Study Title: The Development of a COVID19 Oral Vaccine Consisting of Bacillus subtilis Spores

Study sponsor: DreamTec Research Limited

Principal Investigator

Name: Kwong Wai Yeung

Phone: +852 95184614

Email: Keithkwong@dreamtec.hk

Date: 1 June 2021

The Development of a COVID19 Oral Vaccine Consisting of Bacillus subtilis Spores
study protocol

Common name of the vaccine under test	Bacillus subtilis spore	
Name of the test agent		
Vaccine Registration Applicants main investigators		（Signature）
Head of study Unit		（Unit seal）
Unit of statistical analysis		
Contract Research Organization		
Application Contact Person		
Contact number		
Contact address		
Start and end date of the test		
The location of the original data		

Contents

Summary

1. Test subject

efficacy and safety of B. subtilis spore

2. Test objective

The efficacy and safety of B. subtilis spore were evaluated with simulated oral tablet as control

3. Test vaccine

Test group：Oral approach, 1 capsule of B. subtilis spore once a day. No other medication.

Start in the morning on an empty stomach.

4. Overall design of test

This study was conducted in a single arm design.

5. Test population

Normal healthy people without disease. Excluded those with basic diseases such as hypertension, diabetes and hyperglycaemia. Test schedule

2021.4.01 – 2021.9.30

Main body

1. Introduction

COVID-19 caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). By December 2020, it had infected more than 80 million people and killed more than 1.7 million people all over the world. Due to the lack of effective treatment, the development and use of COVID-19 vaccine had become an important strategy to control the novel pneumonia epidemic.

Covid-19 was a single strand plus RNA virus, whose exposed spike protein (S protein) and receptor binding domain (RBD) on S protein were the main targets for the design of Covid-19 vaccines. In March 2020, the Covid-19 vaccine developed by China based on adenovirus vector and the mRNA technology platform developed by the United States which were the first vaccines entering clinical trials, followed were DNA vaccine and inactivated vaccine. By the end of December 2020, there were inactivated vaccine, nucleic acid vaccine (DNA vaccine and mRNA vaccine), carrier vaccine, protein subunit vaccine, live attenuated vaccine, virus-like particles vaccine. The sixty vaccine candidates in six different technical routes were approved to enter clinical trials. Some vaccines had been approved for conditional marketing or emergency use.

Due to the different development technology routes of different COVID-19 vaccines, there were still different shortcomings in terms of safety, effectiveness, stability of transportation and storage, and capacity.

Although the safety of COVID-19 vaccines in phase III clinical trials had been reported to be good, there were still theoretical safety concerns. For example, live attenuated vaccines needed to replicate in the body and carry a risk of virulent atavism infection or transmission. DNA vaccines carried the risk of foreign DNA entering the body and integrating into the host genome, resulting in oncogene activation, or inactivation of tumor suppressor genes, or chromosomal instability. The synthetic materials and coating materials used in the synthesis of mRNA vaccines may be toxic and might cause apoptosis of the surrounding host cells.

In the introduction of the target product of the Covid-19, WHO proposed that the protection efficacy of the Covid-19 should be at least 50%. Among the four vaccines whose effectiveness had been announced, the inactivated vaccine had a protective efficacy of 79.34%, the carrier vaccine 62-90%, and the mRNA vaccine above 90%, all of which met the requirements. But in the context of COVID - 19 pandemic disease, unfavorable evaluation or

directly compare the clinical efficacy of vaccine were appeared. That was because different vaccine clinical trial design and research field, the research results were different. Vaccine real protection effect still need to be extensively studied through subsequent large-scale phase IV

clinical trials or epidemiological studies after vaccinating.

In terms of storage and transportation of the Covid-19, mRNA vaccine required high storage conditions due to its unstable and easily degradable. A mRNA vaccine developed by the United States and Germany needed to be stored at -70℃. After thawing, vaccine vials could only be stored for 5 days in cold storage (2-8℃). The other mRNA vaccine was stable for only 30 days at 2-8 ° C and needed to be stored at -20 ° C.

Due to the need for virus culture process, the production of inactivated and attenuated vaccines required high bio-safety level and long production cycle, so there was some difficulty in scaling up production capacity.

This product was bacillus subtis spore vaccine. Various types of vaccines such as mRNA, adenovirus and inactivated virus via injection route were developed to prevent the infection of SARS-CoV-2. Although some of them have already been approved to against the COVID-19 pandemics, various drawbacks including severe side effects and instability in storage may hinder their applications. Bacillus subtilis (B. subtilis) is a generally recognized as safe (GRAS) and endotoxin-free gram-positive bacterium, which has been extensively employed as a host for expression of recombinant proteins. Its dormant spores are extraordinarily resistance to harsh environment conditions in gastrointestinal tract. This feature makes it an ideal candidate for oral administration to resist the environment. In this study, an engineered B. subtilis spore expressing the spike protein receptor binding domain (sRBD) of the SARS-CoV-2 on the surface was developed, and the result proved that it successfully increased the neutralizing antibody against sRBD in unvaccinated mice and human individuals after oral administration. These findings may enable the use of B. subtilis spore as oral vaccine against COVID-19 in the future.

The oral vaccine presents antigen through the gastrointestinal mucosa and could produce an immune response similar to that of conventional injection through different immune pathways. With the development of medicine and molecular biology technology, great progress had been made in the study of oral vaccine in the presentation of mucosal antigen, which could effectively induce immune response and immune tolerance in the body. The toxicity of the vaccine was very low, and the LD_{50} could not be measured by oral or peritoneal route. According to the toxicity grading standard, it was basically non-toxic. Long-term toxicity, specific toxicity and reproductive toxicity studies did not show any biological damage. Experimental data showed that the vaccine was extremely safe and well tolerated by patients.

2. Test subject

efficacy and safety of Bacillus subtilis spore.

3. Test objective

The efficacy and safety of " Bacillus subtilis spore " were evaluated with simulated tablet as control

4. Overall design and arrangement of the test

4.1. Test design

This study adopted a one-arm experimental design. The whole study mainly collected qualified normal healthy people without disease from the hospital, and excluded people with basic diseases such as hypertension, diabetes, hyperlipidemia and so on. Once confirmed, they were assigned to administer 1 dose of Bacillus subtilis spore. Follow-up observation and efficacy examination were performed on days 7, 14, 21 and 28.

If subjects had significant laboratory abnormalities or side effect at the end of the study, they should be followed up to normal.

4.2. Dose, method and course of treatment

Group	Dosage	Usage	Survey
Test group	1 Bacillus subtilis spore capsule at a time	Oral administration, once	28 days

Vaccine time window: Oral administration of the vaccine would be given immediately after the subjects were selected.

Essential medicines: over-the-counter medicines such as vitamins and minerals were allowed.

Medicines prohibited: antibiotics, thrombolytic drugs, anticoagulants, insulin, β-blockers, adenosine preparations, leucocyte adhesion inhibitors, other antioxidants, free radical scavengers, etc.

5. Subject selection

5.1. Inclusion criteria

Outpatient service (medical records of outpatient service shall be established), male or female, from 18 years old to 60 years old;

No hypertension, diabetes, hyperlipidemia and other basic diseases;

If the patient was a woman of gestational age, the pregnancy test at the time of screening should be negative; Contraception (oral or injectable contraceptives) should be used throughout the trial;

Obtained the informed written consent of the subject or the subject's immediate family member or the subject's guardian;

There was no serious cardiopulmonary liver and kidney insufficiency.

5.2. Exclusion criteria

Patients under 18 years of age or over 60 years of age;

Dementia who could not cooperate, or affecting the judgment of curative effect;

Women who were pregnant, breastfeeding or who might become pregnant during the study and who were not using effective contraceptives;

Patients suffering from tuberculosis, tumor and other organic lesions;

Known alcohol and drug dependence;

To determine the patients who were not suitable for this clinical observation;

People with coma, bleeding tendency and allergic constitution were excluded;

Treatments such as hormones, diuretics, hypertonic dehydrating agents, thrombolysis, anti-coagulation, and fibrillation that might affect the results of the study;

Staff directly involved in the study;

Other circumstances that other physicians or researchers had judged inappropriate for participating in the clinical trial

5.3. Case withdrawal criteria

Discontinuation of Bacillus subtilis spore due to side effect determined by the investigator;

Discontinuation of Bacillus subtilis spore due to other reasons (including voluntary withdrawal);

Unable to cooperate;

For reasons other than research-related, the investigator did not consider it appropriate to continue the clinical trial.

5.4. Management of cases of loss

Definition of cases of loss: all subjects who had completed the informed consent form and were screened for entry into the study, at any time and for any reason withdrawal, as long as the subjects did not complete the observation period specified in the protocol, was called cases of loss, including the following conditions:

A serious side effect occurred in the subject and, in the judgment of the physician, the case should be discontinued.

During the study, the subjects' original condition worsened or other symptoms occurred during the study that affected the observation of the study, according to the doctors decided that the clinical trial should be stopped.

Significant deviations occurred during the implementation of the clinical trial protocol, making it difficult to evaluate the vaccine effect.

Subjects were unwilling to continue the clinical trial.

Treatment of cases of loss: contacted subjects with reasons, recorded the time of last observation, and completed the assessment items that could be completed. For patients who withdrew from the study due to allergy or other side effect and failure to respond to treatment, the investigator should take appropriate treatment measures according to the actual situation of the subjects. The researchers should properly preserved the relevant experimental data of the cases of loss, not only for filing, but also for carrying out the complete analysis set statistics.

6. Test subject

6.1. Test subject

Generic name: Bacillus subtilis spore

Specifications: Tablets

Batch number:

Storage: under 4°C, sealed in the dark place

Production unit:

6.2. Vaccine packaging

Single 1 capsule, individually packed.

6.3. Administration

Test group：Oral approach, 1 capsule B. subtilis spore once a day. No other medication.

Start in the morning on an empty stomach.

Control group：Oral approach, 1 simulated tablet once a day. No other medication.

Start in the morning on an empty stomach.

6.4. Vaccine management

Preservation conditions of the study vaccine: under 23°C, the vaccine was kept in a closed and dark place.

The quality of the clinical trial vaccine, including the control tablet, should be checked regularly to meet the storage conditions. The test center would be reserved and managed by special personnel.

The use of the study vaccine was the responsibility of the investigator, who should not transfer the study vaccine to any non-clinical trial participant.

When distributing vaccine to subjects, researchers should fill in the registration form of vaccine distribution in a timely and accurate manner.

After the end of the trial, the remaining vaccine would be collected for unified disposal.

6.5. Combination of medicines and prohibited medicines

Other anti-influenza medicines should not be used during the trial.

7. Clinical efficacy indexes and safety evaluation criteria

7.1. Main efficacy indicators

Immunogenicity of vaccines

7.2. Other efficacy indicators

Safety of vaccines

Mortality

7.2.1 Immunogenicity of vaccines:

To test the immunogenicity induced by oral vaccine

Compared vaccine-induced immunogenicity with natural infection immunogenicity

7.2.2 Safety of vaccines

Observed whether mild to moderate symptoms such as fever and chills appeared after taking the vaccine;

Observed whether there were severe symptoms such as coagulation dysfunction and allergy after taking the vaccine;

Observed whether there were serious symptoms such as disability after taking the vaccine.

7.2.3 Mortality

Deaths were recorded for each group.

7.3. Security indicators

General data：physical examination

Laboratory examination：Routine blood examination (including erythrocyte count, leukocyte count, hemoglobin, platelet count, proportion of monocytes, lymphocytes and neutrophils), urine routine (erythrocyte, leukocyte, urine protein), liver and kidney function (including ALT, AST, TBIL, BUN, Cr).

Symptoms accompanying any discomfort were recorded by the investigator

a) No: No symptoms

b) Mild: Weak symptoms sometimes appeared

c) Moderate: persistent but not noticeable after distraction

d) Severe: Persisting no matter when

7.4. Follow-up examination

The first examination was performed on the day of study start (D0). Follow-up was conducted every 7 days (i.e. D7, D14, D21, and D28) for all clinical examinations, all indicators of the trial, and routine laboratory examinations.

Side effect should be recorded during routine daily clinical examinations. If any side effect was found, follow up immediately and informed the researcher.

7.4.1. When the test started

Signed informed consent.
Inclusion criteria and exclusion criteria.
Medical history was collected and the status of medication was inquired.
Routine physical examination.
Routine laboratory tests: Routine blood examination (including erythrocyte count, leukocyte count, hemoglobin, platelet count, proportion of monocytes, lymphocytes and neutrophils), urine routine (erythrocyte, leukocyte, urine protein), liver and kidney function (including ALT, AST, TBIL, BUN, CR), pregnancy test (women of child-bearing age), and other laboratory examination.
Combination medication was recorded.
Assigned random numbers.

8. Observation of side effect

8.1. Definition

Side effect: Any adverse medical event that occurred between the time patients signed the informed consent and were enrolled in the trial and the last follow-up, regardless of whether there was a causal relationship with the experimental vaccine, was considered as side effect.

Serious side effect: Any side effect and hematological and/or other laboratory abnormalities that occur that lead to the use of targeted medical care.

8.2. Criteria for determining the severity of side effect

When completing the side effect table for CRF, the investigator would use mild, moderate, and severe to describe the intensity of the side effect. For unified standards, side effect intensity was classified as follows:

Mild: Did not affect daily life;

Moderate: Affected daily life;

Severe: Severe affected on daily life.

Be careful to distinguish between the severity and intensity of side effect. Severe was used to describe intensity and was not necessarily a serious side effect (SAE). For example, a headache might be severe in intensity but might not be classified as a serious side effect (SAE) unless it met SAE criteria.

8.3. Criteria for determining the relationship between side effect and the study vaccine

The causal analysis of the relationship between all side effect (including serious side effect and general side effect) and the test vaccine was judged according to the five grades of almost certain, probable, possible, unlikely and unrelated. The first three side effects were defined as side effect to the vaccine. The following five aspects were causal analysis took into consideration:

Was there a reasonable sequential relationship between the time of initiation and the occurrence of a suspected vaccine side effect (ADR) (appear when using vaccine).

Did the suspected ADR conform to the type of ADR known to vaccines (consistent with the literature).

Whether the suspected ADR could be explained by the effect of combination medication, previous medication, the subject's clinical status, or other therapies (other explanations).

Did the suspected ADR disappear or decrease after a period of discontinuation of the vaccine.

Whether suspicious ADR reappear (reuse) after re-exposure to the same vaccine.

Causes analysis were carried out according to the following table, and the factors considered in the table were shown in the corresponding numerical table above.

Factors	1 Appear when use vaccine	2 Same as reference	3 Other causes	4 Disappear when stop vaccine	5 Reappear when reuse
Almost certain	+	+	−	+	+
Probable	+	+	−	+	?
Possible	+	+	±	±	?
Unlikely	+	−	±	±	?
Unrelated	−	−	+	−	−

The investigator should evaluate the possible association between side effect and the test vaccine and its combination using the following 5-level classification criteria:

Almost certain：Evidence of use of experimental vaccine; The chronological sequence of the occurrence of side effect and the administration of the experimental vaccine was reliable; The occurrence of side effect was more reasonably explained by the experimental vaccine than by other causes; The repeated vaccine test was positive; The pattern of side effect was consistent with what had been known about this or such vaccine.

Probable： Evidence of use of the experimental vaccine; The chronological sequence of the occurrence of side effect and the administration of the experimental vaccine was reliable; side effect were more likely to be explained by the experimental vaccine than by other causes.

Possible： Evidence of use of experimental vaccine; The chronological sequence of the occurrence of side effect and the administration of the experimental vaccine was reliable; Side effect might be caused by the experimental vaccine or by other causes.

Unlikely：Evidence of use of the experimental vaccine; Side effect were more likely to be caused by other causes; Repeated vaccine tests were negative or equivocal.

Unrelated：Patients did not take the experimental vaccine; Or the time sequence of the occurrence of side effect and the administration of the experimental vaccine could not be trusted; Or there were other significant causes that could lead to side effect.

8.4. Determination of serious side effect

side effect that met the following criteria (one or more) were classified as serious side effect（SAE）：

Die
In danger of life, eg. in danger of immediate death
Resulting in hospitalization
Permanently or severely disabled
Congenital malformation

Medical events that had not yet resulted in death, life danger, or hospitalization should also be considered as SAE when appropriate medical judgment was made that they were likely to cause harm to the subject or that vaccines or surgical treatment was required to prevent the occurrence of these conditions.

8.5. Record of serious side effect

Any serious side effect in the course of a clinical trial must be reported to the sponsor, the principal study institution, the contract research organization, the ethics committee, National Medical Products Administration, and the ministry of health P.R.China within 24 hours (contact details were as follows). At the same time, the investigator must complete the Serious side effect Form, recording the time, severity, duration, action taken, and outcome of the serious side effect.

9. Data administration

9.1. Filing and handing over of case report form

The case report form was completed by the investigator and must be completed by each selected case. After the completed case report form was reviewed by the clinical supervisor, the first copy was transferred to the data administrator for data entry and management.

9.2. Data entry and modification

Data entry and management should be in the charge by the data administrator specially assigned by the group leader hospital. The data administrator prepared the data entry plan, carried on the data entry and the management. In order to ensure the accuracy of the data, two data entry personnel should independently conduct double entry and proofreading.

For the questions in the case report form, the data manager would produce a question-answer form and sent questions to the researcher through the clinical supervisor. The researcher should answer and return the questions as soon as possible. The data manager would modify, confirm and enter the data according to the answers of the researcher, and should send out the question-answer form again if necessary.

9.3. Data locked

After confirmation of the established database was correct under blind review, the main researchers, sponsors and statistical analysts would lock the data. The locked data file would not be changed.

10. Statistic analysis

10.1. Analysis data set

Full analysis set：Refers to the collection of qualified cases and exclusions, but did not include exclusions.

Per Protocol Set：Refers to the collection of cases that met the inclusion criteria and completed the treatment plan, i.e., met the trial protocol case, did not take the banned medicines, the case completed CRF and the prescribed contents.

Security data set：Actual data on at least one treatment and documented safety indicators.

10.2. Statistical analysis method

10.2.1. Statistical analysis of population

Intent-to-treat, ITT：The ITT population was defined as all patients who were randomized to double-blind treatment and had received at least one trial vaccine treatment with a corresponding efficacy evaluation.

Per-Protocol, PP：PP population referred to the patients who had completed the vaccine treatment according to the protocol, and had completed all the evaluation contents without any significant deviation from the protocol.

Safety Population：All patients who had used the study vaccine once and had undergone at least one safety assessment were randomized to be included in the study's safety population. Safety population was the main population for safety evaluation in this study.

10.2.2. Statistical description

Whether it conformed to normal distribution:
Modified the statistical method or carried out data conversion in case of inconsistency;

With and without outliers: Conducted statistical and professional analysis to decide whether to choose or not;

Missing value processing of primary efficacy index data: when a certain primary efficacy data of individual subjects was missing, the data would be collected from the statistics and professional standpoint. If the shedding case was missing, transferred with the previous measurement data; For missing data only one measurement index, all data was used to fill the gap.

The proportion of shedding cases: If it exceeded 20%, it should be analyzed and explained;

Descriptive statistical analysis: Indicated mean, standard deviation, maximum, minimum, median, confidence interval, and frequency (composition ratio), etc.

10.2.3. Analytical method

The experimental group was compared with the control group by superiority comparison.

Measurement data: X^2 test, t-test, paired t-test, rank sum test, paired rank sum test and non-parameter test were used respectively statistical analysis to make statistical comparison and other methods.

Descriptive statistical analysis of side effect was performed.

10.2.4. Statistical expression

The results of repeated measurements were presented in tabular form with statistical graphs in order to easy read.

In general statistical tests, bilateral tests were used. If P was less than or equal to 0.05, it would be considered that the discriminant of the test was statistical significance.

10.2.5. Statistical software

The database was established by MS Access

SPSS/SAS software was used for analysis.

10.2.6. Contents of statistical analysis

The statistical analysis plan was written by the statistician, finalized before the database lock, and consisted of a variety of tables.The main contents of the analysis included:

Case distribution: different data sets in each group, case distribution in each center, comparison of total abscission rate, and detailed list of termination causes.

Comparability analysis: compared demographic data with other base-value indicators to measure the comparability of the two groups.

Effectiveness analysis: X^2 test and t test were used for main indicators and global indicators. Since this study was a multi-center clinical trial, central effect on the efficacy indicators should be considered in the analysis.

Analysis of the factors affecting the efficacy: such as age, sex, disease type, disease condition and so on, there were significant differences between the two groups before the use of vaccine, or if there were significant related factors that affected the vaccine effect, these factors should be used as co-factors when comparing the vaccine effect between the two groups for variables,

covariance analysis or Logistic regression analysis was required. The combination of medication and so on needed a detailed list.

Safety analysis: firstly, according to the requirements of side effect correlation, the side effect and adverse reactions of the two groups were listed and described (including the number of cases of various side effects, the number of cases and the conversion rate of "normal to abnormal" or "abnormal intensification" of laboratory test indicators before and after the test), and the reasons and explanations were listed.

11. Quality control and assurance

11.1. Quality control

During the study, clinical inspectors will be commissioned by the sponsor to visit each study center regularly to ensure that all the contents of the study plan were strictly followed and the study data were filled in correctly.

The whole clinical trial process strictly followed the provisions of the national GCP (Good Clinical Practice) and conformed to the ethical principles. Participants might strictly abide by the standard operating procedures of clinical trial study.

Participants in clinical trials should be relatively fixed, and participants might undergo uniform training and had uniform recording methods and judgment criteria.

The researcher should fill in the CRF truthfully, carefully and use pen or carbon pen.

All observations and findings in clinical trials should be verified to ensure the reliability of the data and to ensure that the conclusions of clinical trials were derived from the original data. There were corresponding data management measures in clinical trial and data processing stage.

Medical records and medical record forms were regarded as the original records and generally could not be changed. When making any corrections, the original record should not be altered. Additional statement could be used to explain the reason, and then signed and dated by the physician participating in the clinical trial.

The researchers should take active measures (notice further consultation, follow up) to control the shedding rate within 20%.

Subjects would record their vaccination status on a diary card.

Each center should submit its normal range and abnormal judgment criteria to the responsible unit of clinical trial and the clinical statistical unit to ensure the accuracy, reliability and abnormal judgment criteria of laboratory examination.

All laboratory data should be recorded in the original medical record and the results of the tests should be glued to the original medical record. Laboratory data within the normal range should also be recorded in the CRF, and data that were significantly higher or outside the clinically acceptable range should be verified by the physician participating in the clinical trial to make the necessary statements.

Administration of vaccines:

Preservation conditions of experimental vaccine: under 23° C, sealed in a dark place.

Periodic review of clinical trial vaccines, including the quality of control tablets; Conformed to storage conditions. The test center would be reserved and managed by special personnel.

The investigator was responsibility to the used test vaccine, who should not transfer the test vaccine to any non-clinical trial participants in the test.

When distributing vaccine to subjects, researchers should fill in the registration form of vaccine distribution in a timely and accurate manner.

After the end of the trial, the remaining vaccine would be collected for unified disposal.

11.2. Quality guarantee

11.2.1. Establish a multi-center coordination committee

The group leader should be responsible for the organization of the clinical trial center and the sponsor to form the clinical coordination committee. The main task of the coordination committee was to coordinate the implementation of the whole clinical trial and to study and solve the problems arising from the clinical trial. The sponsor was responsible for maintaining contact with the National Medical Products Administration.

11.2.2. Enact standard operating procedures for clinical inspectors

Supervisors appointed by the sponsor would monitor the whole process of the clinical trial. This included ensuring that subjects' rights and interests were protected and clinical trials were conducted in strict process in accordance with the requirements of clinical trial protocols and relevant laws and regulations.

12. Medical ethics and related legal issues

12.1. Guidelines for clinical trial on vaccines

The clinical trial would be conducted in accordance with the Helsinki Declaration and the clinical quality management practice (GCP) for vaccines. Before the start of the study, the study plan had been approved by the ethics committee of the hospital of the study leader unit. At the same time, the ethics committee would play a supervisory role throughout the trial process.

12.2. Investigator responsibility

The investigator might ensure that all participants in the study had a detailed understanding of the study protocol, study procedures and evaluation methods, as well as their responsibilities and roles.

12.3. Study subjects and informed consent

Prior to the inclusion of patients in the study, the investigator might provide a complete and comprehensive description of the purpose, procedures, and possible risks of the study to the patient or his or her designated representative. Patients should be made aware of their right to withdraw from the study at any time. Each patient might be given a written patient informed consent form prior to study. The study physician was responsible for obtaining signed informed consent form from each patient before the study and sending one of the signed informed consent forms to the subjects; The other was kept in the study archives. Any changes to the subject's informed consent might be documented and submitted to the IRB for approval. A copy of the new Informed Consent Form would be kept in the "Subject Informed Consent Form" file. Suggestions for modification were attached. The above changes could only be implemented if they were re-approved by the ERC, complied with the health regulations,

and signed by the participating institutions. Each subject or independent witness affected by the modification and any person involved in the informed consent discussion might sign and date two updated informed consent forms. He or she would be given a new form of informed consent. If the subject had a health care provider and agrees to notify the health care provider, it was recommended that the investigator explained the subject and the study to the subject's health care provider.

12.4. Implementation and modification of the study plan

Prior to the commencement of the study, the study protocol, informed consent, and other relevant materials would be submitted to an independent institutional review board (IRB), together with a table of contents or list. Clinical trials could commence only after the applicant had received all the ethical and legal documents necessary. These documents included a list of IRB members and their occupations and qualifications. If the IRB did not disclose the name of the committee, they might issue a statement assuring that the composition of the committee met the GCP standards. The formal IRB approval should mention the study topic, study number, study location, and other relevant documents. Documents might refer to the date of the decision and be signed by the members of the Committee.

Neither the investigator nor the organizer could change the protocol without prior written notice. Once the study plan was launched, any problems were found in the implementation process could be modified and improved under the jointly negotiated by the sponsor and the researcher. A document should be written and signed by the main researcher and the sponsor before implementation. At the same time, a report should be submitted to the ethics committee and the documents should be filed.

12.5. Termination of study

The sponsor or investigator had the right to decide completion time of the study. After communication between both sides noticed IRB as required by law.

Study materials (including completed, partially completed and blank case sheets, study vaccines, etc.) might be returned to the sponsor when the study might end early.

12.6. Relevant legal liability

The applicant should be legally liable for the losses caused by the participants in compliance with the plan,

law and professional standards.

13. Summary of test report

The data management and statistical analysis of this clinical trial were completed by the _____Statistics Teaching and Research Section. After the statistical analysis report was completed, the general statistical analysis report of this study and the statistical report of each analysis center would be written.

According to the statistical report, each experimental unit should write the summary of the sub-center, and the study leader should complete the summary report of the clinical trial and affixed the official seal.

14. Data save

In order to ensure the evaluation and supervision of the National Medical Products Administration and the sponsor, under normal circumstances, all study data records were stored

by the researchers after the end of the study, and the retention period was 5 years.

If the researcher failed to meet the preservation requirements, alternative arrangements might be made with the consent of the sponsor.

The investigator might obtain the Sponsor's written consent before destroying the records.

All the data of this clinical trial belonged to the sponsor. Except for the requirements of the National Medical Products Administration, the investigator should not provide them to any third party in any way without the written consent of the sponsor.

15. Publication and use of study results

DreamTec Research Limited (DTRL) was the owner of the data and results obtained in this study. If the researcher published the relevant content in journals or academic conferences, he/she might obtain the consent of the DTRL in advance.

16. Test plan

Date	Milestone
（1st day）	Completed the formulation of the trial protocol through ethics
	Each center began to enroll the first case in the screening period
	All the centers completed the enrollment of all the patients during the trial period
	All centers completed the follow-up work of all cases
（90th days）	Completed data entry and statistics work
	Completed the test summary report
	Ended of all trials

Research Team / Medical Consultants

Name	Position / Organization	Relevant Qualifications / Working Experience for the Project
Dr. Eric Tung Po Sze (Co-I)	Associate Professor, Hong Kong Metropolitan University	Ph.D. Chemistry (CUHK) M.Sc. Applied Toxicology (University of Surrey, United Kingdom)
Dr. Keith Wai Yeung Kwong (Co-PI)	Chief Scientific Officer and Executive Director, DreamTec Research Limited	B.Sc. in Biochemistry (University of Washington, USA) Ph.D. in Biochemistry (Molecular Medicine) (HKUST)
Dr. Liu Ying (Research Team Members)	Chief Medical Officer, DreamTec Research Limited	B.Sc. in Clinical Medicine (LiaoNing Medical College, China) Ph.D. in Biophysics (Peking University, China) Post-doctoral Fellow in Division Biomedical Engineering (HKUST) Senior Research Associate in Department of Biomedical Sciences (City University of Hong Kong) Technical Manager of Vanway Pharmaceutical Holdings Limited Medical Consultant, Health & Beauty International Holdings Limited
Dr. See Yunn Ho (Medical Consultant)	Functional & Integrative Medicine, LifeHealth Group Limited	M.B. B.S. (London) MRCP (United Kingdom) DRCOG
Dr. Stephen Chan (Medical Consulant)	Chief Medical Officer, LifeHealth Group Limited	M.B. B.S. (NUS) MMed Fam. Med. (NUS) LMCHK

Informed Consent form

TITLE OF THE STUDY
The Development of a COVID19 Oral Vaccine Consisting of *Bacillus Subtilis* Spores

INTRODUCTORY SENTENCE
You are invited to participate in a research study:
The Development of a COVID19 Oral Vaccine Consisting of *Bacillus Subtilis* Spores.

Bacillus subtilis RBD Spores is a health supplement that enhances your immunity to generate and boost neutralizing antibody to prevent the virus from attacking the human body. Postbiotics formula contains "*Bacillus subtilis* coating with RBD of spike protein in SARS-COV2", It induces a series of immune responses in human body to generate significant immune affection therefore provide protection against the viruses.

Features

1. Improving immunity
2. Boost antibody
3. Safe and minimum side effects

PURPOSE OF THE STUDY
To test the antibody level during the period of consuming the Bacillus subtilis RBD Spores

PROCEDURES
- Participants who understand the plan of health food and trial, confirmed meet the guideline and completed consultation with program staff.
- During the trial, the participants must follow the consumption guideline.

- The trial period is 44 days, which included 3 Box (9capsules), laboratory tests and a questionnaire. The trial and questionnaire content are as follows:
  1. It is recommended to stop taking any immune enhancement health products during the trial
  2. Total 9 capsule, consumption 1capsule on day 1, day 2, day 3, day 14, day 15, day 16, day 28, day 29 and day 30 respectively
  3. Please fill in the **Form** during the trial

POTENTIAL RISKS/STRESS/PAIN/DISCOMFORTS/OTHER FACTORS AND THEIR MINIMIZATION
- If you are taking other medicines or similar function drugs at the same time, please consult a doctor before trial

- If you have any drugs allergy, please consult a doctor before trial
- This trial may cause discomfort such as: diarrhea
- If you have any discomfort caused by your own related diseases or physical conditions during the test, please stop taking this product and consult a doctor immediately
- Blood sample is required before this trial
- People who have not been vaccinated. If you accept to start the trial (44 days), you will not be vaccinated during this period. If you vaccinate, the participant at their own risks. Due to the termination of the test, the participant shall be responsible for any cost for this trial
- This plan is self-contained, program in charge shall not be held responsible for any accidents and/or personal injuries howsoever caused to the participant and the participant at their own risks

POTENTIAL BENEFITS
- Enhances participants immunity to generate and boost neutralizing antibody to prevent the virus from attacking the human body.

PARTICIPATION AND WITHDRAWAL

- Your participation is entirely voluntary and that you can choose to withdraw from the study at any time you want without any penalty or negative consequences.

CONFIDENTIALITY

- The test report will be kept by program center

QUESTIONS AND CONCERNS

If you have any questions or concerns about the research study, please feel free to contact Dr. Sunny Wong of Doctor Think Tank Academy at 6846-8772. If you have questions about your rights as a participant of this research study, please contact the Research Ethics Committee of Doctor Think Tank Academy at admin@dttac.com.

<Please complete by a participant>

Participant No. (will be provided by the program staff)

_____

Hypothesis (will be provided by the program staff)

_____

Consent

I have read and understood this trial, and the product developer has also provided me with detailed explanations and answered all my queries. I have already known the purpose and risk of this trial and voluntarily consent to participate in the trial described above. I have been given a copy of this consent form.

Paticipant :_____

Paticipant Signature :_____

Phone no. : _____

Date : _____