CLINICAL TRAIL PROTOCOL

Protocol Title: A Safety and Immunogenicity Study of a Zoster Vaccine in Healthy Adults >= 40 Years.

Collaborators: Henan Center for Disease Control and Prevention

Sponsor: Shanghai Institute of Biological Products Co.,Ltd

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BACKGROUD INFORMATION

Herpes Zoster (HZ or Shingles) is an acute inflammatory skin disease caused by reactivation of varicella-zoster virus (VZV) lurking in human sensory ganglia. The first infection of VZV is varicella, and then the virus lurks in the dorsal root ganglion for a long time. With the immune function weakening, the varicella-zoster virus can be reactivated, and then induce herpes zoster. The incidence and severity of herpes zoster increase with age, and obviously over 50 years old, which is related to the decrease of cellular immunity level. It is estimated that about half of the elderly over 85 have had at least one episode of herpes zoster. China has not carried out nationwide epidemiological studies on herpes zoster, which are generally carried out in local areas. According to epidemiological studies in Guangdong, the incidence rate of herpes zoster is about 5‰, and the lifetime incidence rate is about 3.46%. The incidence rate of the whole population in Beijing is higher than 2‰ and that in Taiwan is 3.4 ~ 5.0 ‰. Thus, the incidence rate of the whole population in China varies from region to region. With the population aging, the incidence of herpes zoster will further increases. Vaccination is currently considered as an effective strategy of controlling herpes zoster.

At present, vaccine produced by SIBP has received clinical approval, ready to carry out phase I/ II clinical trials, safety and immunogenicity of the vaccine will be evaluated by clinical trials.

STUDY OBJECT

First objects: to evaluate the safety of a dose of live attenuated zoster vaccine in healthy people above 40 years old; to analyse VZV specific serum conversion rate, Geometric mean titer, geometric mean fold increase and 95% Confidence. Serum for antibody responses 30 days post-vaccination were compared with control vaccine and placebo.

Secondary objects: to evaluate the safety of a dose of live attenuated varicella vaccine in healthy people above 40 years old; to evaluate the safety of a dose of placebo in healthy people above 40 years old; to evaluate the immunogenicity persistence of subjects on the 90th, 180th and 360th days after vaccination.

STUDY DESIGN

This will be a randomized, blind, one-center, placebo control study conducted by Henan Center for Disease Control and Prevention. There will be three groups: Zoster vaccine (>=4.3LgPFU VZV)、 Varicella vaccine (>=3.3LgPFU VZV)、Placebo (with no VZV).

All subjects will be inoculated with the corresponding vaccine. Then subjects will receive immediate response observation for 30 minutes and systematic safety observation for 7 days after each dose of vaccination. After 7 days of vaccination, the adverse events will be observed by weekly regular follow-up and the subjects' reporting.

All subjects will be collected serum samples at day 0 before the vaccination, day 30th and day 90th after the vaccination. After unmasking，subjects in Group A will be collected serum samples at day 180th and day 360th after the vaccination. All serum samples will be detected FAMA antibody. See Table below.

Subjects and Procedure Table of Phase I Clinical Trials

Group	Age	Dosage and Number of subjects		Inoculation	Serum collection	Safety observation
Zoster vaccine	>=40 years	>=4.3LgPFU VZV	24	Day 0	Day 0	The local and Systemic AE and SAE will be observed for 6 months after inoculation.
Varicella vaccine		>=3.3LgPFU VZV	24			
Placebo		with no VZV	24			
Total			72	/		/

Subjects and Procedure Table of Phase II Clinical Trials

Group	Age	osage and Number of subjects		Inoculation	Serum collection					Safety observation
					Day 0	Day 30	Day 90	Day 180	Day 360	
Zoster vaccine	>=40 years	>=4.3LgPFU VZV	150	Day 0	150	150	150	150	150	The local and systemic AE and SAE will be observed for 6 months after inoculation.
Varicella vaccine		>=3.3LgPFU VZV	150	Day 0	150	150	/	/	/	
Placebo		with no VZV	150	Day 0	150	150	/	/	/	
Total	/		450	/						/

STUDY ENDPOINT

Primary endpoint:

To investigate adverse events (AE) within 30 days and serious adverse events (SAE) within 6 months after inoculation as Primary endpoint in Phase I/ II Clinical Trials.

Secondary endpoint:

To detect the serum conversion rate at day 30 after inoculation;

To detect the serum VZV specific Geometric mean titer（GMT） at day 30 after inoculation;

To detect the serum VZV specific GMT increase fold（GMI） at day 30 after inoculation;

To detect the serum Seroconversion、GMT、GMI at day 90/180/360 after inoculation;

SAFETY OBSERVATION

Systemic adverse reactions: fever, headache, fatigue, nausea, vomiting, diarrhea, muscle pain, cough, allergy (anaphylactic shock, urticaria, vascular edema, etc.).

Local adverse reactions: pain, redness, swelling, induration, rash (injection site), itching, skin mucous membrane.

The events (hospitalization, hospitalization time, disability of work ability, life or death, congenital malformation and so on) occur during clinical trial.

IMMUNOGENICITY OBSERVATION

Conversion rate: pre-vaccination FAMA titer < 1:8 and post-vaccination titer ⩾ 1:8 or a pre-vaccination titer ⩾ 1:8 and at least a 4-fold increase in the post-vaccination titer
GMT: geometric mean titer.
GMI: GMT increase fold.

EVALUATION CRITERIA OF SAFETY

The safety evaluation of each group will be divided into three stages. All the AE from the inoculation to day 14 after inoculation; All the AE from day 0 after inoculation to day 30 after inoculation; All the SAE from day 0 to the 6 months after inoculation.
The first stage is the basis for the Phase II Clinical Trials of the same vaccine, and will be carried out under blind. All the stages are the basis for evaluation of vaccine safety. If each evaluation is not found level 4 local and systemic adverse reactions associated with vaccine and the total incidence rate of level 3 of local and systemic adverse reactions and abnormal laboratory test which associated with the vaccination is lower than 15%, that the vaccine will be acceptable safety.

STUDY STATUS

Record Verification: August 2018
Study Start: November 2018
Primary Completion: December 2019
Study Completion: December 2020

ELIGIBILITY

Inclusion Criteria:
Healthy volunteers aged over 40 years (male or female).
Able to comply with all clinical trial protocol requirements and willing to complete all the visit plan process during the whole clinical trial observation period.
Able to understand the content of informed consent and willing to sign the informed consent.
Able to complete the diary card independently.
Patients with chronic diseases need to be in a stable period.
Axillary temperature ⩽37.0° C.

Exclusion Criteria:
Prior history of herpes zoster.
Prior history of vaccination with herpes zoster vaccine or chickenpox vaccine.
History of allergic disease likely to be exacerbated by any component of the vaccine.
Taking immunoglobulins and/or any blood products within the last 3 months or will receive these products during the study period.
Taking certain pharmaceuticals to be like salicylate kind, including aspirin, and difluorosalicylic, or going to take these medicine during the study period.
Participation in another research study involving receipt of an investigational product in the last 30 days.
Prior administration of live vaccine in last 30 days.
Prior administration of subunit vaccine, inactivated vaccine or allergic therapy in last 14 days.

History of serious disease and the participation in the clinical trial is likely to increase the disease risk and interfere with the observation of clinical trial index.
Taking immunosuppressive therapy in last 6 months.
Any autoimmune disease or immunodeficient state, autoimmune disease or immunodeficient disease.
Active tuberculosis patient.
Acute or chronic infections at the vaccination day (axillary temperature≥ 38.0° C).
Coagulation disorders (coagulation factor deficiency, coagulopathy or platelet disorder) diagnosed by doctors, or obvious bruises or blood coagulation noticed.
Woman who is breast-feeding.
Previous history of mental and neurological diseases (e.g. depression, epilepsy or convulsion)
Planned to move before the end of the study or leave the country for a long time during the scheduled study visit.
(Volunteers in Phase I Clinical Trials) Abnormal Blood Routine and Biochemical Indexes before Inoculation (except for minor abnormalities that are not clinically significant as judged by doctors)
Any other conditions may compromise the safety or availability of participants in the judgment of the investigator.

DATA STATISTICS

Statistics analysis of immunogenicity

The pre-vaccination and post-vaccination geometric mean of antibody and its 95% confidence interval (confidence interval, CI) will be described. The post-vaccination serum conversion rate and their 95% CI will be described. Comparisons will be conducted to evaluate differences in response between study groups using a χ^2 test or Fisher's exact test to compare to the difference of serum conversion rate. Statistical significance will be considered at a level of $\alpha = 0.05$ and all tests will be 2-sided.
If the lower limit of 95%CI of post-vaccination serum conversion rate in the Zoster vaccine group is not lower than 72%, the immunogenicity will reach the design requirements.

Statistics analysis of safety

After the inoculation, the number of adverse reactions (rate), number of cases and adverse reaction grade were recorded. The number of adverse events after inoculation will be described. Comparisons will be conducted to evaluate differences in response between study groups using a χ^2 test or Fisher's exact test to compare to the difference of adverse events rate. Statistical significance will be considered at a level of $\alpha = 0.05$ and all tests will be 2-sided.

APPENDIX Ⅰ. GRADING STANDARDS FOR SEVERITY OF SAFETY INFORMATION

The Event of clinical response and laboratory abnormalities after vaccination is judged by the China State Food and Drug Administration on "Guidelines for the classification of adverse events in vaccine clinical trials ".

Grading of Local Adverse Events

Local Adverse Reactions	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potential Life Threatened (Grade 4)
Pain	Do not affect activity	Influence activities or multiple use of non-narcotic analgesics	Affect daily activities or multiple use of narcotic analgesics	Emergency or hospitalization
Induration	<15 mm	15-30 mm	>30 mm	Gangrene or exfoliative dermatitis
Redness	<15 mm	15-30 mm	>30 mm	Gangrene or exfoliative dermatitis
Swelling	<15 mm and does not affect activity	15-30 mm or affect activity	>30 mm or limit daily activity	Gangrene
Rash (injection site)	<15 mm	15-30 mm	>30 mm	
Itching	Injection site itching	Injection of moderate itching	Overall Itching	

Grading of Systemic Adverse Events

Systemic Adverse Reactions	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potential Life Threatened (Grade 4)
Fever	37.1-37.5℃	37.6-39.0℃	>39.0℃	
Headache	No activity, no treatment	Transient, slightly affected activity requiring treatment (multiple use of non-narcotic analgesics)	Severe effects on daily activities, initial anesthetic response	Refractory, repeated anesthetic treatment. Emergency or hospitalization
Fatigue and fatigue	The normal activity is less than 48 hours, and it did not affect the activity	Normal activity decreased from 20% to 50% > 48 hours, slightly affecting activities	Normal activity decreased by more than 50%, seriously affecting daily activities, unable to work	Unable to take care of oneself, emergency or hospitalization
Nausea and vomiting	1~2 times per 24 hours, intake is normal and does not affect the activity	2 ~ 5 times per24 hours, intake is significantly reduced, or limited activity	> 6 times within 24 hours, no obvious intake, the need for intravenous infusion	requires hospitalization or other nutrition because of hypotension, shock
Diarrhea	Mild or transient, 2 ~ 3 stools per day or mild diarrhea lasting for less than 1 weeks	Moderate or persistent, 4~5 times per day, or more than 1 week diarrhea	> 6 times of water stool per day, or blood diarrhea, orthostatic hypotension	Hypotension shock requiring hospitalization
Myalgia	Not affecting daily activities	Muscle tenderness at the non injection site slightly affects daily activity	Severe muscle tenderness seriously affects daily activities	The symptoms are obvious, muscle necrosis, emergency or hospitalization

Cough	Transient, without treatment	Persistent cough, effective treatment	Paroxysmal cough, treatment can not control	Emergency or hospitalization
Allergy	Pruritus without skin rash	Local urticaria	Extensive urticaria, vascular edema	Severe allergy
Other adverse or clinical adverse reactions (based on the correspondi ng criteria)	Do not affect activities	Slightly affects activities without drug treatment	Serious impact on daily activities requires drug treatment	

APPENDIX Ⅱ. THE RELATIONSHIP BETWEEN ADVERSE EVENTS AND TRIAL VACCINES

Absolutely unrelated: Because of other factors lead to adverse events, there is evidence that adverse events are caused by other causes, not related to vaccination.

Possible unrelated: Adverse events probable be caused by other factors, such as the clinical status of the subjects, other treatment or concomitant medication, inconsistent with the known adverse reactions of vaccination.

Quite possible related: Adverse events are consistent with known information of vaccine, and there is a causal relationship with the vaccine, not by other factors, such as the clinical status of the subjects, or other treatment with medication.

Possible related: Adverse events are consistent with known information of vaccine, and there is a causal relationship with the vaccine, not by other factors, such as the clinical status of the subjects, or other treatment with medication.

Related: Adverse events are consistent with known information of vaccine, and there is a causal relationship with the vaccine, not by other factors, such as the clinical status of the subjects, or other treatment with medication. In addition, adverse events will be repeated when subjects are tested with the vaccine.