

Cover Page

Study Title:

A double-blind, randomized, parallel, placebo-controlled study to evaluate the efficacy and safety of probiotics *Lactobacillus paracasei* (eN-Lac[®]) for the treatment of children with perennial allergic rhinitis.

Study Drug:

Lactobacillus paracasei (LP) 2×10^8 colony-forming units (cfu) per capsule, 2×10^9 cfu per capsule, 10^{10} cfu per capsule

Protocol No.:

GMENA040813

Emergency Contact:

Grace Lin (SAE Contact Responsible)
Virginia Contract Research Organization Co., Ltd.
3F, No. 2, Ln. 258, Ruiguang Rd., Taipei, Taiwan
Tel: 886-2-2657-5399 Fax: 886-2-2657-9678

Sponsor Information:

Genmont Biotech Inc.
No.8, Nan-Ke 7th Rd., Tainan Science-Base Industrial Park, Tainan County, Taiwan
Tel: 886-6-505-2151 Fax: 886-6-505-2151

Contract Research Organization (CRO) Information:

Virginia Contract Research Organization Co., Ltd.
3F, No. 2, Ln. 258, Ruiguang Rd., Taipei, Taiwan
Tel: 886-2-2657-5399 Fax: 886-2-2657-9678

Protocol Author(s):

Dr. Chun-Chun Li
Virginia Contract Research Organization Co., Ltd.

Compliance of Guidance and/or Rules and Regulations:

This protocol is designed as according to the ICH guidance and the current Taiwan health authorities' rules and regulations.

Confidentiality:

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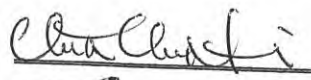
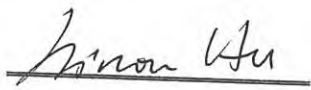
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Internal Signature Page

I have understood the obligations as an officer providing service in the organization(s) listed on the cover page of this document, and agreed to perform the study in my responsible aspects, in compliance to the protocol and good clinical practice (GCP) and the current rules and regulations set forth by the applicable health authorities and international conference on harmonization (ICH).

Affiliation	Name	Position	Signature	Date
Virginia Contract Research Organization Co., Ltd.	Dr. Chun-Chun Li	Protocol Writer		<u>Oct-17-2006</u>
Virginia Contract Research Organization Co., Ltd.	Kent Ko	Study Manager		<u>Oct-17-2006</u>
Virginia Contract Research Organization Co., Ltd.	Simon Hu	Statistician		<u>Oct-17-2006</u>

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Investigator's Signature Page - 1

I have understood the obligations as a clinical trial investigator and agreed to perform and report the study in compliance to the protocol and good clinical practice (GCP) and the current rules and regulations set forth by the applicable health authorities and international conference on harmonization (ICH).

Affiliation	Name of investigator	Position	Signature	Date
MacKay Memorial Hospital - Taipei	Shyh-Dar Shyur, M.D.	Section Chief, Section of Pediatric Allergy & Immunology	Shyh-Dar Shyur	Oct. 19, 2006

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Investigator's Signature Page - 2

I have understood the obligations as a clinical trial investigator and agreed to perform and report the study in compliance to the protocol and good clinical practice (GCP) and the current rules and regulations set forth by the applicable health authorities and international conference on harmonization (ICH).

Affiliation	Name of investigator	Position	Signature	Date
Chang Gung Children's Hospital	Dah-Chin Yan, M.D.	Chief, Division of Taipei Pediatrics, Department of Pediatrics,	Dah-Chin Yan	Oct 18, 2006

Abbreviations and Definition of Terms

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under curve
BUN	Blood urea nitrogen
Cfu	Colony forming unit
CIB	Clinical Investigator's Brochure
COSART	Coding symbols for thesaurus of adverse reaction terms
CRF	Case report form
CRO	Contact research organization
Dp	Dermatophagoides pteronyssinus
Der p5	Dermatophagoides pteronyssinus 5-Glutathione S-transferase
DNA	Deoxyribose nucleic acid
DRC	Daily record card
EC	Ethics committee
ECG	Electrocardiogram
ENT	Ear, nose, and throat
GCP	Good clinical practice

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GRAS	Generally regard as safe
ICD	International classification of disease
ICH	International conference on harmonization
IEC	Independent ethics committee
IFN- γ	Interferon- γ
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IP	Investigational product
IRB	Institutional review board
IRB	Institutional review board
ITT	Intention to treat
LP	<i>Lactobacillus paracasei</i> = eN-Lac [®]
NTSS	Nasal total symptom score
PAR	Perennial allergic rhinitis
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per protocol
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Stand error

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SGOT	= AST
SGPT	= ALT
Th1	T helper cell type I
Th2	T helper cell type II
VCRO	Virginia Contract Research Organization Co., Ltd.
WBC	White blood cell
γ -GT	Gamma glutamyl transpeptidase/transferase

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1. Protocol Synopsis

1.1 Synopsis

Study Title	A double-blind, randomized, parallel, placebo-controlled study to evaluate the efficacy and safety of probiotics <i>Lactobacillus paracasei</i> (eN-Lac®) for the treatment of children with perennial allergic rhinitis (PAR)
Study Phase	Phase II
Investigational Product	<i>Lactobacillus paracasei</i> 1. 2×10^8 colony-forming units (cfu) per capsule 2. 2×10^9 cfu per capsule 3. 10^{10} cfu per capsule
Active Ingredient	<i>Lactobacillus paracasei</i>
Route of Administration	Oral
Study Objective(s)	1. To evaluate the dose response relationship of investigational product in children with PAR 2. To determine the optimal dose of investigational product in children with PAR 3. To evaluate the efficacy profile of investigational product in children with PAR 4. To evaluate the safety and tolerability profiles of investigational product in children with PAR
Diagnosis and Main Subject Inclusion Criteria	1. Subjects with age of 5-16 years old (inclusive) 2. Subjects with a history of PAR for at least 1 year 3. Subjects with either one of the following test results (test results within 12 months before study are acceptable): a) Positive skin-prick test reaction (wheal ≥ 3 mm larger than the diluent control) b) Positive reaction determined by the CAP or MAST system 4. Subjects with mean nasal total symptom score (NTSS) of no less than 5 throughout the screening period (4 to 10 days); at least 4 days should be recorded during the screening period; and the NTSS of the day before day-0 (first dosing day) visit is no less than 5 5. Subjects' parents or their legally acceptable representatives have signed the written informed consent form
Study Structure	Parallel
Duration of Treatment	12 weeks

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Center	2
Blinding	Double blind
Treatment Arm	Four arms
Randomization	Permuted randomization stratified by center
Subject Sample Size	Approximately 140 subjects will be enrolled for treatment for collecting at least 120 evaluable subjects.
Treatment Assignment	Subjects who meet all eligible requirements for entry into the study will be randomized into one of the four treatment groups in 1:1:1:1 ratio as shown below: 1. One capsule of <i>Lactobacillus paracasei</i> 2×10^8 cfu per capsule, once daily 2. One capsule of <i>Lactobacillus paracasei</i> 2×10^9 cfu per capsule, once daily 3. One capsule of <i>Lactobacillus paracasei</i> 10^{10} cfu per capsule, once daily 4. One matching placebo capsules, once daily
Primary Endpoint	Net change of the 12th week evaluation compared to the baseline on the mean daily NTSS (= Mean daily NTSS during screening period – Mean daily NTSS during the 12th week of treatment); NTSS is determined by the severity of allergic symptoms, including sneezing, rhinorrhea, nasal itching, and nasal stuffiness. These symptoms are evaluated using a four-point scale, namely, 0 = Absent, 1 = Mild (present but not disturbing), 2 = Moderate (disturbing but not hampering daytime activities and/or sleep), 3 = Severe (hampering daytime activities and/or sleep). NTSS is calculated by the sum of the scores of the 4 symptoms. NTSS is recorded daily by patient's DRC.

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Secondary Endpoints	1. Net change of the 2nd, 4th and 8th week evaluations compared to the baseline on mean daily NTSS by patient's DRC 2. Net change of the 2nd, 4th, 8th and 12th week evaluations compared to the baseline on each individual symptom score rated by NTSS by patient's DRC 3. Net change of the 2nd, 4th, 8th and 12th week evaluations compared to the baseline on NTSS by investigator's evaluation at site 4. Net change of the 2nd, 4th, 8th and 12th week evaluations compared to the baseline on each individual symptom score rated by NTSS by investigator's evaluation at site 5. Global assessment by the investigator as categorized into levels of complete relieve, partial relieve, no relieve, worse. 6. Net change of the serum interferon-γ (IFN-γ) concentration during the treatment period (IFN-γ at visit 6 – IFN-γ at baseline) 7. Net change of the serum total immunoglobulin E (IgE) concentration during the treatment period (IgE at baseline – IgE at visit 6) 8. Adverse event incidence 9. Change in physical examinations (4th and 12th week evaluations compared to the baseline) 10. Net change of the 4th and 12th week evaluations compared to the baseline on the laboratory test results, including WBC with differential counts, platelet, RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, AST, ALT, albumin, total protein, total bilirubin, alkaline phosphatase, LDH, creatinine, blood urea nitrogen, uric acid, glucose, Potassium, Calcium, Phosphorus, Sodium, Chloride, Magnesium, and Iron. 11. Changes in urinalysis from baseline compared to the 4th and 12th week evaluations, including items of WBC, RBC, pH, protein, glucose, and ketone body. 12. Net change from baseline in vital signs, including blood pressures, pulse rate, body temperature, and respiratory rate
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Statistical Analysis

Evaluability

Three populations will be introduced for statistical analysis. The intent-to-treat (ITT) population will comprise all randomized patients who took at least one dose of study medication. The per-protocol (PP) population is a subset of ITT population and all patients included in this population should satisfy the following conditions.

- (1) dosed with at least 75% of total study medications
- (2) with primary efficacy measurement
- (3) not taking any prohibited medications

Safety evaluations will be performed on ITT population. Efficacy analysis will be performed on ITT and PP populations. The conclusion of efficacy of the study will be made according to the results of ITT analysis.

Analysis

The primary endpoint, net change of the 12th week evaluation compared to the baseline on the mean nasal total symptom score (NTSS), will be analyzed by using the method of ANCOVA incorporating treatment, center, treatment-by-center as factors and their respective baseline values as covariate. This statistical model was utilized to test the hypothesis of:

H₀: treatment effects among the four treatment groups were identical (i.e., no drug effect), vs.

H₁: treatment effects among the four treatment groups were NOT identical.

In addition to the aforementioned statistical analysis, multiple comparisons will also be performed to examine the treatment effect of each dose level compared to placebo.

Secondary efficacy endpoints, including net change of the 2nd, 4th and 8th week evaluations compared to the baseline on NTSS, net change of the 2nd, 4th, 8th and 12th week evaluation compared to the baseline on each individual symptom score rated by NTSS, net change of the serum interferon- γ (IFN- γ) concentration during the treatment period (IFN- γ at visit 6 – IFN- γ at baseline), and net change of the serum total IgE concentration during the treatment period will be analyzed by using ANCOVA incorporating treatment, center, treatment-by-center as factors and their respective baseline values as covariate. Investigator's global assessment on the efficacy will be analyzed by Cochran-Mantel-Haenzel test.

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**Statistical Analysis
(Continued)**

Adverse events will be reported by treatment groups and by physiological systems as appropriate. Incidence of adverse events between treatments will be analyzed by Cochran-Mantel-Haenzel test ($\alpha=0.05$). Changes in physical examinations will be displayed for each individual system. Net changes from pre-treatment in laboratory test results will be analyzed by descriptive statistics with 95% confidence intervals provided. Changes in urinalysis will also be summarized by descriptive statistics. Vital signs will also be summarized descriptively.

All statistical tests utilized will be two-tailed with $\alpha=0.05$. As no inferential conclusion will be made based on the result of this phase II study, the type I error is intentionally not adjusted. Summary statistics will be provided and the trend of treatment effects will also be graphed.

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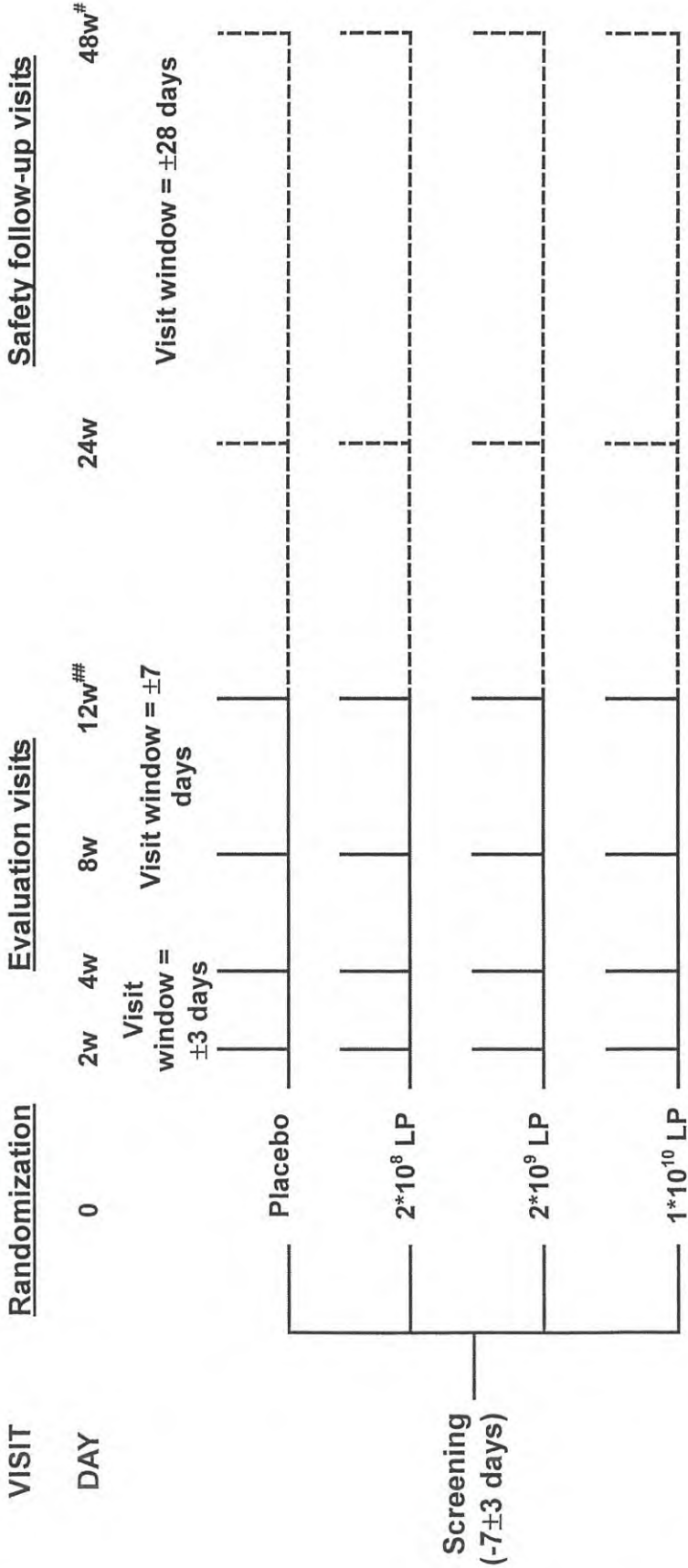
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1.2 Flow Chart

Procedures to be done		Screening visit	Randomization visit	Evaluation visits				Final evaluation visit	Safety Follow-up visit			Protocol Section
		1	2	3	4	5	6	7 [#]	8 [#]			
Visit												
Week		-1	0	2	4	8	12	24	48			
Visit window (day)		±3	Not applicable	±3			±7			±28		
Informed consent signed/given		X									6.1.1	
Inclusion and exclusion criteria		X	X								6.1.2	
Weight		X	X	X	X	X	X				6.1.3	
Height		X									6.1.3	
Demographic data		X									6.1.4	
Medical history (including history of allergic rhinitis)		X									6.1.5	
Urine pregnancy test (applicable only)		X									6.1.6	
Vital signs		X					X				6.1.7	
Physical examinations		X			X		X				6.1.8	
Hematology**		X			X		X				6.1.9	
Biochemistry***		X			X		X				6.1.9	
Urinalysis****		X			X		X				6.1.10	
Allergen tests		X*									6.1.11	
*Previous medication history*****		X									6.1.12	
Subject identifier assigned		X									6.1.13	
Subject randomization number assigned			X								6.1.13	
NTSS recording by patient's DRC		Every day										
NTSS rated by investigator		X	X	X	X	X	X				6.1.14	
Dispense patient diary record card (DRC)		X	X	X	X	X					6.1.14	
Retrieve and review patient DRC			X	X	X	X	X				6.1.14	
Serum IFN-γ		X					X				6.1.15	

Clinical Schematic Diagram



The follow-up visit can be conduct by telephone contact.
The subject can choose to convert to a 3 months open-label LP 2*10⁹ cfu compassionate treatment at the end of study treatment duration. The subject will be considered as a completed case even he/she doesn't convert to the open-label treatment at the end of study treatment duration.

2. Introduction

2.1 Disease Background

Allergic rhinitis is known as one of the most prevalent atopic diseases worldwide ranging from 5 to 22% incidence in different countries¹. This disease is an immune reaction to allergens, typically found to be house dust mites, animals, and pollen. Clinical signs and symptoms of allergic rhinitis include rhinorrhea, nasal congestion, sneezing, and nasal and ocular itching. Except for avoiding allergen contact and desensitization approach, management of allergic rhinitis is focusing on symptom control. Approaches to allergic rhinitis symptom control are mainly by the use of anti-histaminic agents. However, continuing use of anti-histamines may post safety concerns, especially their long-term use in younger patients under the age of 18 years old. Probiotics as an immune-modulator via balancing Th1 and Th2 immune activities, namely, promoting Th1 effects and inhibiting Th2 activity, may produce control and alleviation of allergic rhinitis symptoms². It is therefore a potentially more desirable manner considering the safety nature of probiotics being GRAS (generally recognized as safe) and endogenous. Less adverse effects would be expected even after long-term treatment of probiotics, compared to antihistamines and other symptom control chemical agents.

2.2 Investigational Product Background

As the fetus intestinal tract being sterile, all of the colonized normal flora are acquired after birth, starting from passing through the birth canal during delivering. Normal flora population in the intestinal tract stays stable once it is established, usually at 12 months after given birth. Normal flora species are predominantly found as *Bacteroides* species. *Bifidobacteria*, *lactobacilli*, *staphylococci*, and *clostridia* species were also seen to allocate in different segments of the gastrointestinal tract¹⁴. *Lactobacillus* species, namely, *Lactobacillus casei* and *Lactobacillus paracasei*, have shown to be particularly beneficial due to the known properties of gut wall adhesion and the ability to produce bacteriocin, hydrogen peroxide and biosurfactants. These findings have made the possibility of administering *Lactobacillus* as probiotics a tool to improve health of the host³. In particular, *Lactobacillus casei* has been shown to enhance the immune response to pathogens and reduce the hypersensitivity reaction to allergens in children⁴. The ability of *Lactobacillus casei* to decrease mucosal permeability in the small intestine and diminish the production of harmful materials in the large intestine may explain partially the beneficial effect to the host's body⁵. Nevertheless, the exact mechanism remains unclear.

Probiotics is mostly recognized as viable microorganisms to be given to the

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human body in adequate dose that alters host's normal flora and delivers health effects to the body^{3,6,14}. For probiotics to show effectiveness for enhancing the health status, the given viable microorganisms have to be able to sustain its viability through host's digestive processes, to colonize the intestinal walls for exerting colonization resistance, and to be with no pathogenic or toxic effects to the host⁷. Moreover, colonized microorganisms to stimulate a mucosal and a systematic immune response to produce particular health effects to the host will be of extraordinary value to the use of probiotics to the human body^{3,8,9}.

The clinical use of probiotics is now known to be not simply limited in the disorders of gastrointestinal field, but also in the immune relevant disease areas. Eczema and gastrointestinal disorders that are food allergy related, response to vaccine by the amount of antibody, number of infectious episodes requiring antibiotics in cystic fibrosis children are found to be positively affected by the use of *Lactobacillus casei*^{4,8-12}.

Our study investigational product, *Lactobacillus paracasei*(LP) is sampled by endoscopic biopsy of human gastrointestinal tract and further differentiated by LBS plate. After differentiation, the strain is identified by polymerase chain reaction (PCR) using 16S rDNA species primer for sequence determinations. Strain identification is performed by API CH50¹³. LP is a GRAS (generally recognized as safe) strain and is currently marketed as food in the forms of fortified fermented milk and capsules. It has been estimated that more than 1.5 millions of people in population has been exposed by 4.5 millions of unit packages of LP. No customer complaint has ever been reported. It is then self-explanatory that all pre-clinical studies performed on LP focused on the aspect of pharmacology only. Aiming interferon- γ (IFN- γ), IgG, IgE concentrations in the blood as primary endpoints and counts of macrophage, lymphocyte, and eosinophil in the filtration as secondary endpoints, we have performed a study to evaluate the immune response of 24 *Dermatophagoides pteronyssinus* 5-Glutathione S-transferase (Der p5) sensitized BALB/c mice on LP. After being sensitized, they are treated by either placebo, *Lactobacillus rhamnosus* GG 10^9 cfu, *Lactobacillus paracasei* 10^9 cfu (Sample size of 8 in each treatment group) for 14 days. On the 15th day, they are challenged by Der p5 as allergen by inhalation route for 30 minutes. The 18th hour blood samples are taken after starting inhalation challenging for detecting the levels of the primary endpoints as aforementioned. IFN- γ is observed to increase to a statistically significant level of about 100 pg/ml compared to 20 to 40 pg/ml in the placebo and the *Lactobacillus rhamnosus* GG group. This result in increasing IFN- γ encourages the use of LP in the treatment of mite induced allergy because of the known fact that IFN- γ is a potent inhibitor of allergic reactions. IgE is statistically significantly less in the LP group compared to the placebo and the *Lactobacillus rhamnosus* GG group, indicating less allergic reaction through Th2 route. IgG is seen to increase to double the

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level of the placebo group, implying the desired Th1 reaction in the LP group compared to the placebo group. Placebo and *Lactobacillus rhamnosus* GG group do not differ significantly in the IgE and IgG level changes. The secondary endpoints have consistently shown beneficial effects of LP in allergy control compared to the placebo group in less eosinophil and lymphocyte counts and more macrophages in the alveoli filtration.

A double-blind, randomized, placebo-controlled clinical study for evaluating the efficacy and safety of perennial allergic rhinitis (PAR) is published in year 2004. This study involves 60 Dp sensitized patients under the age of 18 years old who are suffering from PAR. The patients are randomly allocated to the treatment of placebo (Containing: *Streptococcus thermophilus* 10^6 cfu/ml and *Lactobacillus bulgaricus* 10^5 /ml) or LP fortified fermented milk (LP in 10^7 cfu/ml) for a total duration of 12 weeks. The dose given is based on the body weight where 200 ml is given for weight no more than 30 kg and 400 ml for weight more than 30 kg. The results show that all symptoms including nasal and ocular evaluations, practical problems, other symptoms, and activity limitations grading, used to assess PAR conditions have been improved after 12 weeks of treatment. The total score based on these evaluations are proven to be statistically significantly better than placebo in all visits of 4, 8, and 12 weeks of treatment. IgE measures also provide encouraging results that the LP group showed a statistically significant decrease from baseline after 12-week treatment period (732 IU/ml at baseline, 579 IU/ml at 12-week visit; $p=0.032$). On the contrary, the placebo group remained unchanged IgE level throughout the study. IFN- γ in the LP group is consistently indicating Th1 immune reaction by showing increasing IFN- γ from baseline compared to the 12-week treatment visit (33.77 pg/ml at baseline and 41.05 pg/ml at 12-week visit; $p=0.001$). No significant adverse event is observed during the conduct of this study.

2.3 Study Design

This study is an investigational new drug (IND) phase II study aiming to establish a dose-response relationship for LP in the treatment of PAR in children by using the design recommended by the FDA CDER publication in April 2000 for allergic rhinitis product evaluations. Considering the subjective nature of the endpoint for PAR evaluation, double-blind design is employed and placebo is included as control group. Three dose levels are incorporated into the design for establishing dose-response curve. The proper dose level is expected to be determined from this study result. The treatment duration is 12 weeks but an extension for another 9 months follow-up in order to reveal the longer-treatment efficacy and safety profiles will be employed. The outcome derived from this study will be used to design the future phase III study to confirm the efficacy and safety profiles of LP for PAR treatment. Results of this study will be used to serve as part of the New Drug Application (NDA)

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dossier.

3. Study Objectives and Endpoints

3.1 Study Objectives

3.1.1 Primary Study Objectives

The primary study objective is to evaluate the dose response relationship of LP and to determine the optimal dose for LP in the treatment of children with PAR. The response is to be measured primarily by NTSS.

3.1.2 Secondary Study Objectives

The secondary study objectives are to evaluate the efficacy features of LP in children with PAR. Efficacy profile is to be evaluated through a series of secondary efficacy endpoints as listed in **Section Secondary Endpoints**. The safety and tolerability features are also part of the secondary study objectives to be achieved, through the evaluations of vital signs changes, adverse event incidences, blood and urine laboratory test results changes.

3.2 Endpoints

3.2.1 Primary Endpoint

Net change in mean NTSS at the 12th week treatment visit (compared to baseline) will be the primary endpoint used to evaluate the dose response of LP.

NTSS is rated by the severity of 4 nasal symptoms as indicated below (rated by the patient or the person who is caring for the patient (must be rated by the same person during the study), in the evening before going to bed and dosing for each day to reflect the previous 24 hours experience):

Sneezing, rhinorrhea, nasal itching, and nasal stuffiness.

Each of these symptoms is rated from scale 0 to 3 as defined below:

0 = Absent

1 = Mild

(That is, present but not disturbing)

2 = Moderate

(That is, disturbing but not hampering daytime activities and/or sleep)

3 = Severe

(That is, Hampering daytime activities and/or sleep)

NTSS is the sum of scores of the 4 symptoms for each day.

Primary endpoint = Mean NTSS at baseline (during screening days) – Mean NTSS (during the week right before to the 12th week visit)

3.2.2 Secondary Endpoints

Efficacy

The endpoints used to achieve the secondary objectives of this study in the efficacy profiles are listed below:

- Net change of the 2nd, 4th and 8th week evaluations compared to the baseline on NTSS
- Net change of the 2nd, 4th, 8th and 12th week evaluations compared to the baseline on each individual symptom (as shown in Section 3.2.1) score rated in the NTSS items
- Net change of the 2nd, 4th, 8th and 12th week evaluations compared to the baseline on NTSS by investigator's evaluation at site
- Net change of the 2nd, 4th, 8th and 12th week evaluations compared to the baseline on each individual symptom score rated by NTSS by investigator's evaluation at site
- Global assessment by the investigator as categorized into 4 levels as shown below:
 - 4 = complete relieve
 - 3 = partial relieve
 - 2 = no relieve
 - 1 = worse.
- Net change of the serum interferon- γ (IFN- γ) concentration during the treatment period (IFN- γ at visit 6 – IFN- γ at baseline)
- Net change of the serum total immunoglobulin E (IgE) concentration during the treatment period (IgE at baseline – IgE at visit 6)

Safety

The endpoints used to achieve the secondary objectives of this study in the safety profiles are listed below:

- **Vital signs changes**

The vital signs including blood pressures, pulse rate, respiratory rate and body temperature will be assessed for changes compared to baseline.
- **Adverse event incidence**

Adverse event will be recorded for each of the visits starting from the baseline visit.
- **Physical examinations changes**

Physical examinations will be performed for the 4th and 12th week visits.

Changes in physical examination results for these two during-treatment visits will be considered as one of the safety observations.

- **Blood laboratory test result changes**

The blood laboratory tests including the following items will be tested periodically:

- White blood cells with differential counts
- Red blood cells
- Hemoglobin
- Hematocrit
- Platelet
- MCV
- MCH
- MCHC
- AST
- ALT
- Albumin
- Total protein
- Total bilirubin
- Alkaline phosphatase
- LDH
- Creatinine
- Blood urea nitrogen
- Uric acid
- Glucose
- Potassium
- Calcium
- Phosphorus
- Sodium
- Chloride
- Magnesium
- Iron

- **Urine laboratory test result changes (Qualitative changes)**

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The urine laboratory tests including the following items will be tested at the 4th and the 12th week visits:

- White blood cells
- Red blood cells
- pH
- Protein
- Glucose
- Ketone body

4. Study Design

4.1 Type and Design

This study is a phase II, dose response study, designed in a double-blind, parallel, placebo-control setting for PAR children, to establish the response profile for the investigational product in 3 different doses. This study intends to establish a dose response curve for LP and to utilize these response results among 3 different doses along with the placebo control arm to determine the proper dose for LP. This outcome will be used to design the future phase III study to confirm the efficacy and safety profile of LP for PAR treatment.

The design of this study follows FDA CDER publication in April 2000, the Guidance for Industry - Allergic rhinitis: Clinical development programs for drug product. The primary endpoint selected is what suggested in this Guidance, while the treatment duration is much longer than 4 weeks (which is what required in the Guidance) in order to reveal the longer-treatment efficacy and safety profiles. This study will also collect long-term post-treatment safety follow-up up to 1 year (12 weeks treatment period inclusive).

4.1.1 Sample size calculation

A total of 120 evaluable subjects will be enrolled in the study. As the information of the test drugs is limited for this phase II study, sample size calculation results related to the design of the study are estimated base on some assumptions. No inferential conclusion will be made based on this phase II study. The results of the study are mainly to be used in the design of the subsequent confirmatory phase III studies.

In addition, the sample size for examining the highest treatment effect compared to placebo is estimated. The statistical power estimated is at around 70 to 80% based on the size of 30 evaluable subjects per group planned for this study. This power calculation is assumed by the previous PAR clinical trial experience using 12-week LP 2×10^9 cfu as study dose.

Sample size calculation details are given in **Section 10.1**.

4.1.2 Choice of control

This study aims to establish a dose-response relationship for LP in the treatment of PAR in children. Considering the subjective nature of the endpoint for PAR evaluation, placebo is included as control group. Based on the previously performed PAR study on LP, 2×10^9 cfu appeared to be of good effectiveness and is safe for PAR treatment in children. To understand the potency of LP in a lower level and a higher level other than the known 2×10^9 cfu dose level, a scale of 5 or 10 is taken to design the 3 dose levels, namely, 2×10^8 cfu, 2×10^9 cfu, and 1×10^{10} cfu for establishing the dose-response curve for LP. We are expecting to see ascending trend from placebo to 2×10^8 cfu

and continue to rise to 2×10^9 cfu and reaches its plateau at 2×10^9 cfu and 1×10^{10} cfu.

4.2 Avoid/Minimize Bias

Four groups of treatments are made identical in taste/odor, appearance, and packaging to avoid subject selection bias and evaluation bias. Treatment blinding method is given in **Section 6.2.5**.

5. Study Population

5.1 Number of Subjects

Approximately 140 subjects will be enrolled for the study treatment. The study aims to complete at least 120 analyzable subjects for the 4 treatment arms, from a total of 2 centers in Taiwan.

5.2 Eligibility Criteria

5.2.1 Inclusion Criteria

1. Subjects with age of 5-16 years old (inclusive)
2. Subjects with a history of PAR for at least 1 year
3. Subjects with either one of the following test results (test results within 12 months before study are acceptable):
 - a. Positive skin-prick test reaction (wheal ≥ 3 mm larger than the diluent control)
 - b. Positive reaction determined by the CAP or MAST system
4. Subjects with mean nasal total symptom score (NTSS) of no less than 5 throughout the screening period (4 to 10 days); at least 4 days should be recorded during the screening period; and the NTSS of the day before day-0 (first dosing day) visit is no less than 5
5. Subjects' parents or their legally acceptable representatives have signed the written informed consent form

5.2.2 Exclusion Criteria

1. Subjects have clinically significant abnormalities laboratory results as determined by the investigator (Tests performed during 14 days prior to visit 1 or during baseline period can be used for evaluating this criteria)
2. Subjects with acute or significant chronic sinusitis, severe persistent asthma, congenital immunodeficiency, neuropsychiatric disorders, immuno-compromised, massive wound in the oral cavity, use of rhinitis medications, and chronic use of tricyclic antidepressants
3. Subjects need to take prohibited medications during the study or took the medications within the time frame indicated correspondingly prior to the screening visit:
 - Parenteral or oral corticosteroids 30 days
 - Nasal corticosteroids 30 days
 - Topical use of flurandrenolide 30 days

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- Topical use of clobetasol propionate 30 days
 - Topical use of halobetasol propionate 30 days
 - Astemizole 30 days
 - Ketotifene..... 21 days
 - Nedocromil or Sodium cromoglycate 14 days
 - Loratadine..... 10 days
 - Cetirizine..... 7 days
 - Antileukotrienes 7 days
 - Other H₁ antihistamine..... 3 days
 - Nasal decongestant..... 3 days
 - Any food supplements including LP (*Lactobacillus paracasei*) 3 days
4. Subject is undergoing desensitization therapy within 3 months prior to the screening visit or with vasomotor rhinitis
 5. Subject participated investigational drug trial within 4 weeks before entering this study
 6. Patients are pregnant or lactating or plans to become pregnant
 7. Subject with any other serious disease considered by the investigator not in the condition to enter the trial

5.2.3 Withdrawal Criteria

The subjects should be withdrawn from the study if any of the conditions set below has occurred:

1. Subject or his/her legally acceptable representative decides to withdraw his/her informed consent form.
2. Investigator considers that the subject is no longer physically and/or psychologically feasible to remain in the study.
3. Subject with poor drug compliance, defined as less than 75% mean drug compliance (See **Section 7.8**).
4. Subject with poor diary record keeping for NTSS, defined as less than 4 days daily complete records in each week.
5. Subject has developed the condition that prohibited drug(s) become inevitable to be taken by the subject.
6. Subject develops adverse effects that the investigator considers a permanent cessation of the study treatment is necessary.

The investigator should complete the evaluation items for Visit 6 upon a

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subject's withdrawal. This does not include a subject who has not been treated by the study treatment, such as withdraw at Visit 1 or 2. Only the CRF required data should be completed and the study treatment(s) ever dispensed to the subject should be retrieved upon a subject withdraws at Visit 1 or 2.

6. Study Assessment and Procedures

6.1 Study Assessment

6.1.1 Informed Consent

All subjects must provide signed and dated informed consent at Visit 1, prior to any study-related procedures. Only the institutional review board (IRB) and the applicable health authorities approved informed consent form can be used.

6.1.2 Eligibility

Eligibility should be thoroughly checked by the investigator at Visit 1 and 2. See **Section 5.2** for detailed eligibility criteria.

6.1.3 Height and Body Weight

Height is to be measured for the subject not wearing shoes at Visit 1. The measure of height will be rounded to the nearest centimeter.

Body weight is to be measured for the subject not wearing shoes and dressed by light clothes at Visit 1, 2, 3, 4, 5, and 6. The measure of weight will be rounded to the nearest kilogram.

6.1.4 Demography

Demographic data including date of birth and gender will be obtained at Visit 1.

6.1.5 Medical History

The general medical history up to 3 months of study entry (Screening visit) should be recorded at Visit 1. The medical history should include procedural and surgical history within 1 year time. ENT history should be recorded on a life-time basis.

Allergic rhinitis medical history should be recorded on a life-time basis, up to all records available in the medical records of the study site. The history will record the following information:

- Onset of allergic rhinitis
- Etiology of allergic rhinitis
- Type of allergic rhinitis
- Months of the recent year that the symptoms of allergic rhinitis are present
- Allergy test results (Most recent test(s))
 - Type of allergy test performed
 - Date of test performed
 - Results of the test performed

6.1.6 Urine Pregnancy Test

Subject with childbearing potential must be confirmed of not being pregnant at Visit 1 and being informed that contraceptive method must be used during the entire screening and treatment period of this study.

6.1.7 Vital Signs

Subject will be measured of blood pressures, pulse rate, respiratory rate and body temperature at Visit 1 and 6.

6.1.8 Physical Examinations

Subject will be examined at Visit 1, 4 and 6 by standard physical examination items including skin, eyes, ENT, cardiovascular system, respiratory system, gastro-intestinal system, blood and blood forming organs, mental status, and other body systems if applicable for describing the status of the subject's health.

6.1.9 Blood Laboratory Tests

The blood laboratory tests including white blood cells with differential counts, red blood cells, hemoglobin, hematocrit, platelet, MCV, MCH, MCHC, AST, ALT, albumin, total protein, total bilirubin, alkaline phosphatase, LDH, serum creatinine, blood urea nitrogen, uric acid, glucose, calcium (Ca), phosphorus (P), sodium (Na), potassium (K), chloride (Cl), magnesium (Mg), iron (Fe) will be taken at Visit 1, 4, and 6.

6.1.10 Urine Laboratory Tests

The urine laboratory tests including qualitative tests on white blood cells, red blood cells, pH, protein, glucose, and ketone body will be taken at Visit 1, 4, and 6.

6.1.11 Allergen Tests

Either the skin test, CAP or MAST will have to be performed on any of perennial allergens within 12 months before study treatment.

6.1.12 Previous Medications

Previous medications are categorized into allergic medication and other medications. The allergic medication should be recorded for at least 2 years preceding the study participation (Visit 1). All medical procedures used to treat or prevent allergic rhinitis should be considered as allergic medication. Other medications should only be recorded up to 12 weeks before study entry.

6.1.13 Subject Identifier

Subject confirmed eligible at Visit 2 (Visit 1 and 2 can be the same visit) and prior to the study treatment, will be assigned an identification number, namely, subject identifier. The subject identifier contains the first 1 digit of center number, the middle 3 digits of screening number and the last 3 digits of subject randomization number. Subject screened but not randomized will be

identified by "X" and "sequential number" for the last 3 digits of the subject identifier (Example: first screened but not randomized for center 1: 1-001-X01, each center should start from its own sequential number). For the eligible subject will be identified "sequential number" for the last 3 digits (Example: second screened for center 1 and is first eligible for study: 1-002-001).

6.1.14 Nasal Total Symptom Score

The investigator will evaluate the NTSS at site for the subject for Visit 1, 2, 3, 4, 5, and 6. The investigator or his/her designated study nurse(s) will instruct the subject or the person caring the subject how (to reflect the previous 24 hours symptom severity) and when (in the evening before bedtime and dosing) to assess the severity of each of the symptoms included in the NTSS at Visit 1. The subjects' NTSS records will be recorded in the DRC on a daily basis. The DRC will be dispensed to the subject at Visit 1, 2, 3, 4, and 5. The DRC will be requested to be brought back to site at the subsequent visits by the subject to be reviewed by the investigator at each visit for Visit 2, 3, 4, 5 and 6. The symptom scoring system is given in **Section 3.2.1**.

6.1.15 Immune Indicators

The subject will be tested of his/her interferon- γ and total IgE concentrations before treatment. Same tests will be performed at Visit 6.

6.1.16 Concomitant Medications

All concomitant medications starting from Visit 1 to Visit 6 should be recorded.

6.1.17 Investigator's global assessment

Investigator will give an overall evaluation on the efficacy of the investigational product for PAR treatment at Visit 3, 4, 5, and 6 by a categorical rating system. The global assessment categories are as shown below:

- 4 = Complete relieve
- 3 = Partial relieve
- 2 = No relieve
- 1 = Worse

6.1.18 Investigational Drug

Investigational drugs will be dispensed to the eligible subjects starting at Visit 2 and followed by Visit 3, 4, and 5. The subjects will be asked to return the unused drugs at Visit 3, 4, 5, and 6. Drug accountability and inventory will be recorded in the case report forms and the relevant study log.

6.1.19 Compassionate treatment

The subject can choose to convert to a 3 months open-label LP 2×10^9 cfu

compassionate treatment at the end of study treatment duration (Week 12 visit). The subject will be considered as a completed case even he/she doesn't convert to the open-label treatment at the end of study treatment duration.

6.1.20 Adverse Event (AE)

The subject will be asked to report adverse event voluntarily and the investigator will also exam the subject to identify adverse event for all visits during the study, starting from Visit 2. See **Section 9** for AE in more details.

6.1.21 Exit of Study

The subject will be dismissed from the study at Visit 6. The follow-up safety surveillance for Visit 7 and 8 will be based on telephone visit and is not considered as the formal part of the study.

6.2 Study Procedures by Visit

6.2.1 Screen Visit

(Visit 1: -10 to -4 days of the first treatment day)

- Explain the nature of the study and have subjects to read and sign an Informed Consent Form
- Screen subjects for inclusion/exclusion criteria
- Obtain height and body weight
- Obtain demographic characteristics
 - Date of birth
 - Gender
- Obtain allergy and general medical history
- Perform urine pregnancy test for applicable subjects only
- Obtain vital signs
 - Blood pressures
 - Pulse rate
 - Respiratory rate
 - Body temperature
- Perform physical examinations
 - Skin
 - Eyes
 - Ear, nose, and throat

- Cardiovascular system
- Respiratory system
- Gastro-intestinal system
- Blood and blood forming organs
- Mental status
- Other system
- Take blood samples for IFN- γ and IgE measures
- Perform blood lab tests
 - White blood cells with differential counts
 - Red blood cells
 - Hemoglobin
 - Hematocrit
 - Platelet
 - MCV
 - MCH
 - MCHC
 - AST
 - ALT
 - Albumin
 - Total protein
 - Total bilirubin
 - Alkaline phosphatase
 - LDH
 - Creatinine
 - Blood urea nitrogen
 - Uric acid
 - Glucose
 - Calcium
 - Phosphorus
 - Magnesium
 - Iron

- Chloride
- Sodium
- Potassium
- Perform urine tests (Qualitative)
 - White blood cells
 - Red blood cells
 - pH
 - Protein
 - Glucose
 - Ketone body
- Allergy test (Skin-prick, CAP or MAST)
- Record previous medications
- Assign subject identifier
- Evaluate NTSS at site by the investigator
- Instruct the subject or the person caring for the subject for NTSS assessment method
- Dispense DRC to the subject
- Record concomitant medications

6.2.2 Randomization Visit

(Visit 2: Week 0, Day 1)

- Confirm eligibility of subjects
- Assign subject randomization number to eligible subjects
- Obtain body weight
- Evaluate NTSS at site by the investigator
- Retrieve the previously given DRC and review DRC by the investigator
- Dispense new DRC to the subject
- Record concomitant medications
- Dispense investigational product
- Record adverse event

6.2.3 Evaluation Visits

For Visit 3 (14±3 day) and 5 (56±7 days):

- Obtain body weight
- Evaluate NTSS at site by the investigator
- Retrieve the previously given DRC and review DRC by the investigator
- Dispense new DRC to the subject
- Investigator's global assessment on efficacy
- Record concomitant medications
- Retrieve and un-used investigational product and dispense new investigational product
- Record adverse event

For Visit 4 (28±3 days):

- Obtain body weight
- Perform physical examinations
 - Skin
 - Eyes
 - Ear, nose, and throat
 - Cardiovascular system
 - Respiratory system
 - Gastro-intestinal system
 - Blood and blood forming organs
 - Mental status
 - Other system
- Perform blood lab tests
 - White blood cells with differential counts
 - Red blood cells
 - Hemoglobin
 - Hematocrit
 - Platelet
 - MCV
 - MCH

- MCHC
- AST
- ALT
- Albumin
- Total protein
- Total bilirubin
- Alkaline phosphatase
- LDH
- Creatinine
- Blood urea nitrogen
- Uric acid
- Glucose
- Calcium
- Phosphorus
- Magnesium
- Iron
- Chloride
- Sodium
- Potassium
- Perform urine tests (Qualitative)
 - White blood cells
 - Red blood cells
 - pH
 - Protein
 - Glucose
 - Ketone body
- Evaluate NTSS at site by the investigator
- Retrieve the previously given DRC and review DRC by the investigator
- Dispense new DRC to the subject
- Investigator's global assessment on efficacy
- Record concomitant medications

- Retrieve and un-used investigational product and dispense new investigational product
- Record adverse event

6.2.4 Final Visit

Visit 6 (84±7 days):

- Obtain body weight
- Obtain vital signs
 - Blood pressures
 - Pulse rate
 - Respiratory rate
 - Body temperature
- Perform physical examinations
 - Skin
 - Eyes
 - Ear, nose, and throat
 - Cardiovascular system
 - Respiratory system
 - Gastro-intestinal system
 - Blood and blood forming organs
 - Mental status
 - Other system
- Perform blood lab tests
 - White blood cells with differential counts
 - Red blood cells
 - Hemoglobin
 - Hematocrit
 - Platelet
 - MCV
 - MCH
 - MCHC
 - AST

- ALT
- Albumin
- Total protein
- Total bilirubin
- Alkaline phosphatase
- LDH
- Creatinine
- Blood urea nitrogen
- Uric acid
- Glucose
- Calcium
- Phosphorus
- Magnesium
- Iron
- Chloride
- Sodium
- Potassium
- Perform urine tests (Qualitative)
 - White blood cells
 - Red blood cells
 - pH
 - Protein
 - Glucose
 - Ketone body
- Evaluate NTSS at site by the investigator
- Retrieve the previously given DRC and review DRC by the investigator
- Investigator's global assessment on efficacy
- Record concomitant medications
- Take blood samples for IFN- γ and IgE measures
- Record adverse event
- Retrieve un-used investigational product

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- Exit of study
- Dispense compassionate treatment for the subjects who decides to convert to a 3 months open-label LP 2×10^9 cfu compassionate treatment program

6.2.5 First Safety Follow-up Visit

Visit 7 (24 ± 4 weeks, can be conduct by telephone contact):

- Record adverse event

6.2.6 Second Safety Follow-up Visit

Visit 8 (48 ± 4 weeks, can be conduct by telephone contact):

- Record adverse event

7. Investigational Product

7.1 Description of Investigational Product and the Comparator Drug

The investigational product (IP) for this study will be supplied by Genmont Biotech Inc. for active ingredient and by United Biomedical Inc., Asia for final formulation and packaging. The physicochemical properties and the pharmaceutical specifications of the investigational product for this study are provided in the Investigator's Brochure (IB).

The sponsor is responsible to ship the IP to each of the study sites and strict inventorial control for the drug accountability will be implemented.

7.2 Dosage and Administration

Each subject will be instructed to take the 1 capsules each day before going to bed with about 250 ml water.

No dose modification plan is anticipated for this study. Any unexpected adverse event should be handled according to the **Section 5.2.3** and **Section 9**.

7.3 Dose Rationale

This study aims to establish a dose-response relationship for LP in the treatment of PAR in children. Considering the subjective nature of the endpoint for PAR evaluation, placebo is included as control group. Based on the previously performed PAR study on LP, 2×10^9 cfu dose appeared to be of good effectiveness and is safe for PAR treatment in children. To understand the potency of LP in a lower level and a higher level other than the known 2×10^9 cfu dose level, a scale of 10 is taken to design the 3 dose levels, namely, 2×10^8 cfu, 2×10^9 cfu, and 1×10^{10} cfu for establishing the dose-response curve for LP. We are expecting to see ascending trend from placebo, followed by 2×10^8 cfu and continues to rise to 2×10^9 cfu and reaches its plateau at 2×10^9 cfu and 1×10^{10} cfu.

7.4 Treatment Assignment

Subjects become eligible at Visit 2 will be assigned a random number and each random number corresponds to a treatment group. Four treatment groups are equally distributed in the randomization numbers prepared. The random codes will be generated based on permuted block randomization method and stratified by center.

7.5 Packaging and Labeling

The IP will be packaged as capsules appeared to be identical in all aspects

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(like the symbols shown below are all round) for the 4 treatment groups as pictured below:

Test drug Study Group	Placebo capsule ○	2×10^8 ($2 \times 10^{7.5}$ - $2 \times 10^{8.5}$) cfu capsule ⊕	2×10^9 ($2 \times 10^{8.5}$ - $2 \times 10^{9.5}$) cfu capsule ⊙	1×10^{10} ($1 \times 10^{9.5}$ - $1 \times 10^{10.5}$) cfu capsule ●
Placebo	1	0	0	0
2×10^8 cfu	0	1	0	0
2×10^9 cfu	0	0	1	0
1×10^{10} cfu	0	0	0	1

The capsules will be packaged in bottle or blister and placed in a box for each dispensation at Visit 2, 3, 4, and 5. All boxes will be labeled for study number, center number, subject identifier, prescription instructions, investigator's name, storage conditions, manufacturing and expiry dates, and the descriptions of "Clinical trial use only" and "Keep the reach out of children". The label on the box will be made in duplicate with a perforated line to separate the two duplicates. One duplicate is detachable and is to be removed from the box at the time of drug dispensation to the patient. This removed label should be placed on the CRF appropriate page.

The quantity of capsules packaged in the box for Visit 2, 3, 4, and 5 are 1 pack of 17 capsules, 1 pack of 20 capsules, 1 pack of 38 capsules, and 1 pack of 42 capsules.

7.6 Handling and Storage

The IP will be handled by the investigator or the designated pharmacist for management and dispensation. IP should be stored at -18 ± 2 °C, protected from light and humidity.

7.7 Product Accountability

All subjects will be given a pre-fixed quantity of IP at Visit 2, 3, 4, and 5. The quantity given will be recorded in the CRF and the drug accountability log. At the time the subject returns the un-used drugs and empty bottle or blisters and box, the capsules will be counted at site and the number left will be recorded in the CRF. Subject DRC will record daily information for whether or not the subject has taken the IP and also in quantity.

7.8 Assessment of Compliance

Subject's treatment compliance will be assessed by the following formula:

For each visit, the compliance will be calculated:

$$[(\text{Capsule counts actually used}) \div (\text{Capsule counts prescribed to be used})]$$

7.9 Treatment for Investigational Product Overdose

Considering the nature of the IP that has already been marketed as food in fortified milk, overdose situation of subject will be treated by supportive treatment. However, the subject or the person caring for the subject should contact the investigator by phone to determine if there is any immediate medical treatment needed. Regardless the decision of the need for immediate hospital medical care for the overdose event, the subject should be arranged to come back to the clinic as soon as possible for evaluation before continuing any further study medication treatment. This post-overdose visit can be an additional visit or a regular study visit. The sponsor's appointed study monitor should be contacted by the investigator of any over-dose report as soon as he/she is aware of the event.

The investigator should consider the following actions to take for the post-overdose visit:

1. Ask the subject to come back to the clinic and observe the overdosed lesions to see if there is any further medical treatment needed for resolving the complications induced by the overdose of study medication.
2. To determine if the subject is suitable to continue the study treatment and when the subject should resume his/her dose of study medication.
3. To determine whether or not the subject be withdrawn from the study due to reasons listed in **Section 5.2.3**.
4. Perform all study procedures required for Visit 6.

Any unfavorable effects caused by the overdose event must be reported as an AE or SAE.

8. Concomitant Treatments

8.1 Permitted Treatments

The investigator should try to minimize the concomitant treatments for the subject during the study. If the concomitant treatments are deemed necessary, the investigator should try to maintain stable dose and therapy type during the study to minimize possible interference to the study endpoint assessments.

8.2 Prohibited Treatments

Investigator will try to minimize the concomitant medications for the patients during the trial duration. Patients are not allowed to take the following medications during the study:

1. Parenteral or oral corticosteroids
2. Nasal corticosteroids
3. Topical use of flurandrenolide
4. Topical use of clobetasol propionate
5. Topical use of halobetasol propionate
6. Astemizole
7. Ketotifene
8. Nedocromil or Sodium cromoglycate
9. Loratadine
10. Cetirizines
11. Antileukotrienes
12. Other H1 antihistamine
13. Nasal decongestant
14. Any food supplements including LP (*Lactobacillus paracasei*)

Besides, subjects are not allowed to take any oral systematic antibiotics within one week prior to the primary evaluation at final visit (Visit 6).

9. Adverse Events (AE) and Serious Adverse Events (SAE)

9.1 Definition of a AE

An AE is any untoward medical occurrence in a subject during the participation of a study, regardless the relationship of the occurrence to the treatment of the IP. An AE can be any unfavorable signs or symptoms or diagnosed new diseases or deterioration of existing chronic or intermittent diseases, significantly unexpected deteriorated condition of the study indication, which is associated to the use of the IP. Abnormal can be considered as aforementioned signs and can be considered as an AE.

The investigator is responsible for the detection, reporting, and documentation of AE.

9.2 Definition of a SAE

A serious adverse event is an AE that leads to any of the following medical occurrence:

- Results in death
- Is life-threatening, meaning the subject is at risk of death at the time of event.
- Requires hospitalization or prolongation of existing hospitalization, hospitalization refers to at least an over-night stay.
- Results in disability/incapacity.
- Is a congenital anomaly/birth defect.
- Events requiring medical and/or surgical intervention and based on medical and/or scientific judgment is important and should be considered serious.

9.3 Disease-Related Events

The disease-related event is defined as an event that can be explained by the study indication. The disease-related events and conditions are usually recorded according to the protocol and should not be considered as an AE. For those events that the investigator considers to be more severe than expected, should be reported as AE or SAE as appropriate. Considering the nature of the study subjects to be late stage cancer patients, the nature course of the disease leading to death or life-threatening conditions are considered as AEs or SAEs with investigator's opinion to distinguish whether or not the event is a consequence or progression of the pre-existing disease(s).

For all events that result in death or are life-threatening, must be reported

SAEs.

9.4 Lack of Efficacy

Lack of efficacy is not to be considered as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definitions the AE or SAE.

9.5 Clinical Laboratory Abnormalities

Abnormal laboratory findings and/or assessments that are judged by the investigator as clinically significant will be reported as AEs or SAEs if they meet the definitions set forth. For the condition that the abnormal laboratory and/or assessment findings are considered as the underlying disease related, and are not unexpectedly worsened during the study, no AE or SAE should be reported.

9.6 Reporting and Recording of AE and SAE

All AEs and SAEs should be documented in the source documents and the relevant CRF and SAE form when applicable. The investigator may be asked to provide photocopies of the medical records for completion the AE or SAE report. The medical records submitted to the relevant parties will be concealed of the subjects' names. It is the responsibility of the investigator to report AEs or SAEs by diagnosis terminologies, if possible. When the diagnosis is possible for the reported AE or SAE, no signs and symptoms used to establish that particular diagnosis should be reported.

The investigator will be asked to determine the intensity and causality of each AE and SAE based on the investigator's clinical judgment. Three levels of intensity and five levels of causality are used to evaluate each AE and SAE as shown below:

Intensity:

- Mild: Easily tolerated by the subject, causing minimal discomfort and not interfering with daily activities.
- Moderate: Sufficiently discomforting and is interfering with normal daily activities.
- Severe: Make normal daily activities prevented.

*There is no direct relationship for severity and seriousness of an AE.

Causality:

- Highly probable: Should be reserved for those events which have no related uncertainty in their relationship to test drug administration.

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- Possible: The suspected adverse event may follow a reasonable temporal sequence from test drug administration but could have been produced or mimicked by the patient's clinical state or by other modes of therapy concomitantly administered to the patient.
- Unlikely: Whether or not there was a temporal relationship between the test drug and the suspected adverse event, it is more likely than not that the event could have been produced by the patient's clinical state or other modes of therapy administered to the patient.
- Unrelated: Should be reserved for those events which occur prior to unrelated test drug administration (i.e., washout or single-masked placebo) or those events which cannot be even remotely related to study participation (e.g., injuries sustained in an automobile accident).

It is usually important for the investigator to take information of underlying diseases, concomitant drugs, temporal relationship of the onset of the event to the time of dosing the IP, and re-challenging outcomes, into account when making a causal relation decision.

It is the investigator's responsibility to follow proactively the outcome of each AE/SAE until resolution or stabilization of the condition or lost of follow-up.

Serious, alarming and/or unusual adverse events must be reported to one of the following individuals within 24 hours of the investigator's knowledge of the event:

POSITION	NAME	AFFILIATION	TELEPHONE NUMBER	FAX NUMBER
SAE Contact	Grace Ling	Virginia Contract Research Organization Co., Ltd.	886-2-2657-5399	886-2-2657-9678

An Adverse Event Form should be completed for all serious adverse events and forwarded to the sponsor within 24 hours. When new significant information is obtained as well as when outcome of an event is known, the investigator should inform the sponsor. In applicable cases, sponsor may request a letter from the investigator summarizing events related to the case. Investigators should follow patients as far as possible until an outcome to the events is known.

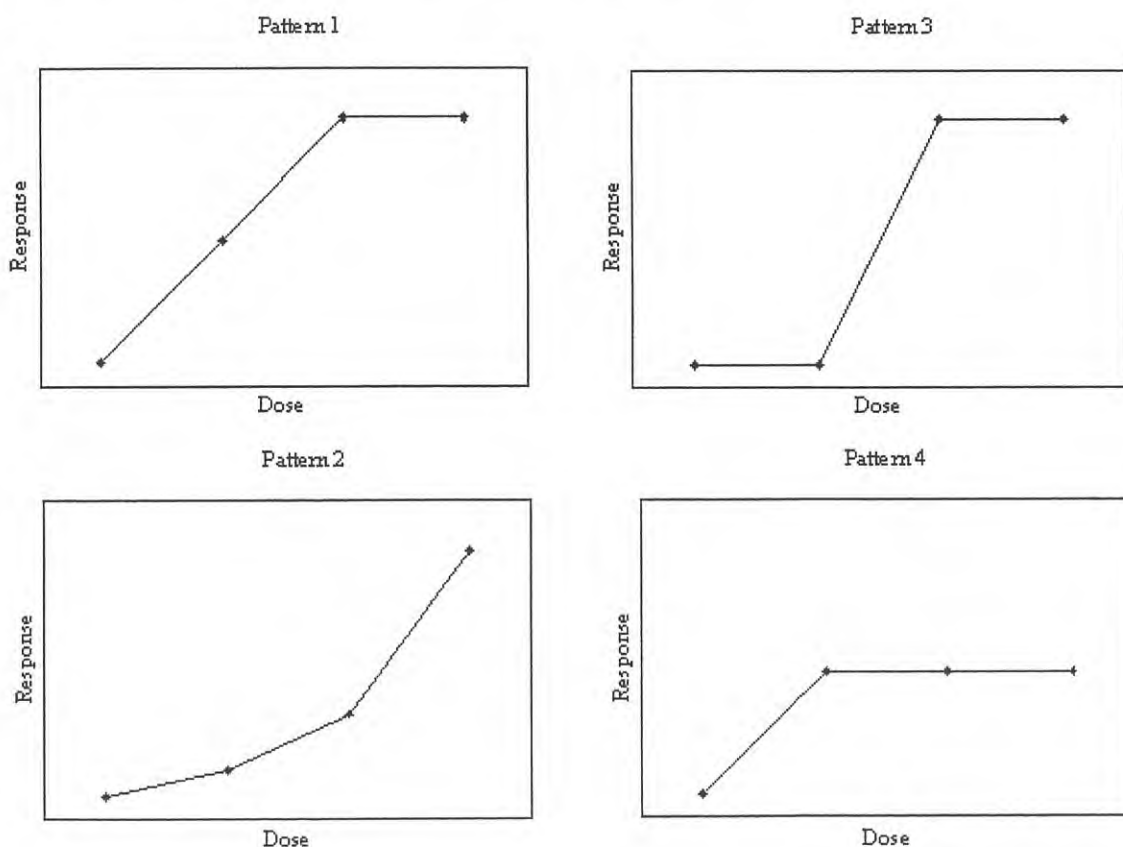
The investigator is responsible to communicate details of medical emergencies in trial patients to the Ethics Committee. Sponsor is responsible to inform the events to the regulatory authorities.

10. Statistical Considerations and Statistical Analysis

10.1 Sample Size Justifications

The study will enroll approximate 140 subjects to collect 120 evaluable subjects. As the information of the test drugs is limited for this phase II study, sample size calculation results related to the design of the study are provided below under some assumptions.

Four dose response patterns which serve as alternatives to the null hypothesis of no drug effect are illustrated in the following four figures.



The difference between the highest and lowest response is δ in Patterns 1-3 and $\delta/2$ in Pattern 4. Assume that δ is equal to σ (the within-dose-level standard deviation of response) and the pharmacologic dose response is log-linear, the per-dose sample size required for 80%, 90% and 95% power to detect the specified dose-response pattern is listed in the following table.

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Pattern	Dose level means	Per-dose sample size (two-sided, $\alpha=0.05$)		
		80% power	90% power	95% power
1	$(0, \sigma/2, \sigma, \sigma)$	13	18	22
2	$(0, \sigma/9, \sigma/3, \sigma)$	16	21	26
3	$(0, 0, \sigma, \sigma)$	10	14	17
4	$(0, \sigma/2, \sigma/2, \sigma/2)$	70	94	116

Treatment effect of Pattern 1, 2 or 3 is anticipated to be seen in this study, therefore, the size of 120 is expected to be sufficient. However, no inferential conclusion will be made based on this phase II study and the results of the study will be, in part or in full, referenced in the design of the subsequent confirmatory studies.

In addition, the sample size calculation for examining the highest treatment effect compared to placebo is also provided. According to the clinical experiences, subjects with perennial allergic rhinitis would have a mean $\pm$ SD NTSS of 7.5 ± 1.8 at baseline. In addition, a previous study showed that 12-week *Lactobacillus paracasei* 2×10^9 colony-forming units (CFU) can relieve the nose symptoms by 37.51% (percentage change), compared to 20.99% of the placebo¹⁵. By summing up the information, the post-treatment NTSS of 4.69 is assumed in the treatment group (for the highest response), and 5.93 is assumed for placebo. Under these assumptions the per-group sample size for 70%, 80%, and 90% power to detect the effect size is listed below.

Active Mean	Placebo Mean	SD for both groups (equal variance)	Per-group sample size (two-sided, $\alpha=0.05$)		
			70% power	80% power	90% power
4.69	5.93	1.8	27	34	45
		2	33	41	55

10.2 Population to be Analyzed

Three populations will be introduced for statistical analysis. The intent-to-treat (ITT) population will comprise all randomized patients who took at least one dose of study medication. The per-protocol (PP) population is a subset of ITT population and all patients included in this population should satisfy the following conditions.

- (1) dosed with at least 75% of total study medications
- (2) with primary efficacy measurement

(3) not taking any prohibited medications

Safety evaluations will be performed on ITT population. Efficacy analysis will be performed on ITT and PP population. The conclusion of efficacy of the study will be made according to the results of ITT analysis.

10.3 Background and Demographic Characteristics

Demographic characteristics including age, race, status of menopause, height and weight will be summarized by descriptive statistics. Frequency table will be presented for race and status of menopause including counts and percentage, while mean, standard deviation, maximum, minimum, median, inter-quartile range, and 95% two-sided confidence interval will be provided for age, height and weight.

10.4 Efficacy Parameters

For each efficacy evaluation which based on diary card, at least 4 days should be recorded during the evaluation week. For efficacy evaluation during the baseline period, at least 3 days should be recorded. The mean daily NTSS or mean daily individual score will be the average score of available days (the days with complete records).

10.4.1 Primary endpoint

The primary endpoint, net change of the 12th week evaluation compared to the baseline on the mean daily NTSS recorded by DRC, will be analyzed by using the method of ANCOVA incorporating treatment, center, treatment-by-center as factors and their respective baseline values as covariate. This statistical model was utilized to test the hypothesis of:

H₀: treatment effects among the four treatment groups were identical (i.e., no drug effect), vs.

H₁: treatment effects among the four treatment groups were NOT identical.

In addition to the aforementioned statistical analysis, multiple comparisons will also be performed to examine the treatment effect of each dose level compared to placebo.

All statistical tests utilized will be two-tailed with $\alpha=0.05$. As no inferential conclusion will be made based on the result of this phase II study, the type I error is intentionally not adjusted. Summary statistics will be provided and the trend of treatment effects will also be graphed.

10.4.2 Secondary endpoints

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The secondary efficacy endpoints will be:

- (1) Net change of the 2nd, 4th and 8th week evaluation compared to the baseline on NTSS of DRC
- (2) Net change of the 2nd, 4th, 8th and 12th week evaluation compared to the baseline on NTSS evaluated by the investigator
- (3) Net change of the 2nd, 4th, 8th and 12th week evaluation compared to the baseline on each individual symptom score rated by NTSS of DRC
- (4) Net change of the 2nd, 4th, 8th and 12th week evaluation compared to the baseline on each individual symptom score rated by NTSS by investigator's evaluation at site
- (5) Global assessment by the investigator
- (6) Net change of the serum interferon- γ (IFN- γ) concentration during the treatment period (IFN- γ at visit 6 – IFN- γ at baseline)
- (7) Net change of the serum total immunoglobulin E (IgE) concentration during the treatment period (IgE at baseline – IgE at visit 6)

All these secondary efficacy endpoints, including net change of the 2nd, 4th and 8th week evaluations compared to the baseline on NTSS, net change of the 2nd, 4th, 8th and 12th week evaluations compared to the baseline on each individual symptom score rated by NTSS, net change of the serum interferon- γ (IFN- γ) concentration during the treatment period (IFN- γ at visit 6 – IFN- γ at baseline), and net change of the serum total IgE concentration during the treatment period will be analyzed by using ANCOVA incorporating treatment, center, treatment-by-center as factors and their respective baseline values as covariate. Investigator's global assessment on the efficacy will be analyzed by Cochran-Mantel-Haenzel test

Safety

Safety profile will be evaluated by the following line-up of endpoints.

- (1) Adverse events
- (2) Changes in physical examinations
- (3) Net changes from pre-treatment in laboratory test results
- (4) Changes in urinalysis
- (5) Vital signs

Adverse events will be reported by treatment groups and by physiological systems as appropriate. Incidence of adverse events between treatments will be analyzed by Cochran-Mantel-Haenzel test ($\alpha=0.05$). The categories of adverse event severity and the relationship to study drug will be tabulated. The coding system used will be the COSTART.

Changes in physical examinations will be displayed for each individual system. Net changes from pre-treatment in laboratory test results will be analyzed by descriptive statistics with 95% confidence intervals provided. Changes in urinalysis will also be summarized by descriptive statistics. Vital signs will also be summarized descriptively.

10.5 Concomitant Therapy and Medical History

General medical history will be coded with the ICD-10 dictionary. These data, as recorded at screening visit (Visit 1), will be presented in incidence table by ICD-10 terms and listed for each subject by treatment group. The incidences will be calculated. Ongoing medical conditions will be presented separately from the cured diseases.

Concomitant therapies will be coded according to the WHO-DRUG dictionary. The incidences of using the medications will be computed.

10.6 Compliance/Extend of Exposure

Subjects' compliance will be calculated according to the formula described in **Section 7.8**.

The compliance will be analyzed by descriptive statistics. Days of subjects expose to the study medication will be calculated from the day of the first treatment to the day of exit. Summary statistics will be provided for the days of exposure.

10.7 Multi-Center Study

The study will be conducted at 2 centers. The center effect and treatment-by-center factor will be incorporated to the ANCOVA model, and all the descriptive statistics for all variables of individual center will be listed separately.

10.8 Missing Values

Last observation carried forward (LOCF) will be utilized to estimate missing values in the primary efficacy endpoint. No missing value estimation technique will be utilized for variables other than primary efficacy endpoint.

10.9 Interim Analysis

No interim analysis will be performed for this study. The statistical analysis will only be conducted at the end of the study after database lock.

11. Study Administrative Structure

11.1 Informed Consent and Institutional Review

All subjects in this research study should be completely informed about the purpose, duration and important procedural details of the study. Informed Consent must be obtained using a written form which has been approved by the appropriate Independent Ethics Committee (IEC) or Institutional Review Board (IRB).

The Informed Consent Form will be understood and signed by each subject prior to enrollment into the study. The investigator will keep the original signed copies of all consent forms in his/her files and will provide a duplicate copy to the subject. A copy of the letter indicating IEC or IRB approval must be provided to the study sponsor prior to the study initiations.

11.2 Confidentiality/Publication of the Study

Any information the study sponsor shares with you regarding this study, including this protocol, is considered proprietary information and should be kept confidential. Each investigator will be required to sign the signature page which affirms he/she has read/understood the obligations of Investigators. Once the study has begun, the investigator will comply with the protocol as written except in instances where there are with medical urgency. The sponsor and the IEC/IRB should be notified of these cases as soon as possible. Any other changes on the protocol must be approved by both the sponsor and the IEC/IRB prior to commencement.

The information provided by the study sponsor in this protocol and the associated Clinical Investigator's Brochure (CIB) and the data generated by this clinical study are to be considered as confidential property of the study sponsor. The data and information associated with this study may be used by the study sponsor, now and in the future for the purposes of presentation, publication at discretion of the study sponsor, or for submission to regulatory agencies. In addition, relative to the release of any proprietary information, the study sponsor reserves the right of prior review of any publication or presentation of data from this study. The center recruited most of the patients will be responsible to write up manuscript for publication use, provided that the trial sponsor has approval on the contents of the manuscript.

In signing this protocol, the investigator agrees to the release of the data from this study and acknowledges the above publication policy.

11.3 Record Keeping

11.3.1 Data Collection

The clinical investigator must maintain detailed records on all study subjects. Data for this study will be recorded on Case Report Forms (CRFs) provided by the sponsor. All data should be recorded completely, promptly, and legibly on the CRFs. Corrections should be made in a manner that does not obscure or eliminate the original error, by striking through the original data with one thin line, and all corrections on the CRF should be initialed and dated and reason of correction noted if possible. Each original CRF page should be made available to the sponsor when completed. The investigator should maintain a copy of all completed CRFs in the study files.

11.3.2 Drug Accountability

The principal investigator is to keep a current record of the inventory and dispensing of all test drugs. This record will be made available to the sponsor monitor for the purpose of drug accountability checks. Any significant discrepancy and/or deficiency should be recorded, with an explanation. All supplies to be sent to the investigator must be accounted for and the test material must not be used in any unauthorized situation.

The principal investigator, upon receipt of the clinical supplies, will conduct drug inventory records. The drug inventory record should be returned to the sponsor and be maintained for the investigator's records.

The principal investigators' responsibility should return all unused supplies to the sponsor at the completion of the study.

11.3.3 Record Retention

All records relating to the conduct of this study are to be held by the investigator until advised by the study sponsor that the records may be destroyed.

The investigator will allow representatives of sponsor's monitoring members (and of the applicable regulatory authorities) to inspect all study records, CRFs, and corresponding portions of the study patient's office and/or hospital medical records at regular intervals across the study. These inspections are for the purpose of verifying the adherence to the protocol, the completeness and accuracy of the data being filled in the CRF, and compliance with applicable regulations.

Sponsor and the investigator agree that the study subject medical records will be maintained in a confidential manner. Study report will not identify any patient by name. These reports may be submitted to the Department of Health of Republic of China and any other applicable health authorities by the sponsor.

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13. Appendices

13.1 Declaration of Helsinki

World Medical Association Declaration of Helsinki: Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and as amended by the World Medical Assembly in Tokyo, Japan in 1975, in Venice, Italy in 1983, in Hong Kong in 1989, in Somerset West, Republic of South Africa, 1996 and the 52nd General Assembly in Edinburgh Scotland in October 2000.

A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

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8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognised. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. Basic Principles

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

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14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject

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has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorised representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorised surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. Medical Research Combined with Professional Care (Clinical Research)

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28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.