SARS-CoV-2 infection, and the known XFBD formulation, based on pre-clinical and small clinical studies, this randomized, placebo-controlled trial will evaluate the efficacy and safety of XFBD formulation in persons who have active SARS-CoV-2 infection and mild to moderate COVID-19 symptoms.

Why XFBD for COVID-19?
Xuanfei Baidu granules (XFBD) were developed by Dr. Zhang Boli, a member of the Chinese Academy of Engineering, and his team. They used this on the frontline in Hubei, Wuhan, under the direction of Dr. Zhang Boli and Dr. Liu Qingquan, Director of the Capital Medical University Beijing Hospital of Traditional Chinese Medicine.

Expert Recommendation on Usage: Suitable for mild, moderate, and severe cases. For critical cases, at doctor's discretion, based on the patient's condition.

Typically, in China, TCM prescriptions need to be boiled into a decoction and taken orally. For convenience, this TCM medicinal for COVID-19 control has been manufactured as a drink mix at the Tianjin Tasly Pharmaceutical Co., LTD (https://www.tasly.com), a well-established and leading TCM research and manufacture center to integrate technology and innovation to update the practice of TCM for human health.

The granules are already packaged into 10g packet per dose, 2 packets per day. These TCM packets have passed quality control tests for potency and standardization. To be taken in the morning and evening mixed into hot water to be taken 1 hour after a meal and 1 hour before or after conventional medicines:

Chinese	Latin	Amount (g) of crude medicinal for 1000g of final XFBD product	Source
麻黄 (A,B)	Ephedrae Herba	150	*Ephedra sinica* Stapf
苦杏仁 (A,B)	Armeniacae Semen Amarum	375	*Prunus sibirica* L.
生石膏 (A,B)	Gypsum Fibrosum	750	$CaSO_4 \cdot 2H_2O$
薏苡仁 (B,C)	Coicis Semen	750	*Coix Lacryma-jobi* L.yar.*mayuen*
苍术 (G)	Atractylodis Rhizoma	250	*Atractylodes chinensis* (DC.) Koidz.
广藿香 (G)	Pogostemonis Herba	375	*Pogostemon cabLin* (Blanco) Benth.
青蒿 (H)	Artemisiae Annuae Herba	300	*Artemisia annua* L.
马鞭草 (E)	Verbenae Herba	500	*Verbena Officinalis* L.
虎杖 (F)	Polygoni Cuspidati Rhizoma et Radix	750	*Polygonum cuspidatum* Sieb.et Zucc.
芦根 (C)	Phragmitis Rhizoma	750	*Phragmites communis* Trin.
葶苈子 (D)	Descurainiae Semen	375	*Descurainia sophia* (L.) Webb. ex Prantl.
化橘红 (H)	Citri Grandis Exocarpium	375	*Citrus grandis* (L.) Osbeck
甘草 (A,B)	Glycyrrhizae Radix et Rhizoma	250	*Glycyrrhiza uralensis* Fisch.

This prescription was derived from **four** previous prescriptions that have been in routine use in TCM over centuries and have been shown to be safe.

A. 麻杏石甘汤 Maxing Shigan Tang (麻黄 Ephedrae Herba, 苦杏仁 Armeniacae Semen Amarum, 石膏 Gypsum Fibrosum, 甘草 Glycyrrhizae Radix et Rhizoma) is a traditional preparation recorded from Shang Han Lun used to diffuse the lungs, calm panting, and clear heat. (23) The traditional

idea is cough and shortness of breath come from the lungs being congested or “unable to allow normal qi movement of the lungs.” (24) The ephedrae herba and gypsum fribrosum are a known pair to reduce fever and diffuse the lungs. (25) Ephedrae herba has been banned by the FDA in dietary supplements; however, the usage in TCM has not been restricted. (26) The concern stemmed from the various overdoses of epinephrine found in the plant *Ephedra sinica* Stapf in which the dried aerial parts are used in TCM. It has been found that the amounts of epinephrine and norepinephrine detected in the decoction of *maxing shigan tang* was much lower than in ephedrae herba alone. (27) Another common concern is the amount of amygdalin present in armeniacae semen amarum as it can be toxic in large amounts. There are a couple of studies showing that the concurrent usage of gypsum fibrosum and glycyrrhizae radix et rhizoma can decrease the amount of amygdalin content found in the prescription. (28-29) The studies showed that by combining the use of gypsum fibrosum and glycyrrhizae radix et rhizoma, the total levels of amygdalin are, in fact, lower than the levels if armeniacae semen amarum were used alone. These reports support the theory of TCM prescribing which uses specific combinations of medicinals to decrease toxicity and enhance efficacy. Rather than having direct bearing on acceptable amygdalin levels, these reports are intended to reinforce the efforts to mitigate toxicities and to show that the toxicity of using armeniacae semen amarum on its own is higher than that used in combination.

B. 麻杏薏甘汤 Maxing Yigan Tang (麻黄 Ephedrae Herba, 苦杏仁 Armeniacae Semen Amarum, 薏仁 Coicis Semen, 甘草 Glycyrrhizae Radix et Rhizoma) is a variation of the prescription above with coicis semen instead of gypsum fibrosum. Coicis semen, also colloquially known as Job’s tears, is used to disinhibit water and drain dampness (such as reducing edema), strengthen the spleen and stop loose stools, and resolve toxins and dissipate congestion. This medicinal is also a common food item in cereals, teas, and even distilled liquors.

C. 千金苇金汤 Qianjin Weijing Tang (芦根 Phragmitis Rhizoma, 薏仁 Coicis Semen, etc.) is a prescription used to transforms phlegm and clears the lungs. This prescription has been used in randomized controlled trials on its own or in combination with other prescriptions for the treatment of bronchiectasis, asthma, and community-acquired pneumonia. (30-31)

D. 葶苈大枣泻肺汤 Tinglidaozao Xiefei Tang (葶苈子 Descurainiae Semen / Lepidii Semen, etc.) is a prescription used to drain the lungs, reduce inflammation, disinhibit water, and calm panting. Descurainiae Semen / Lepidii Semen is commonly used in combination with glycyrrhizae radix et rhizoma and armeniacae semen amarum to treat symptoms of cough and shortness of breath. (32) This prescription, combined with maxing shigan tang as described above, also showed positive results in a small randomized controlled trial for elderly patients with community-acquired pneumonia. (33)

Other consideration to developing the prescription, additional medicinals:

E. Antibacterial and Antiviral Activity: 马鞭草 Verbenae Herba contains compounds that have shown to be inhibitory towards bacteria (such as gram-negative E.coli and gram-positive Staphylococcus aureus) and viruses such as hepatitis B virus (HBV). (34) This medicinal has a low toxicity profile but should not be used in pregnant patients. (35-36)

F. Microvascular Thrombosis: From the autopsy, patients had significant micro-clotting, or microvascular thrombosis. 虎杖 Polygoni cuspidti rhizoma et radix can help clear heat (such as reduce fever), suppress cough, transform phlegm, and dissipate stasis (such as dissolving blood clots). [personal correspondence with Dr. Zhang Bo Li dated March 31, 2020] Verbenae herba also has blood quickening and stasis dissipating actions that could help break up the micro-clots without having a full anticoagulating effect. (34)

G. Gastrointestinal: Both 藿香 Pogostemonis Herba and 苍术 Atractylodis Rhizoma help with gastrointestinal discomfort. Pogostemonis herba harmonizes the stomach (such as helping nausea, bloating, gastroprotective effects, etc.) and disperses damp. (37-38)

H. Transforming Phlegm: 化橘红 Citri grandis exocarpium can help the phlegm to resolve mucus plugs in the lungs. (39) This is dried pomelo peel, which can be found in foods such as teas and candies.

I. Clearing heat: 青蒿 Artemisiae Annuae Herba is better known as the source of artemisinin used for malaria. In TCM, artemisiae annuae herba is described mainly as an antimalarial agent but also a heat-clearing agent. The component artemisinin has varying degrees of anti-inflammatory and antiviral effects for DNA and RNA viruses. (40) It may also help regulate the immune system, such as reducing the release of proinflammatory cytokines. (41)

Wuhan Experience: Wuhan Jiangxia *Fangcang* Hospital used TCM prescriptions and other traditional methods (such as acupuncture, guasha, medicinal patches, etc.) in the treatment of COVID-19 while continuing the patient's previous conventional medicines for underlying health conditions. From February 14th to March 10th, the hospital treated a total of 564 patients with mild (71%) and moderate (29%) COVID-19. Upon hospitalization, approximately 30% of the patients had symptoms of fatigue and shortness of breath, while another approximately 40% had cough. Within the 14-day treatment and subsequent observation period, 482 patients recovered and were discharged. Among the patients admitted, none of their conditions progressed to severe or critical. It is of note that at Wuhan Jiangxia *Fangcang* Hospital, two main prescriptions with the addition of other TCM treatment modalities were used. The medical staff was also free of infection [personal correspondence with Dr. Zhang Bo Li dated March 31, 2020]

For the *Xuanfei Baidu* prescription, which was given to 273 patients, none of them progressed to severe or critical condition. 250 patients achieved two consecutive negative viral RNA tests in which the average time frame was about 11.02±3.59 days, with a 95% confidence interval (CI). 230 patients saw a significant improvement in their CT scans in about 13.13±4.20 days with a CI 95%. [personal correspondence with Dr. Zhang Junhua, dated April 28, 2020]

At another *fangcang* hospital which had 330 patients, TCM was not used or if used, in an unstandardized manner, and 32 patients (9.7%) of those patients progressed to severe or critical condition. Other *fangcang* hospitals that utilized TCM prescriptions also saw a decrease in patients' progression of disease to approximately 2-5%. [personal correspondence with Dr. Zhang Bo Li dated March 31, 2020]

Summary: Today, in China, mild and moderate cases are mainly treated with comprehensive TCM. The rate of mild or moderate cases progressing to severe was significantly reduced. Before the widespread usage of TCM, nationwide China saw a progression of disease of about 10% of their mild/moderate cases while after TCM utilization, the percentage dropped to 2-5% depending on the hospital. Overall, they saw an improvement in clinical symptoms. [see personal correspondence with Dr. Zhang Bo Li dated March 31, 2020]. Due to the challenges of the rapidly evolving outbreak, these are clinical observations and not evidence from a controlled study.

Preclinical Studies of XFBD

Tianjin University of Traditional Chinese Medicine conducted an acute toxicity study for XFBD in mice at the concentrations of 91.39 g/kg, 114.24 g/kg, and 142.8 g/kg by single gavage followed by a 14-day observation. The data showed that mice given 142.8 g/kg appeared to be in prone positions with movement reduction, which resolved within 4 hours. The female mice in 142.8 g/kg group had soft or loose stools, but the mice recovered on the 4th day. No significant differences were found in the body weight between mice in the administration group and control group when measured on the 1st, 3rd, 7th, and 14th day after administration. No deaths were observed in the 14 days. After gross anatomical observation, there were no apparent abnormalities found in mice from either group. Therefore, we conclude that the maximum tolerated dose of XFBD given by single gavage in mice should be more than 142.8 g /kg (equivalent to 84 times of the clinical dosage). [personal correspondence with Dr. Zhang Junhua, dated Apr 28, 2020]

Long term toxicity studies are ongoing and will be updated as data becomes available.

While all medicinals in the XFBD are widely used and within the appropriate dosing range, formal toxicity studies have not been conducted. Symptom comparisons and toxicities will be one part of both the pilot and the complete trial.

XFBD Availability

This prescription is traditionally decocted in a pot from crude medicinals. However, it is now being manufactured with quality control mechanisms in place to make RCTs feasible. This TCM medicinal for COVID-19 control has been manufactured as a drink mix at the Tianjin Tasly Pharmaceutical Co., LTD (https://www.tasly.com). Tianjin Tasly Pharmaceutical Co., LTD, is a well-established and leading TCM research and manufacture center to integrate technology and innovation to update the practice of TCM for human health. XFBD is currently being manufactured for clinical use. XFBD had been used in clinical trials of over 280 patients and is being used in clinical care for approximately 6,000 patients. [personal correspondence with Dr. Zhang Junhua, dated Apr 28, 2020]

Mitigation of Risk from XFBD

XFBD contains ephedrae herba with levels of ephedrine and pseudoephedrine. In TCM prescription theory and analysis, ephedrine and pseudoephedrine levels are lower in the XFBD combination than in the ephedrae herba plant alone. The ephedrine and pseudoephedrine levels in each packet is at most 15mg or 30mg per day. In some over-the-counter (OTC) medication, the daily dose of pseudoephedrine can exceed 300 mg, which is 10 times the daily dosage of ephedrine and pseudoephedrine in XFBD. However, to mitigate the potential risk, patients with uncontrolled blood pressure and heart disease will be excluded.

The ephedrine and pseudoephedrine levels in each packet is at most 30mg per day. (58) In some over-the-counter (OTC) medication, the daily dose of pseudoephedrine can exceed 300 mg, which is 10 times the daily dosage of ephedrine and pseudoephedrine in XFBD. In one study, they found the mean lethal dose (LD50) of ephedra alkaloids, which would include ephedrine and pseudoephedrine, in mice to be 610 mg/kg taken orally. There were no abnormal clinical symptoms observed in mice administered 289 mg/kg ephedra alkaloids. (59)

Amygdalin (AMG), or laetrile, contained in XFBD averages to be 36.7-39.3 mg, or less than 40 mg, per packet. (60) Taken twice a day, the total daily dose is around 80 mg. In the 2015 Chinese Pharmacopeia, the accepted amount of armeniacae semen amarum is 5-10 g per day in which amygdalin levels cannot be above 24 mg/g. Amygdalin levels for armeniacae semen amarum are tested for before the medicinal can be sold on the market. (Appendix 3) Therefore, the acceptable limit of amygdalin is 120-240 mg per day. XFBD contains less than 80 mg of amygdalin per day. (Appendix 4)

An in vivo study was conducted with rabbits being directly fed ground up apricot seeds as well as having an extract that was injected intramuscularly. The rabbits were taking 60 and 300 mg/kg of ground up apricot seeds, which is equivalent to 3.12 mg AMG/kg and 15.6 mg AMG/kg respectively, for 14 days. After 14 days, the researchers found no significant changes between the experimental groups, 60 and 300 mg/kg of ground up apricot seeds, and control groups with no apricot seeds. All the biological marker changes were non-significant. (61) This would be equivalent to a 60kg adult taking 3.6 g or 18 g of AMG containing apricot seeds per day, which would be 187.2 mg and 936 mg of AMG respectively. Both doses are significantly higher than the daily amount in XFBD.

In the Journal of Chinese Traditional Patent Medicine in 2003, Xiu et al. (62) found oral administration to have greater toxicity risks since intestinal microorganisms are the major converter of amygdalin to hydrocyanic acid. If humans ingest 4 g of amygdalin per day for half a month or receive injection intravenously for one month, common toxicities such as those to the digestive system as well as cardiovascular abnormalities will be observed. Reducing the daily dose to 0.6 to 1 g can prevent these toxicities. The 80 mg of amygdalin per day in XFBD fits within these parameters.

Over the years, various cases of cyanide toxicity due to oral ingestion of AMG have been reported. Many of these cases were of people ingesting large amounts of apricot kernels or other amygdalin containing seeds all at one time. The people in these cases had typically ingested AMG containing seeds above the acceptable amount (i.e. 15 g of apricot kernels which is more than the 5-10g recommended dose from the Chinese Pharmacopeia). (63)

In Wuhan, the TCM experts utilizing this prescription cited no adverse effects with patients with underlying conditions (such as diabetes, hypertension) or any adverse interactions with the patients' long term conventional medicines. [personal correspondence with Dr. Zhang Bo Li dated March 31, 2020] However,

due to the nature of introducing any new medication, some experts cite potential concerns for those with congestive heart disease, cancer, end-stage liver failure as well as patients on dialysis. Patients with uncontrolled underlying conditions will be excluded.

Justification for Dose

Xuanfei Baidu prescription was developed from four old prescriptions: Maxing Shigan Tang, Maxing Yigan Tang, Qianjin Weijing Tang, and Tinglidaozao Xiefei Tang. Each of these has a long history of being used for clinical symptoms relevant to COVID-19. For example, since the Jin Dynasty, Maxing Shigan Tang has been documented to be used for persisting fever, cough, panting (shortness of breath), and chest pain. (63) In modern times, the same prescription is prescribed for bronchial asthma, acute and chronic bronchitis, and pneumonia. (68)

As SARS-CoV-2 is a relatively new virus, there is limited peer reviewed literature on an appropriate dosing regimen beyond the clinical data obtained in Wuhan, China. Of the 273 patients who received Xuanfei Baidu at Wuhan Jiangxia Fangcang Hospital for 2 to 3 weeks, 250 patients achieved two consecutive negative viral RNA tests in which the average time frame was about 11.02±3.59 days; and 230 patients showed a significant improvement in their CT scans in about 13.13±4.20 days. Based on these observations, Dr. Zhang Boli, a member of the Chinese Academy of Engineering who worked on the frontlines of Wuhan's outbreak, determined the dosing regimen to be two weeks. [personal correspondence with Dr. Zhang Junhua, dated April 28, 2020] Currently, Dr. Zhang Boli and colleagues have difficulty repeating this trial because of the low number of COVID-19 cases in China.

As this proposed trial is a no-contact community based clinical trial for an infectious disease, there will be substantial difficulties in monitoring systemic concentrations. The amount of ephedrine and pseudoephedrine is 30 mg per packet which is 60 mg per day. This dose is within the same boundaries as most over-the-counter pseudoephedrine medications. The 80 mg daily dose of amygdalin is also substantially lower than the dosage that manifest in toxicities. (63)

The individual ingredient doses present in XFBD are within acceptable dosing range and report no toxicity under normal usage. (Chinese Pharmacopeia Vol 1, 2015).

Justification for the Control Arm

Considering the heterogeneity of disease progression in those with COVID-19, it is extremely important that this study include a control group. To this end, this trial will have a double-blind placebo control arm to best determine the efficacy and safety of XFBD in the outpatient setting for persons with COVID-19.

Justification for Placebo Controlled Design

There is public interest in several putative therapeutic agents for COVID-19. A well-powered placebo-controlled trial will provide the best opportunity to recruit outpatients with COVID-19 and rigorously evaluate the safety and efficacy of this agent.

Justification for Disease Severity Included

In the recent experiences in China cited above, TCM was utilized among patients with mild to moderate Covid-19 and progression to severe disease diminished. Demonstration that XFBD reduces the rate of such progression and the need for hospitalization in a randomized control trial ting as proposed here would be meaningful. This pilot trial is to demonstrate the feasibility of recruiting and enrolling patients with mild to moderate COVID-19. The severity categorization is summarized in table 3.

Table 3. Baseline Severity Categorization

Asymptomatic SARS-CoV-2 infection

- Positive testing by standard RT-PCR assay
- No symptoms

Mild COVID-19

- Positive testing by standard RT-PCR assay
- Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of

breath or dyspnea
- No clinical signs indicative of Moderate, Severe, or Critical Severity

Moderate COVID-19
- Positive testing by standard RT-PCR assay
- Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion
- Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥ 20 breaths per minute, saturation of oxygen (SpO2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute
- No clinical signs indicative of Severe or Critical Illness Severity

Severe COVID-19
- Positive testing by standard RT-PCR assay
- Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress
- Clinical signs indicative of severe systemic illness with COVID-19, such as rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, SpO2 ≤ 93% on room air at sea level or respiratory PaO2/FiO2 ratio < 300
- No clinical signs indicative of for Critical Severity

Critical COVID-19
- Positive testing by standard RT-PCR assay
- Evidence of critical illness, defined by at least one of the following:
  - Respiratory failure defined based on resource utilization requiring at least one of the following: Endotracheal intubation and mechanical ventilation, oxygen delivered by high flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, Extracorporeal membrane oxygenation (ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)
  - Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors)
  - Multi-organ dysfunction/failure

For this trial patients with SARS-CoV-2 infection (i.e., positive testing by standard RT-PCR assay) without symptoms will not be randomized unless they develop symptoms with 14 days of viral testing. Patients with severe or worse Covid-19 will be excluded.

Justification for Age Restriction

Children and adolescents will not be included in this trial. Initial information about the epidemiology of COVID-19 indicates that the overwhelming burden of severe disease occurs among older adults, especially those with comorbidities. Given significant gaps in knowledge regarding SARS-CoV-2 infection in this population and a low incidence of severe morbidity/mortality in children, the risk/benefits do not warrant the inclusion of this population into this trial at this time.

The elderly above the age of 75 are excluded in consideration of the higher possibility of multiple underlying conditions that may or may not be controlled at the time of infection. While the trials done in Wuhan saw no interaction with maintenance medications, the presence of multiple medications may have increased risk and complications that are not yet studied. Future trials will address this cohort of patients.

Justification for Comorbidity Restrictions

Individuals with multiple comorbidities have greater risks present, and there is no available data for patients with multiple comorbidities. Individuals with uncontrolled underlying conditions also present with more risk and complications. Without safety data available for these populations, these patients are to be excluded.

Justification for Vaccinated Individuals

The phase 3 clinical trial data for both available messenger RNA (mRNA) vaccines showed efficacy in preventing severe symptomatic COVID-19 disease. The mRNA-1273 (Moderna) vaccine showed 94.1% efficacy at 14 days after the second dose (64) while the BNT162b2 (Pfizer) vaccine showed 95% efficacy at 7 days after the second dose. (65) Out of 36,659 California healthcare workers, 379 persons tested positive for SARS-COV-2 at least 1 day after vaccination, and 270 (71%) of those persons tested positive within the first 2 weeks of receiving the first dose. (66). There was no regular testing after the vaccination, therefore, it is safe to assume those who were reinfected experienced certain symptoms. In Los Angeles, about 62% have gotten their first dose and 53% have received both. (67) With any level of probability for symptomatic reinfection, the vaccinated population are still eligible for XFBD.

3. STUDY DESIGN

The pilot phase is a double-blind, placebo-controlled randomized component designed to document safety and efficacy endpoint assessments and to determine the feasibility of recruitment and enrollment of symptomatic, community dwelling, adult, outpatients with COVID-19 as well as patient compliance with the protocol.

The pilot phase will enroll a total of 60 participants (30 in each arm). Participants will be followed for 14 days on treatment with an additional 10 weeks off treatment. Participants who do not start study treatment will be replaced. Participants will be randomized 1:1 as individuals. Participants will receive either XFBD (10 g orally twice a day) for 14 days or a placebo twice a day for 14 days.

3.3 Stratification

Randomization will be stratified by “high” versus “low” risk of severe disease, where “high” risk is defined by any of the following:

- Patients aged 60 years and older
- Patients having at least one of the following conditions under control:
  - Chronic lung disease including pulmonary fibrosis, COPD, pulmonary hypertension, moderate to severe asthma
  - Immunocompromised status due to disease (for example, those living with HIV with a CD4+ T-cell count of <200/mm^3)
  - Immunocompromised status due to medication (for example, persons taking 5 mg or more of prednisone equivalents a day, cancer therapies)
  - Solid organ transplant, hematologic stem cell transplant, rheumatological disease or inflammatory bowel disease on immunosuppressants
  - Severe obesity (body mass index [BMI] >40; may be based on self-report of height and weight)
  - Hypertension requiring treatment by more than one agent.
  - Cardiovascular disease including coronary artery disease, congestive heart failure, valvular heart disease
  - Diabetes
  - Chronic kidney disease including stage 3-4 CKD.
  - Chronic liver disease including cirrhosis, autoimmune hepatitis, uncontrolled hepatitis.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Recruitment

4.1.1 Recruitment

This trial will recruit study participants through community health care sites and programs (Appendix 2 that lists the initial site) that are performing SARS-CoV-2 testing of symptomatic patients. The initial site is based in Los Angeles County.

4.1.2 Race and Ethnicity

Every effort will be made to maximize recruitment of a diverse participant population. The

race/ethnicity of Los Angeles County is: 47.9% Hispanic; 26.7% White; 8.27% Black; 14.2% Asian. For this pilot study, this should reasonably ensure a diverse population.

4.2 Inclusion Criteria

4.2.1 Participant provides informed consent prior to initiation of any study procedures.

4.2.2 Individual 18 to 75 years of age.

4.2.3 Documentation of confirmed active SARS-CoV-2 infection, as determined by an FDA authorized molecular test conducted at any US clinic or laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent from any respiratory specimen collected <96 hours prior to study entry.

4.2.4 Mild or Moderate COVID-19 experiencing at least one SARS-CoV-2 infection symptom including:

Mild Covid-19

- Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea

Moderate Covid-19

- Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion
- Presence of clinical signs consistent with moderate illness with COVID-19, such as respiratory rate ≥ 20 breaths per minute, saturation of oxygen (SpO2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute from a health care encounter within 48 hours.

4.2.5 Agrees to not participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 during the study period up until reaching hospitalization or 28 days, whichever is earliest.

4.2.6 Agrees to not utilize TCM outside of this study.

4.2.7 Willing to be randomized to XFBD and placebo control arm for 14 days, and followed up to 12 weeks.

4.2.8 Willing to comply with the study related questionnaires, procedures and measurements.

4.2.9 Will to not become pregnant during the 14 days of test substance ingestion using appropriate accepted methods of contraception. Acceptable methods of contraception include: postmenopausal 1 year of amenorrhea and over 50 years of age; prior tubal ligation or hysterectomy; or barrier contraception using condom or diaphragm plus spermicide.

4.2.10 Able to provide the identity of their health care provider or health system clinical care entry information.

4.2.11 Able to utilize telephone and telehealth platform to comply with the study related questionnaires, procedures and measurements. Established during the recruitment process.

4.2.12 Able to speak and communicate in English, Spanish, Mandarin Chinese or Cantonese.

4.3 Exclusion Criteria

4.3.1 Need for hospitalization.

4.3.2 Severe or Critical COVID-19:

Severe COVID-19

- Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress
- Clinical signs indicative of severe systemic illness with COVID-19, respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, SpO2 ≤ 93% on room air at sea level or respiratory PaO2/FiO2 < 300

Critical COVID-19

- Evidence of critical illness, defined by at least one of the following:
- Respiratory failure defined based on resource utilization requiring at least one of the following: Endotracheal intubation and mechanical ventilation, oxygen delivered by high flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)
- Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors)
- Multi-organ dysfunction/failure

4.3.3 Positive SARS-CoV-2 molecular test in the absence of Covid-19 symptoms. However if patients develop symptoms within 14 days of the positive test and fulfil all other enrollment criteria, they are eligible for participation.

4.3.4 Receiving the following classes of agents found in 5.4.1. Prohibited Medications

4.3.5 Use of drugs for anti-SARS-CoV-2 treatment including remdesivir, baricitinib, lopinavir/ritonavir fixed dose combination, ribavirin, chloroquine, hydroxychloroquine, and azithromycin, dexamethasone, bamlanivimab, casirivimab plus imdevimab convalescent plasma, or participation in a clinical trial involving any of these drugs whether for treatment or prophylaxis.

4.3.6 Participating in a study where co-enrollment is not allowed.

4.3.7 Known allergy/sensitivity or any hypersensitivity to components of XFBD

4.3.8 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

4.3.9 Has known prior kidney disease.

4.3.10 Has known cirrhosis, acute liver disease or uncontrolled chronic liver disease.

4.3.11 Has known severe coronary artery disease.

4.3.12 Has known narrow angle glaucoma.

4.3.13 Has greater than two or a single uncontrolled underlying comorbid condition including cardiovascular disease (coronary artery disease, heart failure, valvular heart disease), hypertension, diabetes, chronic lung disease, chronic kidney disease, chronic liver disease, immunocompromised (HIV or daily users of more than 5 mg/day of prednisone), prior organ transplant.

4.3.14 Fulfills the FDA EUA criteria of at high risk for progressing to severe COVID-19. This includes high-risk individuals specified in the EUA who meet at least one of the following criteria: Body mass index (BMI) ≥35; Chronic kidney disease; Diabetes mellitus; Immunocompromising condition/immunosuppressive disease; Currently receiving immunosuppressive treatment; Aged ≥65 years; or Aged ≥55 years and have: Cardiovascular disease, or Hypertension, or Chronic obstructive pulmonary disease/other chronic respiratory disease. If the patient is not able to receive the EUA agent because of unavailability this exclusion may be waived.

4.3.15 Women who are currently pregnant or breastfeeding.

4.4 Co-enrollment Guidelines

For specific questions and approval for co-enrollment in other studies, the coordinator should contact the protocol team via e-mail or phone prior to enrollment.

5. STUDY TREATMENT

5.1 Regimens, Administration, and Duration

Participants will be randomized to receive one of the following two regimens:

ARM A:
Days 1 - 14: XFBD (administered as 1 packet of granules dissolved in warm water) orally twice daily for 14 day, 1 hour after food in the morning and at night with at least 8 hours in between doses

ARM B:
Days 1 - 14: Placebo (administered as 1 packet of granules dissolved in warm water) orally twice daily for 14 day, 1 hour after food in the morning and at night with at least 8 hours in between doses

5.2 Study Product Formulation and Preparation

5.2.1 XFBD: Supplied as 10 g granules in plastic packaging. Store at controlled room temperature 20-25°C.

5.2.2 Placebo: Supplied as 10 g granules in plastic packaging visually matching the XFBD. Store at controlled room temperature 20-25°C.

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition/Distribution

XFDB are manufactured by Tianjin Tasly Pharmaceutical Co., LTD (https://www.tasly.com), a well-established TCM research and manufacture center to integrate technology and innovation to update the practice of TCM for human health.

5.3.2 Study Product Accountability
A dedicated study team member will operate an accountability and dispensing log. The drug will be secured and stored in a safe location.

5.4 Concomitant Medications

Whenever a concomitant medication is initiated or a dose changed, investigators must review the concomitant medication's and study agent's most recent package insert, Investigator's Brochure to obtain the most current information on drug interactions, contraindications, and precautions.

5.4.1 Prohibited Medications

5.4.1.1 Non-study TCM prescriptions
5.4.1.2 Ephedrine and pseudoephedrine products
5.4.1.3 MAO inhibitors, ergot derivatives, digoxin, Artemether, Lumefantrine
5.4.1.4 Strong inducers or inhibitors of CYP3A and other CYP enzymes, including apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort, boceprevir, cobicistat, danoprevir

and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole, bupropion, fluoxetine, paroxetine, quinidine, terbinafine, fluconazole, fluvoxamine, ticlopidine, ciprofloxacin, enoxacin, gemfibrozil, clarithromycin, idelalisib, nefazodone, nelfinavir, tizanidine, repaglinide, tolbutamide, s-warfarin, lansoprazole, omeprazole, desipramine, dextromethorphan, nebivolol, midazolam, triazolam, clopidogrel, phenobarbital, theophylline

5.4.2 Potential Drug-Drug Interactions

Medicinal	Latin	Drug-Drug Interactions (DDI)	Special Consideration
麻黄	Ephedrae Herba	**Do Not Use Together:** • MAO Inhibitors - ephedrae herba's main component is ephedrine and MAO inhibitors may enhance the hypertensive effect of ephedrine. • Ergot Derivatives - ephedrae herba's main component is ephedrine and ergot derivatives may enhance the hypertensive effect of ephedrine • Inhalation Anesthetics - ephedrae herba's main component is ephedrine and inhalation anesthetics may sensitize the heart to arrhythmic actions of ephedrine. • Digoxin[a] – ephedrae herba's main component is ephedrine and digoxin may sensitize the heart to arrhythmic actions of ephedrine **Potential DDIs:** • Calcium channel blocker • Angiotensin II Antagonists • Alpha-/Beta-blockers • Alpha-/Beta-agonists • Guanethidine (NE blocker) • Methyldopa • Clonidine • Theophylline • Phenobarbital	Renal failure – ephedrine is mostly excreted renally
苦杏仁	Armeniacae Semen Amarum	**Potential DDIs:** • CNS depressants (benzodiazepines, barbiturates)	
生石膏	Gypsum Fibrosum	**Potential DDIs:** • Tetracyclines • Levodopa • Digoxin	
苍术	Atractylodis Rhizoma		Increases CYP3A4 activity (69)
广藿香	Pogostemonis Herba		
青蒿	Artemisiae Annuae Herba	**Do Not Use Together:** • Artemether – enhances toxic effect of Artemisinin • Lumefantrine – enhances toxic effect of Lumefantrine **Potential DDIs:** • Dapsone	Increases CYP3A4 and 2B6 activity

马鞭草	Verbenae Herba		
虎杖	Polygoni Cuspidati Rhizoma et Radix	Zidovudine – decreases clearance, increases toxicity (68)	Long term, large dosage can reduce synthesis of coagulation factors in the liver
芦根	Phragmitis Rhizoma		
葶苈子	Descurainiae Semen		
化橘红	Citri Grandis Exocarpium		Inhibits CYP3A4, 1A2 (70)
甘草	Glycyrrhizae Radix et Rhizoma	**Potential DDIs:** (68) • Diuretics (other than potassium-sparing ones) • Digoxin • Aspirin • Reserpine • Glucocorticoid • Sulfonamides • Theophylline	Medications metabolized by the liver – induces liver enzymes and can accelerate the metabolism of liver metabolized drugs Induces CYP3A4, 2B1, 1A2

[a] This has been theorized due to the mechanism of action for ephedrae herba and digoxin. However, no clinical study has been conducted to confirm the interaction.

Drugs that are listed above as “Do Not Use Together” are prohibited and patients receiving such agents are ineligible for study participation. Given the short duration of administration of the XFBD patients receiving drugs listed as “Potential DDIs” are eligible, but, in the event of adverse events, such a DDI will be considered by the medical monitor in consultation with the patients’ health care provider.

6. CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations (SOE)

Table 6.1

Evaluations	Screening[a]	Entry	Post Entry Evaluation								Premature Study Discontinuation
		Day 0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28	Day 42	Week 12	
Visit Location	Remote										
Informed Consent	X										
Documentation of Positive SARS-CoV-2 Molecular Test	X										
COVID-19 Symptom Screen	X										
Medical/Medication History Form	X										
Identify health care providers	X										
Identify Secondary Contacts[b]	X										
Study Kit Dispensed[c]		X									
Self-administration of Study Agent PO BID		X	X	X	X	X					
Confirmation of First Dose			X								
Distribution of Symptom Self Reporting Application		X									
Daily study questions via study App or phone			X	X	X	X	X				X
Adverse Events Tracking					X	X	X	X			
Review of Adherence				X	X	X					X
At home specimen collection for SARS-CoV-2 viral RNA testing			X		X	X					
Study Endpoint Determination			X	X	X	X	X	X	X	X[d]	X

[a] Participants must begin study treatment within 96 hours of onset of their first symptom. [b] To enable updating data in the event the participant is hospitalized or dies. [c] Study kit contains: Copy of informed consent, Information about the study, Instructions on study procedures, QR Code and Internet link for Symptom Self Reporting Application, Study agent, Instructions on what to do if they have worsening symptoms/become hospitalized [d] Direct contact and medical record review.

6.2 Study Enrollment Procedures

6.2.1 Recruitment and Informed Consent

This trial will recruit study participants through community health care sites and programs (Appendix 2 that lists the sites) that are performing SARS-CoV-2 testing of symptomatic patients.

It is expected that potential participants will be referred to this trial immediately upon SARS-CoV-2 diagnosis by FDA approved nucleic acid testing.

At the time of disclosure of the SARS-CoV-2 positive test results by the health care provider, the patient will be informed about the study opportunity and provided with the study contact information. If agreed to by the patient, the health care provider will directly provide the trial coordinating office with the patients contact information. In this case, the health care provider will document in the patients EHR their consent to provide the trial staff with their contact information.

The trial office will operate from 8:00 AM to 6 PM seven days per week to accept calls from these SARS-CoV-2 positive patients inquiring about the study. For patients, whose contact information is provided by their health care providers, contact will be made the same day.

The study is designed to minimize in-person contact between participants and study staff. The informed consent process, screening, and randomization are performed remotely.

If the patient signs up for COVID-19 testing through the Los Angeles county website, the patient can consent to being contacted by clinical trial study coordinators (Appendix VII). If a consenting patient tests positive, the initial recruitment telephone or video conference call will be made.

At the initial recruitment telephone or video conference encounter the script information will be read to the study participant in their primary language (English, Spanish, Cantonese, Mandarin). Potential participants expressing interest will be provided with the electronic informed consent in their primary language, California Experimental Subjects Bill of Rights and an authorization for medical information (HIPAA) as a digital document. Potential participants will be informed that entry to the study must be within 96 hours of symptom onset.

At this initial recruitment telephone or video conference encounter with the potential participants verbal consent the screening eligibility assessment may be completed. If potential participants wish to review and sign the informed consent first, the screening and eligibility assessment can be completed at the next telephone or video conference encounter.

6.2.2 Informed Consent Process - Remote

Potential participants will be provided with the electronic informed consent (eIC), California Experimental Subjects Bill of Rights and HIPAA agreement as digital documents.

The informed consent process is done using videoconferencing or telephone between the study coordinator (delegated by the principal investigator) and includes discussion of the California Experimental Subjects Bill of Rights, discussion of the informed consent using the text of the approved informed consent as the text for the discussion of the informed consent and an explanation of the HIPAA authorization. The consent process and documentation is consistent with 21 CFR part 11 in addition to parts 50, and 56, and 45 CFR 46.

The research participant will be given the opportunity to discuss with their family and others including their health care providers. All questions raised by the potential participant will be answered by the study

coordinator. Participants who have reviewed the eIC, and had all questions addressed, volunteer to participate will use the electronic signature of the eIC to document. An official form of identification, such as a digital image of the patient's birth certificate, government-issued passport or a driver's license will be obtained to verify the identity of the patient. They will receive a digital signed copy of the eIC via email and a physical unsigned blank.

6.2.3 Screening Visit - Remote

For potential participants who elect to complete the screening and eligibility assessment after the informed consent process has been completed, this screening telephone/telemedicine visit will be conducted.

6.2.4 Documentation from a health care/provider encounter - Remote

If the screening evaluation indicates either an encounter with a health care provider or symptoms greater than mild COVID-19 with shortness of breath (see table 3 above), documentation from the health care provider encounter will be obtained. This must include vital signs, SpO2 to permit classification of COVID-19 as mild or moderate which are eligible or greater than moderate which are not eligible for participation. The participants consent and HIPAA authorization will be required to obtain this health information from the provider.

6.2.5 Screen Failures

In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured including the reason for screen failure.

6.2.6 Registration and Randomization

When the potential research participant signs, the documents using the digital documents and the screening and eligibility assessment confirms eligibility, the research participant will be registered and randomized.

6.2.7 Study Entry Visit (Day 0) - Remote

Upon receipt of the signed eIC, HIPAA authorization, and health information if required for greater than mild COVID-19, and completion of the screening and eligibility assessment for those eligible the study entry remote visit will be conducted.

Screening and entry remote visits may be combined for mild COVID-19, but moderate COVID-19 will require separate visits so the medical information from the health provider can be reviewed to ensure they qualify as moderate COVID-19. The study entry visit is a remote contact telephone contact or video conference encounter. Participants must begin study treatment within 96 hours of the onset of symptoms.

Participants will be informed that they are eligible.

6.2.8 Study Kit Dispensed

The kit will include:

6.1.1.1 Study agent
6.1.1.2 Blank copy of informed consent and HIPPA authorization
6.1.1.3 Information about the study
6.1.1.4 Instructions on study procedures
6.1.1.5 3 sets of COVID-19 Test Home Collections Kits [a]
6.1.1.6 QR Code and Internet link for Symptom Self Reporting Application (Appendix VI)
6.1.1.7 Instructions on what to do if they have worsening symptoms/become hospitalized

[a] An FDA Emergency Use Authorization approved home kit solution such as the Fulgent COVID-19 by RT-PCR test will be used. (73) It is a nasal swab collection followed by a FDA EUA approved PCR test conducted in the CLIA/CAP laboratory of Fulgent Genomics, determining the presence or absence of RNA from SARS-CoV-2 virus. The kit will include instructions, a swab and tube, alcohol prep pad, kit ID stickers, biohazard bag, absorbent sheet, return label, return box, and return envelope. The participant will be provided sample collection instructions and how to return the sample both in an illustrated print out and video. (74) The print outs are available in the supplemental materials.

6.2.9 Study Day 1 (day of first study substance administration) – Remote

Study staff will confirm the first dose taken by the participant by telephone. Participants who refuse the first dose after 2 days will be discontinued from the study.

Study staff will also confirm by telephone the completion of first nasal swab home kit to be mailed out within 24 hours. The nasal swab home kit can be completed within days 1 to 3 to accommodate shipping limitations.

The participant will utilize an application (app) available to self-report symptoms once daily as Patient-reported outcomes (PRO). The application clarifies to the study participant the information they are providing is not a substitute for standard COVID-19 care with their health care provider. The participant's completion of the self-report or PRO will be reviewed. If the participant does not complete their self-report, study staff will initiate contact to facilitate the completion of the daily self-report PRO. If the self-report or PRO discloses onset or worsening of the symptom of shortness of breath or worsening of other symptoms the participant will be instructed to call 911, telephone their health care provider or go to the health care provider urgent or emergency care facility.

Study staff will obtain and review the participant's EHR for pertinent information for the primary, secondary and exploratory endpoints.

6.2.10 Study Day 3 – Remote

The participant will continue to self-administrate the study agent twice a day daily. They will have an application available to self-report taking the daily doses. The participant will also self-report symptoms to the same application once daily. The application clarifies to the study participant the information they are providing is not a substitute for standard COVID-19 care with their health care provider. The participant's completion of the self-report or PRO will be reviewed. If the participant does not complete their self-report, study staff will initiate contact to facilitate the completion of the daily self-report PRO. If the self-report or PRO discloses onset or worsening of the symptom of shortness of breath or worsening of other symptoms the participant will be instructed to call 911, telephone their health care provider or go to the health care provider urgent or emergency care facility.

Study staff will obtain and review the participant's EHR for pertinent information for the primary, secondary and exploratory endpoints.

If the participant has had a resolution of listed symptoms for 3 days, study staff will confirm by telephone and change contact schedule to once weekly.

6.2.11 Study Day 7 – Remote

Study staff will also confirm by telephone the completion of the second nasal swab home kit to be mailed out within 24 hours. The nasal swab home kit can be completed within days 7 to 9 to accommodate shipping limitations.

The participant will continue to self-administrate the study agent twice a day daily. They will have an application available to self-report taking the daily doses. The participant will also self-report symptoms to the same application once daily. The application clarifies to the study participant the information they are

providing is not a substitute for standard COVID-19 care with their health care provider. The participant's completion of the self-report or PRO will be reviewed. If the participant does not complete their self-report, study staff will initiate contact to facilitate the completion of the daily self-report PRO. If the self-report or PRO discloses onset or worsening of the symptom of shortness of breath or worsening of other symptoms the participant will be instructed to call 911, telephone their health care provider or go to the health care provider urgent or emergency care facility.

Study staff will obtain and review the participant's EHR for pertinent information for the primary, secondary and exploratory endpoints.

If the participant has had a resolution of listed symptoms for 3 days, study staff will confirm by telephone and change contact schedule to once weekly.

6.2.12 Study Day 14 – Remote

Study staff will confirm by telephone the completion of the final nasal swab home kit to be mailed out within 24 hours. The nasal swab home kit can be completed within days 14 to 16 to accommodate shipping limitations.

The participant will self-administrate the last two doses of the study agent and self-report taking daily dose for last time. Study staff will contact by telephone to verbally confirm the number of doses taken to reconcile any differences with the self-report.

The participant will continue to self-report symptoms to the application once daily. The application clarifies to the study participant the information they are providing is not a substitute for standard COVID-19 care with their health care provider. The participant's completion of the self-report or PRO will be reviewed. If the participant does not complete their self-report, study staff will initiate contact to facilitate the completion of the daily self-report PRO. If the self-report or PRO discloses onset or worsening of the symptom of shortness of breath or worsening of other symptoms the participant will be instructed to call 911, telephone their health care provider or go to the health care provider urgent or emergency care facility.

Study staff will obtain and review the participant's EHR for pertinent information for the primary, secondary and exploratory endpoints.

If the participant has had a resolution of listed symptoms for 3 days, study staff will confirm by telephone and change contact schedule to once weekly.

6.2.13 Study Day 21 – Remote

Study staff will contact by telephone to verbally reconcile any differences with the self-report.

The participant will continue to self-report symptoms to the application once daily. The application clarifies to the study participant the information they are providing is not a substitute for standard COVID-19 care with their health care provider. The participant's completion of the self-report or PRO will be reviewed. If the participant does not complete their self-report, study staff will initiate contact to facilitate the completion of the daily self-report PRO. If the self-report or PRO discloses onset or worsening of the symptom of shortness of breath or worsening of other symptoms the participant will be instructed to call 911, telephone their health care provider or go to the health care provider urgent or emergency care facility.

Study staff will obtain and review the participant's EHR for pertinent information for the primary, secondary and exploratory endpoints.

6.2.14 Study Day 28 – Remote

The participant will self-report symptoms to the application for the last time. The application clarifies to the study participant the information they are providing is not a substitute for standard COVID-19 care with their health care provider. The participant's completion of the self-report or PRO will be reviewed. If the participant does not complete their self-report, study staff will initiate contact to facilitate the completion of

the daily self-report PRO. If the self-report or PRO discloses onset or worsening of the symptom of shortness of breath or worsening of other symptoms the participant will be instructed to call 911, telephone their health care provider or go to the health care provider urgent or emergency care facility.

Study staff will obtain and review the participant's EHR for pertinent information for the primary, secondary and exploratory endpoints.

6.2.15 Study Day 42 – Remote

Study staff will contact by telephone to gather pertinent information for the primary, secondary and exploratory endpoints. If the self-report or PRO discloses onset or worsening of the symptom of shortness of breath or worsening of other symptoms the participant will be instructed to call 911, telephone their health care provider or go to the health care provider urgent or emergency care facility.

Study staff will obtain and review the participant's EHR for pertinent information for the primary, secondary and exploratory endpoints.

6.2.16 Study Week 12 – Remote

Study staff will contact by telephone to gather pertinent information for the primary, secondary and exploratory endpoints. If the self-report or PRO discloses onset or worsening of the symptom of shortness of breath or worsening of other symptoms the participant will be instructed to call 911, telephone their health care provider or go to the health care provider urgent or emergency care facility.

Study staff will obtain and review the participant's EHR for pertinent information for the primary, secondary and exploratory endpoints.

6.2.17 Discontinuation Evaluations

Evaluations for Participants Who Do Not Start Study Treatment
Participants who are randomized but do not take the first (directly observed/confirmed) dose of study treatment do not need to be followed. An off study eCRF should be completed recording this and any evaluations completed for these participants should also be recorded on the Day 0 eCRFs.

Premature Treatment Discontinuation Evaluations
Participants who discontinue study treatment early should remain on study and all evaluations should be performed as outlined in the SOE.

Premature Study Discontinuation Evaluations
Participants who discontinue study participation should undergo premature study discontinuation evaluations as outlined in the SOE within 14 days of study discontinuation. If study discontinuation occurs on or prior to Day 13, all procedures should be performed as described in the SOE for premature study discontinuation evaluations. If study discontinuation occurs after Day 13, all evaluations EXCEPT treatment adherence should be performed.

For participants who prematurely discontinue from the study for reasons other than withdrawal of consent, sites will attempt to obtain information regarding vital status and endpoints per the SOE (see section 6.1).

6.2.18 COVID-19 Symptom Screen

Participants will be asked about their first symptoms related to COVID-19 and their current symptoms, to document eligibility. This will include when and what symptoms the participant noticed having. This data will be collected via the Study App.

6.2.19 Medical History

The medical history must include all signs and symptoms regardless of grade and all diagnoses within the past 14 days. This data will be collected via the Study App.

6.2.20 Medication History

A medication history must be present, including drug name, dosage, and indication, for the past 3 months. The participants will be able to type it out into a word box in the Study App.

6.2.21 Clinical Assessments

Some events require clinical evaluations by the patient/participants health care providers. Copies of these encounters by the health care providers will be obtained by the study team for review, documentation and coding.

Refer to section 7.2 for AE collection requirements.

6.2.22 Concomitant Medications

At entry and post-entry, we will record new and discontinued concomitant medications.

6.2.23 Study Treatment (Intervention) Modifications

Record any modification to treatment, treatment interruption, and permanent discontinuation of treatment, and the reason for the modification, interruption, or discontinuation.

6.2.24 Secondary Contact

Sites will capture secondary contact information for two individuals that the site can contact if the participant cannot be reached (e.g., spouse, friend, neighbor, etc.).

7 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of Adverse Events

An AE is any unfavorable and unintended sign, symptom, or diagnosis that occurs in a study participant during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

Information sources include study assessments including daily and weekly PRO of telephone calls; health information obtained from the patients' health care providers and health system encounters including outpatient visits, urgent care, emergency room or inpatient visits.

Review by the study coordinator and medical monitor will be performed and those deemed a clinically significant worsening from baseline will be documented as an AE.

A clinically-significant finding could include: worsening from baseline (eg, by at least 1 grade); concomitant signs or symptoms related to the abnormal study assessment; further diagnostic testing or medical/surgical intervention required; if study drug is withheld, or discontinuation from study drug Determination of clinical significance must be made by the medical monitor.

Events that do not meet the definition of an AE or SAE include: planned hospital admissions or surgical procedures for a condition that existed before the subject signed the informed consent are not to be considered AEs unless the condition deteriorates in an unexpected manner during the study (eg, surgery had to be performed earlier than planned); anticipated day-to-day fluctuations of pre-existing disease(s), condition(s), and signs or symptoms present or detected prior to the start of the study that are not more severe than expected for the subject's condition; and worsening of the COVID-19 including hospitalization, or death due to COVID-19.

7.2 Adverse Event Collection Requirements for This Protocol

Post-entry, all AEs must be recorded on the eCRFs **within 72 hours** if any of the following criteria have been met:

- All Grade ≥2 AEs
- All AEs that led to a change in study treatment/intervention regardless of grade
- All AEs meeting SAE definition

Serious Adverse Events (SAEs)

An SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening illness
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above).

7.3. Relationship to Study Drug

Investigators should use their knowledge of the subject, the information from the patients health care providers and the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to study drug, indicating on the eCRF that an AE is either related or unrelated. The following guidance should be taken into consideration when determining the relationship of an AE to study drug:

- Temporal relationship of event onset to initiation of study drug
- Course of the event, considering especially the effects of dose reduction,
- discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the subject or environment, or use of concomitant medications known to be associated with the event
- Presence of treatment-unrelated factors that are known to be associated with the occurrence of the event
- Whether there is a reasonable alternative explanation for the event

All AEs (including SAEs) will be assessed for the relationship of the AE to the study drug using the following definitions: not related; unlikely; possibly; probably; or definitely. For reporting and data analysis purposes, AEs reported with a causality assessment of “Definitely”, “Probably”, and “Possibly” are to be considered as “having a reasonable causal relationship” to study drug.

7.4 Study Monitoring

7.4.1 Adverse Events

The study coordinator and medical monitor will review and assess EA reports for potential impact on the study participant safety and protocol conduct. The XFBD001 protocol chairs will review all serious adverse events, and this review will be conducted on a weekly basis in a blinded fashion.

8 TOXICITY MANAGEMENT

8.1 Toxicity Grading

Criteria for participant management, dose interruptions, dose adjustments and discontinuation, or changes in treatment will be described only for toxicities attributable to the XFBD. The grading system for toxicities is CTCAE version 5.

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

8.2 Potential Toxicities

The side effects which are described with the components of the XFBD are listed in Table 8.2.

Table 8.2 Side Effects of the Components of XFBD

Medicinal	Latin	Potential Side Effects	Allergic Reactions
麻黄	Ephedrae Herba	tachycardia, palpitations, increased blood pressure, nausea, vomiting, dizziness, strokes, seizures, sudden death, psychosis, insomnia, heatstroke, nervousness, anxiety, sweating avoid taking with MAO inhibitors	To any *ephedra* plant (i.e. Mormon Tea)
苦杏仁	Armeniacae Semen Amarum	dizziness, sudden fainting, palpitations, headache, nausea, vomiting, seizures, coma, cyanosis	To almonds or any component of almonds
生石膏	Gypsum Fibrosum	upset stomach, loss of appetite	To calcium sulfate, calcium or sulfates
薏苡仁	Coicis Semen	upset stomach, frequent urination, excessive sweating Use with Caution: Pregnancy	To coix seed, also known as Job's tears
苍术	Atractylodis Rhizoma	nausea, dry mouth, bad taste in mouth, upset stomach, increased gastrointestinal motility	To any plant in the genus Atractylodes, such as ragweed
广藿香	Pogostemonis Herba	nausea, upset stomach, increased gastrointestinal motility	To any plant in the Pogostemon genus (i.e. Patchouli)
青蒿	Artemisiae Annuae Herba	nausea, vomiting, upset stomach, decreased blood pressure, decreased heart rate, decreased blood sugar, increased CYP3A4 and 2B6 activity	To any *Artemisiae* or mugwort plant
马鞭草	Verbenae Herba	nausea, vomiting, dizziness, headache, abdominal pain **Contraindicate for pregnant patients**	To any *Verbena* plants, also known as verbena or vervain
虎杖	Polygoni Cuspidati Rhizoma et Radix	nausea, vomiting, stomach upset, abdominal pain, diarrhea, dehydration; large doses can cause liver damage and could result in leukopenia and hematuria **Contraindicate for pregnant patients**	To *Polygonum cuspidatum*, also known as Japanese Knotweed, Japanese Fleeceflower
芦根	Phragmitis Rhizoma	fatigue, loss of appetite, diarrhea	To any *Phragmites*, also known as common reed

葶苈子	Descurainiae Semen	nausea, vomiting, stomach upset	To *Descuriania sophia* also known as flixweed or tansy mustard To similar plants such as garden cress, maca or dittany
化橘红	Citri Grandis Exocarpium	large doses can lead to sore or dry throat	To the pomelo fruit or peel; citrus fruits
甘草	Glycyrrhizae Radix et Rhizoma	large doses can lead to fatigue, muscle weakness, increased blood pressure, headache, stomach upset, reduced testosterone levels; long term use can lead to abnormal weight gain	To any *Glycyrrhiza* plant also known as licorice root

8.3 Management of Side Effects

It is possible that some participants will experience transient or prolonged AEs during the study. However, it is important to note that, in this trial, the visits will be conducted remotely and hence, AEs will be assessed remotely.

Management of AEs and side effects will be by the participant's health care providers. The single exception is to stop the study medication or placebo in the event of greater than grade 1 AE. Clear instructions to participants to call 911, go to their local urgent care or emergency care center, or contact their health care provider are provided during the enrollment, consent process and by the app participants use to report symptoms.

Patients report symptoms (PRO) that include potential adverse events daily and weekly on the app. In the event, they have symptoms necessitating an encounter with the health provider, contact between the health provider by the study coordinator will be made. Participants will be given a card indicating they are on the trial and the telephone number for the study team. Participants are instructed to notify the study coordinator when they seek a health encounter. A copy of the medical records related to that encounter are to be obtained to collect additional data to appropriately grade any potential toxicity.

8.3.1 Gastrointestinal Effects

Sore or dry mouth or throat, bad taste in mouth, loss of appetite, upset stomach, nausea, vomiting increased gastrointestinal motility, abdominal pain, diarrhea, are listed as potential side effects of the components of XFBD.

Symptom of loss of appetite (anorexia) is coded as a grade of nausea for the purposes of this trial.

Table 8.3.1 – Selected Gastrointestinal Adverse Event Grading (CTCAE)

Grade	1	2	3	4	5
Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL		
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated		
Diarrhea	Increase of <4 stools per day over baseline;	Increase of 4 - 6 stools per day over baseline;	Increase of ≥7 stools per day over baseline;	Life-threatening consequences;	Death

	mild increase in ostomy output compared to baseline	moderate increase in ostomy output compared to baseline; limiting instrumental ADL	hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	urgent intervention indicated	
Vomiting	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, TPN, or hospitalization indicated	Life-threatening consequences	Death

Grade 1 abdominal pain, nausea, diarrhea and vomiting do not require treatment discontinuation. In the event of GI symptoms, the study staff should review with the participant if XFBD is being taken with food. For grade 1 side effects, participants may be referred to their primary health care providers. For grade 2 nausea the study agent may be continued. For all other grade 2 or greater events or grade 3 nausea participants are instructed to discontinue study medication or placebo and must be referred to their health care provider for management.

8.3.2 Cardiovascular Effects

Rapid heart rate, decreased heart rate, palpitations, increased blood pressure, decreased blood pressure, dizziness, fainting, cyanosis are listed as potential side effects of the components of XFBD.

Table 8.3.2 – Selected Cardiovascular Adverse Event Grading (CTCAE)

Grade	1	2	3	4	5
Chest pain – cardiac	Mild pain	Moderate pain; pain on exertion; limiting instrumental ADL; hemodynamically stable	Pain at rest; limiting self care ADL; cardiac catheterization; new onset cardiac chest pain; unstable angina		
Cyanosis		Present			
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL		
Hypertension	Systolic BP 120 - 139 mm Hg or diastolic BP 80 – 89 mm Hg;	Systolic BP 140 – 159 mm Hg or diastolic BP 90-99 mm Hg if previously WNL; change in baseline medical intervention indicated; recurrent or persistent (≥24 hrs); symptomatic increase by	Systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated;	Life threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Death

		>20 mm Hg (diastolic) or to >140/90 mm Hg; monotherapy indicated initiated			
Hypotension	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated; hospitalization indicated	Life-threatening consequences and urgent intervention indicated	Death
Palpitations	Mild symptoms; intervention not indicated	Intervention indicated			
Syncope				Fainting, orthostatic collapse	

In the event of grade 1 or greater cardiovascular symptoms, the study staff must refer the participant to their primary health care providers. For grade 2 or greater events participants must be referred to their health care provider for evaluation and study agent is discontinued.

8.3.3 Nervous and Psychiatric Events

Headache, psychosis, insomnia, heatstroke, nervousness, anxiety, strokes, seizures, coma; are listed as potential side effects of the components of XFBD.

Table 8.3.3 – Selected *Nervous System and Psychiatric* Adverse Event Grading (CTCAE)

Grade	1	2	3	4	5
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	
Depressed levels of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences; coma; urgent intervention indicated	
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL		
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty falling asleep, staying asleep or waking up early		
Psychosis	Mild psychotic symptoms	Moderate psychotic symptoms (disorganized speech;	Severe psychotic symptoms (paranoid, extreme	Life-threatening consequences; threats of harm to self or others;	Death

		impaired reality testing)	disorganization) hospitalization not indicated; new onset	hospitalization indicated	
Stroke	Incidental radiographic findings only	Mild to moderate neurologic deficit; limiting instrumental ADL	Severe neurologic deficit; limiting care ADL; hospitalization	Life-threatening consequences; coma; urgent intervention indicated	Death
Seizure	Brief partial seizure and no loss of consciousness	Brief generalized seizure	New onset seizures (partial or generalized); multiple seizures despite medical intervention	Life-threatening consequences; prolonged repetitive seizures	Death

Grade 1 Anxiety and insomnia do not require treatment discontinuation. For grade 2 anxiety or insomnia the study agent is discontinued. For all other grade 1 or greater events in table 8.3.3 participants are instructed to discontinue study medication or placebo and must be referred to their health care provider for management.

8.3.4 Other side effects

Fatigue, excessive sweating, muscle weakness, weight gain, dehydration, liver damage, reduced testosterone levels, sudden death, blood in the urine, frequent urination, or low white blood cell count.

Table 8.3.4 – Selected Other Adverse Event Grading (CTCAE)

Grade	1	2	3	4	5
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self-care ADL		
Urinary frequency	Present	Limiting instrumental ADL, medical management indicated			
Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated	Hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 – 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life threatening consequences;	Death

				seizures	
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	
Testosterone deficiency	Asymptomatic; mild symptoms with no intervention indicated	Replacement therapy initiated			
Hepatic failure			Asterixis; mild encephalopathy; drug-induced liver injury (DILI); limiting self-care ADL	Life-threatening consequences; moderate to severe encephalopathy; coma	Death
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications, or hospitalization indicated; elective invasive intervention indicated; limiting self-care ADL	Life-threatening consequences; urgent invasive intervention indicated	Death

In the event of grade 1 or 2 fatigue the study agent may be continued, the study participant may contact their primary health care provider. The study agent should be discontinued, and the patient referred to their primary health care providers for grade 3 fatigue.

In the event of all other grade 1 or greater other side effects in table 8.3.4 the study staff must refer the participant to their primary health care providers and discontinue study agent.

Dehydration, hypoglycemia, white blood cell decreased, testosterone deficiency, hepatic failure (measure of hepatic damage) and hematuria are captured on review of medical records for participants who have a health care encounter.

9 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

- Drug-related toxicity or allergic reaction (see section 8.0).
- Requirement for prohibited concomitant medications (see section 5.4.1).
- Request by participant to terminate treatment.
  NOTE: The reason for treatment discontinuation should be documented (e.g. concern for AE, lack of efficacy, or other reason).
- Clinical reasons believed life threatening by the physician, even if not addressed in the section 8.0 of the protocol.

9.2 Premature Study Discontinuation

9.2.1 Failure to take the first dose (directly observed/confirmed over telephone) of study treatment within 2 days of study entry.
9.2.2 Request by the participant to withdraw consent.
9.2.3 Request of the health care provider if she or he thinks the study is no longer in the best interest of the participant.
9.2.4 At the discretion of the IRB/EC, FDA, NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter.

In the event that a participant prematurely discontinues from the study, unless they have withdrawn consent, sites will attempt to obtain information regarding vital status (including date last seen alive, hospitalization, date of death, and primary cause of death) from other sources (such as family members, other designated contacts, or clinic records) per section 6.2.15.

10 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

This is a double-blind placebo-controlled pilot trial to document safety and efficacy endpoint assessments and to determine the feasibility of community recruitment and enrollment of symptomatic adult outpatients with COVID-19.

The observational data from Wuhan comparing hospitals with and without the use of this TCM demonstrated a reduction of 10% progression without this TCM to 2-5% with this TCM. A key difference in patient care in the US is that patients with mild and moderate symptoms are staying home having been asked to self-quarantine. Initial data on hospitalization rates in the US in early 2020 points to rates of above 20%.

A reasonable target of reduction through the use of the Xuanfei Baidu Granules would likely reduce the progression rate among those with mild/moderate symptoms, from 20% to 10%, which has the potential of an almost 30% reduction of fatalities, depending on the distribution of severity of disease at diagnosis in the population.

10.2 Outcome Measures

Primary and secondary outcome measures listed below will be utilized in the future studies' primary Statistical Analysis Plan, which will define the content of the Primary Analysis Report.

10.2.1 Primary Outcome Measure

10.2.1.1 To document the feasibility of recruitment in the community setting by assessment of the number of positive cases identified per week.

10.2.1.2 To document the proportion of patients who agree to participate as measured by enrollment and randomization.

10.2.1.3 To document the treatment emergent side effects and safety profile of the XFBD and placebo.

10.2.1.4 To document the rate of hospitalization or death within 42 days of enrollment in the XFBD and placebo treated groups.

10.2.2 Secondary Outcome Measures

10.2.2.1 To document the effect of XFBD on Symptom Severity Score within 28 days of

study entry.

10.2.2.2 To document the proportion of patients who are compliant taking greater than 90% of the test substance as measured by self-report

10.2.2.3 To document the proportion of patients who comply with symptom monitoring.

10.2.2.4 To document the proportion of patients who comply with repeated clinical testing.

10.2.2.5 To document cumulative incidence of serious adverse events, and adverse events leading to early discontinuation of XFBD or placebo.

10.2.2.6 To document cumulative incidence of grade 3 and 4 adverse events.

10.2.2.7 To obtain levels (detectable versus not detectable, and continuous on log10 scale) of SARS-CoV-2 RNA from nasal swabs at approximately days 1, 7 and 14 among a subset.

10.3 Randomization and Stratification

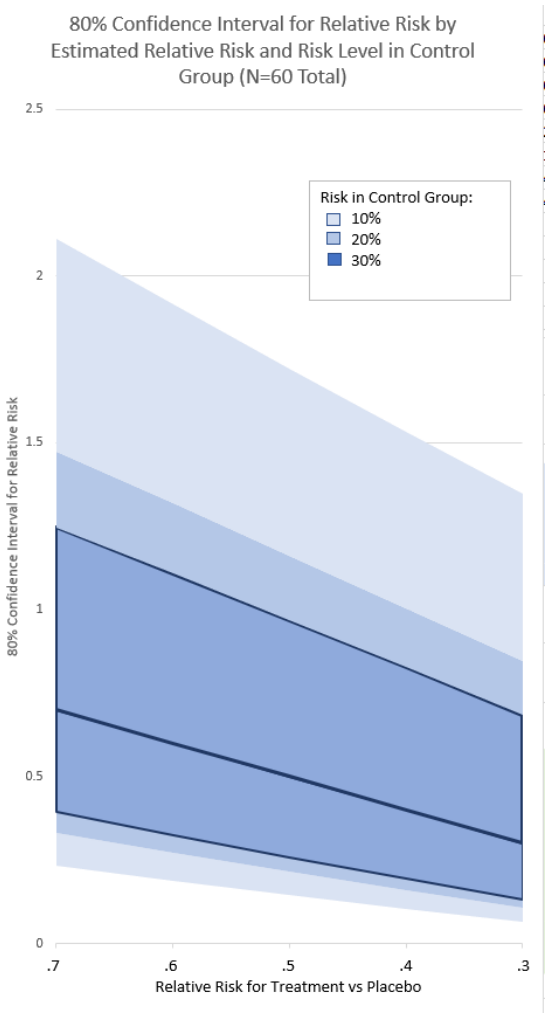
Eligible participants will be randomized using a 1:1 ratio to each of the study arms. Housemates of participants previously enrolled will be independently randomized so that housemates will not be clustered within treatment group.

Randomization will be stratified by “high” vs “low” risk of severe disease, where “high” risk is defined by any of the following: age ≥60 years, or having any of a number of conditions, as described in section 3.3.

10.4 Sample Size and Accrual

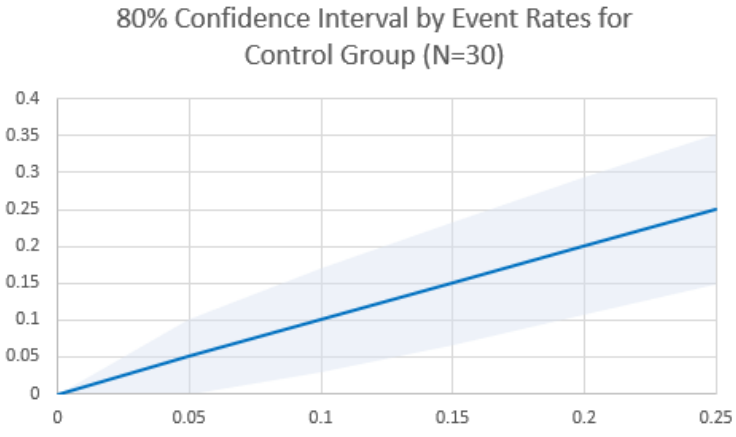
Pilot studies have many important purposes, as described in the objectives for this study (sections 1.1, 1.2, and 1.3). However, the use of pilot studies to determine effect sizes for future larger studies is not recommended since such estimates tend to be both biased and very unstable due to the small pilot study size.(75) We illustrate this graphically for this study in Figure 1. Our current estimate is that the event rates in the control and XFBD groups will be 0.20 and 0.10, respectively. Thus, the relative risk estimate is 0.50. If these estimates are in fact attained in the pilot study, it will support our assumption, yet only mildly, since the 80% confidence interval for that relative risk (given the 20% event rate in the control group) will be 0.26-0.97. Furthermore, the environment in which COVID-19 statistics are emerging is rapidly evolving due to changes in such factors as testing rates and exposure rates within subpopulations. At the time when we are putting forward a new trial proposal, we will look at the most recent data in order to make the best possible estimate for the treatment effect.

Figure 1



In addition to the relative risk, the event rate in the control group will be estimated in order to establish an appropriate sample size for a future study. Again, we will look at the most recent data available at the time of the study proposal to inform our hypothesis. The control group event rate, however, is expected to vary by the type of population sampled, so data specific to our sampling methods will be useful. As shown in Figure 2, the confidence intervals aren't narrow, yet they provide guidelines for sensitivity analyses in estimating future necessary sample sizes.

Figure 2



10.5 Data and Safety Monitoring

A DSMC will not be established for the pilot study. The data and safety monitoring will be the responsibility of the investigators and medical monitor, reviewing the data contemporaneously.

10.6 Analyses

All descriptive statistics will be documented in total and stratified by age, race/ethnicity, gender, risk group and assigned treatment, when applicable. This pilot study is not powered to find statistically significant differences by treatment group.

All analyses involving randomized comparisons will include all randomized participants who received the first (**confirmed**) dose of study treatment, according to a modified intention-to-treat approach. However, as the study is blinded, the use of a modified intention-to-treat approach should not introduce bias into the comparison of randomized arms in this pilot study or in future larger-scale studies.

10.6.1 Primary Outcome Measure

The first two primary outcomes involve participant enrollment, and these results will help us to plan recruitment for a subsequent larger clinical trial. For example, these results may indicate that special efforts may be needed in the future to recruit certain underrepresented populations. The second two primary outcomes involve health events that will be analyzed with logistic or negative binomial regression models stratified and/or adjusted for covariates, for future planning purposes only.

10.6.2 Secondary Outcomes

Symptom severity scores will be determined from the COVID-19 symptom PROs reported daily by participants. Each symptom is rated by the participant on a scale from 0-4. Although the seriousness of the symptoms are not equal, summing the individual symptom ratings will give a rough measure of the participant's disease severity. These daily symptom severity scores will be summed over the 28-day period using area under the curve (AUC). Comparisons of this AUC, as well as weekly symptom severity scores, by age, race/ethnicity, gender, risk group and assigned treatment will be performed using Wilcoxon rank sum tests. For this, and all comparisons by demographic or treatment variables, the results will be considered for planning purposes only. Secondary outcomes 2, 3, and 4 involve compliance proportions and will be documented in total and compared by demographic and treatment variables using Fisher exact tests. Secondary outcomes 5, 6, and 7 involve event rates which will be calculated in total and compared by demographic and treatment variables using negative binomial regression. Detectable versus not detectable SARS-CoV-2 RNA from nasal swabs at days 7 and 14 will be compared by demographic and treatment variables using Fisher exact tests, and continuous measures of SARS-CoV-2 RNA (on log10 scale) will be assessed for normality and tested using t-tests or Wilcoxon rank sum tests, as appropriate.

10.7 Unblinding

In the event that single patient unblinding is required for emergency disclosure, the sponsor investigators and medical monitor should be contacted by telephone and will make the determination should an event arise. The sponsor investigator or pharmacist will make that information available to the treating physician.

<u>Planned Unblinding</u>
Unblinding of all study participants will take place after the last participant has completed the study, all data have been entered into the database and cleaned for primary and secondary endpoints.

11 DATA COLLECTION AND MONITORING

11.1 Records to Be Kept

Electronic case report form screens will be made available to sites for data entry. Participants will be identified by the patient identification number provided upon randomization.

11.2 Data Management

Instructions concerning entering study data on eCRFs will be provided. Study coordinators are responsible for keying the data in a timely fashion.

Given the epidemic spread of SARS-CoV-2 and the risk for visiting personnel, the study can be monitored remotely by clinical trial monitors.

12 PARTICIPANTS

12.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix 1) and any subsequent modifications will be reviewed and approved by the IRB or EC responsible for oversight of the study. Informed consent will be obtained from the participant through appropriate remote consenting procedures. The eIC will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be provided to the participant and this fact will be documented in the participant's record.

12.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by IRB/EC, the FDA, OHRP, other local, US, and international regulatory entities as part of their duties.

12.3 Study Discontinuation

The study may be discontinued at any time by the FDA, IRB/EC, or OHRP as part of their duties to ensure that research participants are protected, or the industry supporters.

13 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be published and submitted to clinicaltrials.gov.

14 BIOHAZARD CONTAINMENT

As the transmission of SARS-CoV-2 and other droplet-borne pathogens can occur through contact with persons with active SARS-CoV-2 secretion precautions will be employed by all personnel in the clinical research setting and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

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APPENDIX I: SAMPLE INFORMED CONSENT

SAMPLE INFORMED CONSENT

Study Title: A Randomized, Double-Blind, Placebo-Control Pilot Trial of Xuanfei Baidu Granules (XFBD), a Traditional Chinese Medicine (TCM), in Persons with COVID-19

Principal Investigator: Darcy Spicer MD

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

You have been asked to participate as a subject in a medical experiment. Before you decide whether you want to participate in the experimental procedure, you have a right to the following information:

CALIFORNIA LAW REQUIRES THAT YOU MUST BE INFORMED ABOUT:

1. The nature and purpose of the study.
2. The procedures in the study and any drug or device to be used.
3. Discomforts and risks reasonably to be expected from the study.
4. Benefits reasonably to be expected from the study.
5. Alternative procedures, drugs, or devices that might be helpful and their risks and benefits.
6. Availability of medical treatment should complications occur.
7. The opportunity to ask questions about the study or the procedure.
8. The ability to withdraw from the study at any time and discontinue participation without affecting your future care at this institution.
9. Be given a copy of the signed and dated written consent form for the study.
10. The opportunity to consent freely to the study without the use of coercion.

I have carefully read the information contained above and I understand fully my rights as a potential subject in this study.

Date: _____ Time: _____

Signature: _____
(Research Participant)

INFORMED CONSENT FOR RESEARCH

Study Title: A Randomized, Double-Blind, Placebo-Control Pilot Trial of Xuanfei Baidu Granules (XFBD), a Traditional Chinese Medicine (TCM), in Persons with COVID-19

Principal Investigator: Darcy Spicer MD

Department: Medicine

24-Hour Telephone Number: 323-865-3000

INTRODUCTION

We invite you to take part in a research study. Please take as much time as you need to read the consent form. You may want to discuss it with your family, friends, or your personal doctor. If you find any of the language difficult to understand, please ask questions. If you decide to participate, you will be asked to sign this form. A copy of the signed form will be provided to you for your records.

KEY INFORMATION

The following is a short summary of this study to help you decide whether you should participate. More detailed information is listed later in this form.

1. Being in this research study is voluntary–it is your choice.

2. You are being asked to take part in this study because you had recent symptom(s) and test that showed you have been infected with the virus that causes COVID-19. The purpose of this study is to document the safety of taking a traditional Chinese medicine (TCM) in patients with COVID-19 and to gain information to determine whether a study with TCM can be conducted. Your participation in this study will last for about 6 weeks with a follow-up contact at week 12. Procedures will include taking the study agent which may be the traditional Chinese medicine called Xuanfei Baidu Granules or a placebo for 14 days. You will provide nasal swabs on approximately days 1, 7, and 14 after discussion with the study coordinator. You will complete questions using an app on a tablet or phone daily for 21 days and again at 28 days and week 12. You must have access to a computer, laptop, tablet or smart phone to take part in this study

3. There are risks from participating in this study. The most important risks are due to ephedrine or pseudoephedrine which is present in one of the plants used to make the traditional Chinese medicine granules. It is very important that you do not take additional traditional Chinese medicines or other medications that include ephedrine or pseudoephedrine. The traditional Chinese medicine granules also include amygdalin or laetrile which can cause cyanosis (bluish or purplish discoloration of the skin or mucous membranes such as the lips). More

detailed information about the risks of this study can be found under the "Risk and Discomfort" section.

4. The possible benefits to you for taking part in this study may include possible improvement in your COVID-19 symptoms.

5. If you decide not to participate in this research, your other choices may include continuing the care and treatments with your health care providers.

DETAILED INFORMATION

PURPOSE

The purpose of this study is to document the safety of taking a traditional Chinese medicine (TCM) in patients with COVID-19 and to gain information to determine whether a study with TCM can be conducted. The study will test a traditional Chinese medicine which has been made into a granule formulation called Xuanfei Baidu Granules. You are invited as a possible participant because you have symptoms and a test that shows you have the virus that causes COVID-19. About 60 or more participants will take part in the study. Half of the participants will receive the Xuanfei Baidu Granules and the other half will receive a placebo granule which does not contain the TCM.

Participating in this research study doesn't replace your medical care or treatment for COVID-19 or other health problems. If during the study, you have new or worsening symptoms you must contact your health care provider to manage your care. This is true even if it is thought to be a side effect of the granules.

PROCEDURES

All visits for this study will be done using phone or videoconferencing technologies.

If you decide to take part, this is what will happen:

Screening Encounter: The information in this informed consent will be reviewed with you. If you decide to participate you will be asked to sign this informed consent and a document called a HIPAA authorization using electronic methods. The HIPAA authorization permits the study team access to your clinic or hospital information for the 12 weeks covering your study participation including the COVID-19 test you recently received. You will complete a medical history and symptom screening survey, and list the medicines you have taken in the past 3 months. We will determine if you are eligible for taking part in the study based on your medical history. If you are eligible, you will be asked to identify someone the study team can contact in the event you have been hospitalized and are not available. In addition, we will need to know who your health care providers are so that we may contact them to obtain copies of your health records before and during the study.

If you agree to fulfill the criteria required for this study you will be randomized (1:1) to receiving the Xuanfei Baidu Granules or the placebo granules. You have a 50:50 chance of receiving the Xuanfei Baidu Granules or the placebo granules. The members of the study team will not know which arm of the study you are in. After you have been randomized, a study kit will be sent to you by courier. We will have you download the

study app to your device and provide assistance to assure that it is working properly. The day you receive the kit and start taking the granules is called Day 1. During the study you must notify the study team if any of your regular medications are changed or new medications are started.

Day 1: You will complete the survey questionnaire on the app and begin taking the study granules twice per day. The study team will contact you to confirm you have taken your first dose. You will do a home specimen collection (nasal swab) for the COVID-19 virus. The results of the nasal swab for the COVID-19 viral testing will be reported to the public health department in the same way as your original test.

Days 2-14: You will complete the survey questionnaire on the app and continue taking the study granules twice per day, once in the morning and once in the evening 1 hour after food. The study team will contact you on the 3rd, 7th, and 14th day to ask additional questions. On days 7 and 14 you will do a home specimen collection (nasal swab) for the COVID-19 virus.

Days 15-21: You will complete the survey questionnaire on the app. You will have completed taking the study granules by day 14.

Days 28, 42 and 84: You will complete the survey questionnaire on the app. The study team may contact you by phone with additional questions.

If necessary, the investigators can find out what arm a participant is in if needed in an emergency.

This trial is not meant to replace your medical care or treatment for COVID-19 or other health problems. If during the study, you have new or worsening symptoms you must contact your health care provider to manage your care.

If you are experiencing any of these signs, **seek emergency medical care immediately**:

- Trouble breathing
- Persistent pain or pressure in the chest
- New confusion
- Inability to wake or stay awake,
- Bluish lips or face
- High fever above 38.9 °C (102°F)

This list is not all possible symptoms. Please call your medical provider for any other symptoms that are severe or concerning to you.

If there is an emergency, please do not contact the study coordinator and directly call emergency services.

Call 911 or call ahead to your local emergency facility: Notify the operator that you tested positive for the COVID-19 causing virus.

RISKS AND DISCOMFORTS

Side effects which have been reported from traditional Chinese medicines that contain the components of the study granules include:

- General: fatigue, excessive sweating, muscle weakness, weight gain, reduced testosterone levels, sudden death:
- Cardiovascular: rapid heart rate, decreased heart rate, palpitations, increased blood pressure, decreased blood pressure, dizziness, fainting, cyanosis (bluish or purplish discoloration of the skin or mucous membranes such as the lips), sudden death;
- Gastrointestinal: sore or dry mouth or throat, bad taste in mouth, loss of appetite, upset stomach, nausea, vomiting increased gastrointestinal motility, abdominal pain, diarrhea, dehydration, liver damage:
- Nervous system: headache, psychosis, insomnia, heatstroke, nervousness, anxiety, strokes, seizures, coma;
- Kidney: blood in the urine, frequent urination;
- Other: low white blood cell count.

Nasal swabs: For self-collection of nasal swabs you may feel discomfort from the insertion of the swab into your nostril.

Surveys/Questionnaires/Interviews: Some of the questions may make you feel uneasy or embarrassed. You can choose to skip or stop answering any questions you don't want to.

Breach of Confidentiality: There is a small risk that people who are not connected with this study will learn your identity or your personal information.

Reproductive Risks: We do not know whether this study medication might hurt an unborn baby. You must use birth control while on this study. These are some birth control measures that you can use: condom or diaphragm with spermicidal.

If you are pregnant, you cannot take part in this study.

If you are breastfeeding and do not want to stop, you may not take part in this study.

Unforeseen Risks: There may be other risks that are not known at this time.

BENEFITS

There may be no direct benefit to you. The potential benefits to you may include improvement in your COVID-19 symptoms.

Your participation in this study may help us learn about the side effects of traditional Chinese medicines.

PRIVACY/CONFIDENTIALITY

We will keep your records for this study confidential as far as permitted by law. However, if we are required to do so by law, we will disclose confidential information about you. Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who are required to review this information. We may publish the information from this study in journals or present it at meetings. If we do, we will not use your name and individual data will not be presented.

The University of Southern California's Institutional Review Board (IRB) may review your records. Organizations that may also inspect and copy your information include the Food and Drug Administration.

Federal law provides additional protections of your medical records and related health information. These are described in the HIPAA Authorization document. You will be asked to sign a separate HIPAA Authorization for Research form authorizing the access, use, creation, and disclosure of your health information.

Your data or specimens will be analyzed and stored at the University of Southern California. Your information or samples that is/are collected as part of this research will be used or distributed for future research studies without your additional informed consent. Any information that identifies you (such as your name) will be removed from your private information or samples before being shared with others.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

ALTERNATIVES

There may be alternative(s) to participating in this study. These include standard medical care provided by your health practitioner, participation in research studies, or use of traditional Chinese medicine without participating in this study.

Remdesivir (Veklury®), an antiviral agent, is currently the only drug that is approved by the Food and Drug Administration for the treatment of COVID-19. It is recommended for use in hospitalized patients who require supplemental oxygen.

The FDA has issued an emergency use authorization (EUA) for baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized adults (and certain children) requiring supplemental oxygen, invasive mechanical ventilation or extracorporeal membrane oxygenation. An EUA has been issued for convalescent plasma for hospitalized patients. An EUA allows use of the medication while there is limited information available. The issuance of an EUA does not constitute FDA approval of a product.

Dexamethasone, a corticosteroid, has been found to improve survival in hospitalized patients who require supplemental oxygen, with the greatest effect observed in patients who require mechanical ventilation. Therefore, the use of dexamethasone is strongly recommended in this setting.

For patients with mild to moderate COVID-19 who are not hospitalized by who are at high risk for disease progression FDA has authorized the use of bamlanivimab or casirivimab plus imdevimab for adults (and certain children over 12).

High-risk individuals specified in the EUA are those who meet at least one of the following criteria:

- Body mass index (BMI) ≥35
- Chronic kidney disease
- Diabetes mellitus
- Immunocompromising condition/immunosuppressive disease
- Currently receiving immunosuppressive treatment
- Aged ≥65 years
- Aged ≥55 years and have:
    - Cardiovascular disease, or
    - Hypertension, or
    - Chronic obstructive pulmonary disease/other chronic respiratory disease

PAYMENTS

You will not be compensated for your participation in this research.

COST

You and/or your health plan/insurance will be billed for the tests and procedures you need for routine health care and COVID-19 treatment while you are in this study. You will be billed in the same way as if you were not in a study. You will be responsible for any co-payments and deductibles required by your insurance. Some health plans/insurance companies will not pay these costs for people taking part in studies. Check with your health plan/insurance company to find out what they will pay for. If you have any questions about which tests or procedures will be billed to you and/or your health plan/insurance, ask the study doctor.

The study traditional Chinese medicine will be provided to you at no cost. The home test kit will be done at no cost.

You and your third-party payer will continue to be responsible for payment for your health care and COVID-19 treatment.

INJURY

If you think you have been hurt by taking part in this study, contact your health care provider and tell the study coordinator. If this is an emergency call 911. If it is urgent, go to your local urgent care center or emergency room or hospital.

If you require treatment because you were injured from participating in this study, treatment will be provided by your health plan. You or your health plan/insurance will be billed for the cost of this treatment.

There are no plans to offer any type of payment for injury. However, by signing this form you have not given up any of your legal rights.

NEW INFORMATION

We will tell you about any new information that may affect your health, welfare, or willingness to stay in the research.

VOLUNTARY PARTICIPATION

It is your choice whether to participate. If you choose to participate, you may change your mind and leave the study at any time. Refusal to participate or stopping your participation will involve no penalty or loss of benefits to which you are otherwise entitled.

If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether the investigator can continue to collect data from your records. If you agree, this data will be handled the same as the research data. No new information or samples will be collected about you or from you by the study team without your permission.

The study site may be required, after your withdrawal, to report any safety event that you may have experienced due to your participation to all entities involved in the study. Your personal information, including any identifiable information, that has already been collected up to the time of your withdrawal will be kept and used to guarantee the integrity of the study, to determine the safety effects, and to satisfy any legal or regulatory requirements.

PARTICIPANT TERMINATION

You may be removed from this study without your consent for any of the following reasons: you do not follow the study investigator's instructions, at the discretion of the study investigator, your condition gets worse, or the investigator closes the study. If this happens, the study investigator will discuss other options with you.

OTHER RELATED RESEARCH

You may consent to being contacted for other related research studies. If you choose to participate in other studies, we will not be sharing your study information with other research institutes without your consent.

CONTACT INFORMATION

If you have questions, concerns, complaints, or think the research has hurt you, talk to the study investigator at Darcy Spicer 323-865-3000.

This research has been reviewed by the USC Institutional Review Board (IRB). The IRB is a research review board that reviews and monitors research studies to protect the rights and welfare of research participants. Contact the IRB if you have questions about your rights as a research participant or you have complaints about the research. You may contact the IRB at (323) 442-0114 or by email at irb@usc.edu.

STATEMENT OF CONSENT

I have read (or someone has read to me) the information provided above. I have been given a chance to ask questions. All my questions have been answered. By signing this form, I am agreeing to take part in this study.

Name of Research Participant	Signature	Date Signed (and Time*)

I am willing to be contacted for other related research studies.

_____(initials) YES, I agree _____(initials) NO, I do not agree

Person Obtaining Consent

I have personally explained the research to the participant using non-technical language. I have answered all the participant's questions. I believe that the participant understands the information described in this informed consent and freely consents to participate.

Name of Person Obtaining Informed Consent	Signature	Date Signed (and Time*)

APPENDIX II: RECRUITMENT SITES

1. **Allied Pacific IPA**
   1680 S Garfield Ave, 2nd Floor
   Alhambra, CA 91801
   Telephone: 626-282-0288

2. **County of Los Angeles Department of Public Health**
   5050 Commerce Drive
   Baldwin Park, California 91706

3. **Greater El Monte Community Hospital**
   1701 Santa Anita Ave,
   South El Monte, CA 91733

4. **Garfield Medical Center**
   525 North Garfield Avenue,
   Monterey Park, CA 91754

5. **USC Keck Medical Center**

6. **USC Verdugo Hills Hospital**

APPENDIX III: THE SOURCE AND AUTHENTICATION OF MEDICINALS IN XUANFEI BAIDU GRANULES (XFBD)

Example English Translation for Ephedrae Herba
Full Chinese Document in Supplement Materials

8.1.1. Ephedrae Herba (麻黄)

8.1.1.1 Resource Overview

1. Chinese Pharmacopeia Botanical Sources

   The 2015 Chinese Pharmacopeia refers to three botanical sources for ephedrae herba: *Ephedra sinica* Stapf, *Ephedra intermedia* Schrenk et C. A. Mey. or *Ephedra equisetina* Bge. The grassy green stems are harvested and dried in the autumn.

2. Analysis of Botanical Sources

   a. Production

Species	Growing Environment	Main Production Region	Authentic Production Region
Ephedra sinica Stapf.	Mostly Wild	Chifeng, Inner Mongolia	Inner Mongolia, Gansu
Ephedra intermedia Schrenk et C. A. Mey.	Wild	Gansu, China	
Ephedra equisetina Bge.	Wild	Xinjiang, China	

   b. Confusion of Differentiating Botanical Sources

   Historically, all three kinds of ephedra plants were used for medicinals. [1]. China used to be the world's largest producer of ephedrine extract so the demand for wild ephedra was overwhelming, leading to the destruction and misuse of wild resources. In the early 2000s, the chemical synthesis of ephedrine on an industrial scale was successful. Therefore, the demand for wild ephedra fell substantially. Confusion on differentiating ephedra plants has essentially disappeared, and *Ephedra sinica* Stapf. is what is available on the main medicinal market.

   c. Current Resource Status and Future Trends

   The resource types of ephedra are divided into two categories: wild and cultivated ephedrae herba. For wild ephedrae herba, Chifeng, Inner Mongolia produces *Ephedra sinica* Stapf with an annual output of 1,000-2,000 tons, accounting for more than 60% of the usage in China. This is followed by *Ephedra intermedia* Schrenk et C. A. Mey. produced in Gansu and *Ephedra equisetina* Bge produced in Xinjiang. The other type is cultivated *Ephedra sinica* Stapf., which is mainly produced in Lanzhou, Gansu, Ordos, and elsewhere in Inner Mongolia, and the output is not as large (see Tiandi.com https://www.zyctd.com/zixun/202/20533.html for information on Chinese herbal medicine and market research information). Currently, the wild resources of ephedrae herba are abundant. At one point, they were greatly reduced due to the demand to extract ephedrine. However, this burden has been alleviated with the ability to completely synthesize the compound chemically. The ephedrae herba use in traditional Chinese medicine is relatively small in comparison, thus no longer posing a threat to the wild resource. The harvest is government-regulated so the price has been reasonable since the fall of 2011. The market for ephedrae herba is very stable. A small amount of cultivated ephedrae herba has been available since the beginning of the 2000s, and these cultivators have received government permission to continue their small-scale research. At this time, the wild resources have recovered and have strong self-regeneration capabilities. The main source of ephedrae

herba will continue to be from the wild.

d. Resource Availability

Wild *Ephedra sinica* Stapf. is readily available for medicinal use. Cultivation technology is now mature so there is no risk of insufficient resource in the foreseeable future.

8.1.1.2 Quality Assurance

1. 2015 Chinese Pharmacopeia Book 1 Quality Standards and Regulations

Refer to 8.2.1.1 The raw herb shall not have less than 0.80% of ephedrine hydrochloride and pseudoephedrine hydrochloride; the decoction pieces have the same requirements.

2. Production Sites and Other Factors that Affect Quality (Mainly the Chemical Content)

a. Different Varieties

Different varieties of ephedrae herba have differing amounts of active ingredient. Jin Ling et. al [2] found that the varieties of ephedrae herba in Gansu and Inner Mongolia have different amounts of ephedrine and pseudoephedrine, which were 0.78-1.97% and 0.47-0.97% respectively

b. Different Production Region

Different production areas did not amount to any significant differences in the amounts of active ingredient. For example, Chen Kang et al. [3] showed that the ephedrine and pseudoephedrine content for the regions Inner Mongolia, Shanxi, and Ningxia were 1.30-1.56%, 1.08-1.83% and 1.30-2.16% respectively.

8.1.1.3 Selection of Variety and Production Region

1. Selection

Ephedra sinica Stapf. from Chifeng, Inner Mongolia, as the main production region, was selected for the production of Xuanfei Baidu granules (XFBD). The resource is readily available. Since its native to the region and the locals also use the same variety, the confusion of differentiating plant varieties can be avoided.

2. Quality Inspection Results

The quality inspection results of the decoction pieces of ephedrae herba can be found at 8.2.1.3 and 8.2.1.4. The quality of the decoction pieces selected for XFBD research and production meets quality assurance standards.

Figure 8-1: Ephedrae Herba Decoction Pieces Quality Inspection Results

Serial Number	**Batch Number**	**Production Region**	**Appearance**	**Microscopic Identification**
2	1910000801	Inner Mongolia	Pass	Pass
Physical and Chemical Identification	**Thin-Layer Chromatography (TLC)**	**Moisture % cannot be greater than 9.0%**	**Total Ash % cannot be greater than 9.0%**	**Total % of Ephedrine and Pseudoephedrine cannot be less than 0.80%**
Pass	Pass	7.2%	7.3%	3.25%

[1] 肖培根主编. 新编中药志（第三卷）[M].北京：化学工业出版社, 2002,297-309.

[2] 晋玲, 张弦飞, 崔治家, 等. HPLC法测定不同产地和种属麻黄中麻黄碱与伪麻黄碱的含量[J]. 中兽医医药杂志, 2013, 32(01):43-46.

[3] 陈康, 林文津, 林励. HPCE法测定不同产地麻黄中麻黄碱和伪麻黄碱的含量[J]. 中药材, 2005, 28(8):664-665.

APPENDIX IV: EXPERIMENTAL DATA AND LITERATURE REVIEW OF THE CHEMICAL COMPOSITION

Example English Translation for Ephedrae Herba
Full Chinese Document in Supplement Materials

13.1.1 Research and Analysis of the Chemical Composition of Ephedrae Herba

The 2015 Chinese Pharmacopeia refers to three botanical sources for ephedrae herba: *Ephedra sinica* Stapf, *Ephedra intermedia* Schrenk et C. A. Mey. or *Ephedra equisetina* Bge. [1] Xuanfei Baidu uses *Ephedra sinica* Stapf as its raw material. Ephedra herba has been used in the clinical practice of traditional Chinese medicine for more than 2,000 years. It was first documented in the Shennong Materia Medica. Its effect was recorded as: "Mainly for stroke, cold damage headaches, malaria, promoting sweating, removing evil heat, suppressing cough, calming rapid gasping, eliminating cold heat, and breaking accumulations." [2] The chemical components in ephedra herba are mainly alkaloids, flavonoids, volatile oils, phenolic acids, saccharides, and tannins.

Alkaloids: Alkaloids are the main components as well as the active ingredients in most ephedra plants. The highest content is three pairs of stereoisomeric amphetamines. The stem of the ephedra plant contains L-ephedrine hydrochloride, L-methylephedrine, L-Norephedrine, R-pseudoephedrine, R-Norephedrine, and trace amounts of R-methylephedrine. [3] Among them, L-ephedrine accounts for at least 60% of the total alkaloid content in *Ephedra sinica* Stapf, 30-40% of *Ephedra intermedia* Schrenk et C. A. Mey., and 85-90% in *Ephedra equisetina* Bge. The ephedra stem contains a small amount of benzylamine and an ephedrine of unknown structure [4].

Flavonoids: Flavonoids are another important component of ephedra plants. Li Zijiao et al. [5] measured the total flavonoid content of ephedra to be about 0.29%. Flavonoids mainly include apigenin, apigenin–5–O–rhamnoside, kaempferol, kaempferol–7–O–rhamnoside, quercetin, leucocyanidin, leucopelargonidin, leucodelphinidin, herbacetin, and others. In addition, ephedra contains Mahuannin A and Mahuannin B as well as catechins [6–7].

Volatile oil: The known volatile oil isolated from *Ephedra sinica* Stapf are 1-alpha-terpinenol, beta-terpinenol, 2, 3, 4, 6-tetramethylpyrazine, (+)-alpha-terpineol, and menthyl-2-ene-7-ol. *Ephedra intermedia* Schrenk et C. A. Mey. mainly contains palmitic acid. *Ephedra equisetina* Bge. has relatively high content of 6,10,14-trimethylpentadecane-2-ketone, 3,7,11,15-tetramethyl-2-hexadecen-1-ol, methyl stearate, tetramethylpyrazine, and others. [8]

Organic acids: Several organic acids have been isolated from ephedra, including cinnamic acid, benzoic acid, ferulic acid, isoferulic acid, vanillic acid, palmitic acid, 4-hydroxybenzoic acid, 4-hydroxyphenylacetic acid, Linoleic acid, rhododendrol glucoside, and others.

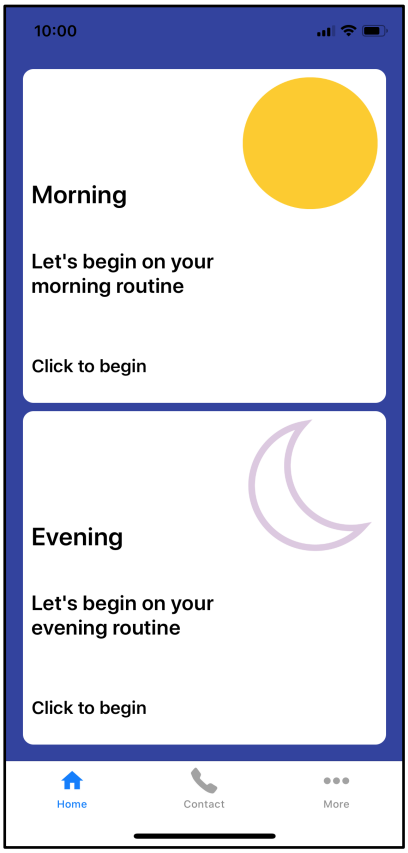
Saccharides and tannins: Ephedrae plants have many polysaccharides that can have an effect on coagulation and oxidation. Kuang et al. [9] isolated hyper-branched acidic polysaccharide (ESP-B4) from ephedra which seemed to show some immunosuppressive activity. Konno et al. [10] isolated ephedrae herba polysaccharide A, B, C, D, and E from *Ephedra distachya* which appeared to have a blood glucose lowering effect. The tannins found in ephedra are usually condensed tannins. 16 compounds have been isolated, such as catechol tannins. Riclo et al. [11] conducted a study on Ephedra Americana and concluded that the younger stems had higher content in total phenols and proanthocyanidins, while woody stems had mostly low molecular weight compounds.

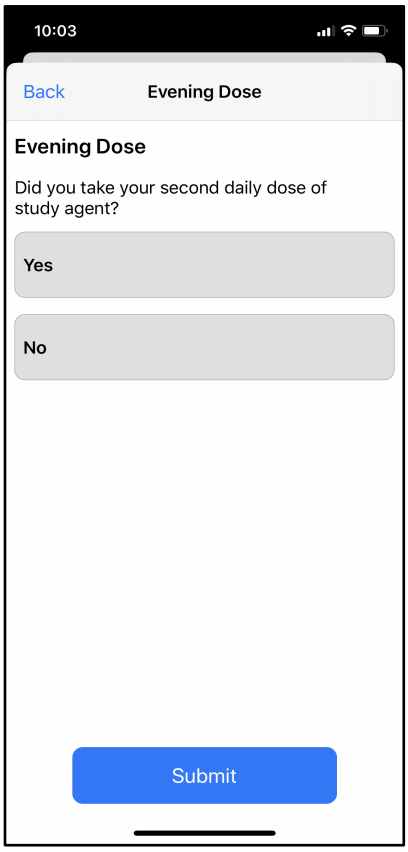
[1] 国家药典委员会. 中华人民共和国药典(一部) [S]. 北京: 中国医药科技出版社，2015.
[2] 丁丽丽,施松善,崔健,等.麻黄化学成分与药理作用研究进展[J]. 中国中药杂志, 2006, 31(20): 1661–1664.
[3] 李佳莲, 方磊, 张永清, 等. 麻黄的化学成分和药理活性的研究进展[J]. 中国现代中药, 2012, 14(7): 21–27.
[4] 周玲,吴德康,唐于平,等.麻黄中化学成分研究进展[J].南京中医药大学学报, 2008, 24(1): 71–72, 74.
[5] 李姿娇,杨屹,丁明玉,等.麻黄非麻黄碱部分中黄酮、生物碱和有机酸的分析[J]. 分析试验室, 2005, 24(4): 67–69.
[6] Okawa M, Kinjo J, Nohara T, et al. DPPH (1,1– diphenyl– 2– picrylhydrazyl) radical scavenging activity of flavonoids obtained from some medicinal plants[J]. Biological ＆Pharmaceutical Bulletin, 2001, 24 (10): 1202.
[7] Mantani N, Andoh T, Kawamata H, et al. Inhabitory effect of Ephedrae herba, an oriental traditional medicine, on the growth of influenza A/PR/8 virus in MDCK cells [J]. Antiviral Research, 1999, 44(3): 193.
[8] 张梦婷,张嘉丽,任阳阳,等.麻黄的研究进展[J].世界中医药, 2016, 11(9): 1917–1 921, 1928.
[9] Kuang H X, Xia Y G, Liang J, et al. Structural characteristics of a hyperbranched acidic polysaccharide from the stems of Ephedra sinica and its effect on T–cell subsets and their cytokines in DTH mice[J]. Carbohydrate Polymers, 2011, 86(4): 1705–1711.
[10] Konno C, Mizuno T, Hikino H. Isolation and hypoglycemic activity of Ephedrans A, B, C, D and E，Glycsns of Ephedra Distachya Herbs[J]. Planta Med, 1985, 2: 162.

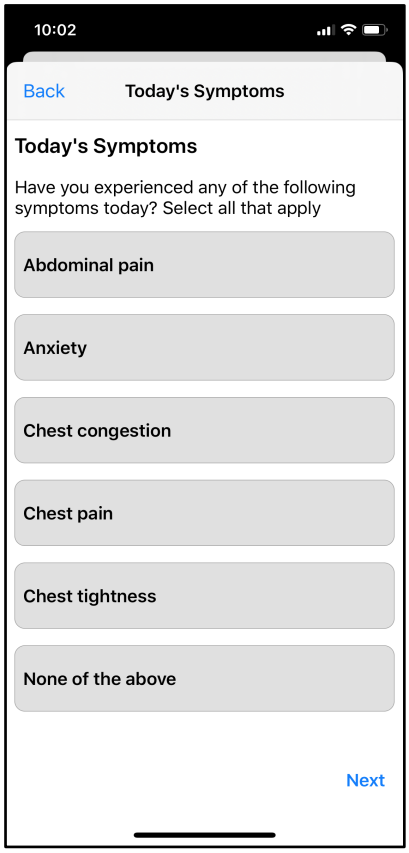
[11] Riclo R A, Sena G A, Vai V M. Determination of the presence of condensed tannins in Ephedra Americana Humb. et Bonpl. Ex Wild [J]. Activa Farm Bonaerense, 2004, 23(1): 11–14.

APPENDIX VI: SCORE PHONE APPLICATION

iPhone QR code	Android QR code







APPENDIX VII: LA COUNTY TESTING SITE CONSENT AND AUTHORIZATION TO BE CONTACTED FOR FUTURE COVID-19 RESEARCH STUDIES