# Title: To investigate the PREvention of OM-85 on Bronchiectasis Exacerbations (iPROBE) in Chinese patients

## PHASE IV

## iProbe Clinicaltrials.gov identifier NCT01968421

## February 2, 2020

# PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED TRIAL OF BRONCHO-VAXOM FOR PREVETION OF BRONCHIECTASIS EXACERBATION

## PHASE IV

**Confidential Material**

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|---|---|
| **Name of Sponsor:** | |
| **Name of (Principal) Investigator:** | Jinming Gao |
| **Hospital/University/Institution:** | Peking Union Medical College Hospital |
| **Address:** | #1 shuaifuyuan, Dongcheng District, Beijing 100730, China |
| **Phone:** | 86-10-65295035 |
| **Fax:** | 86-10-65124875 |
| **e-mail:** | gjinming@yahoo.com |
| **Study coordinator:** | Lun Li |
| **e-mail:** | meikeba@163.com |
| **Phone:** | 86-10-69155031 |
| **Fax:** | 86-10-65124875 |
| **CV attached:** | **Yes: ☐ Please see attached** |

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# 1 RATIONALE FOR THE STUDY

Bronchiectasis is a common, but underrecoginsed disease, in the Asia-Pacific and affected patients suffer from chronic sputum production and recurrent exacerbations. The prevalence of bronchiectasis in China is estimated as high as over 10% in adult patients although there lack of exact epidemiological data. Bronchiectasis is largely idiopathic although there is diverse aetiology. There are three distinct pathogenic elements, namely infection, inflammation and enzymatic actions. There appear to be two stages to the disease process: the initial insult that sets off the disease and then the ongoing, inflammatory process encompassing recurrent infection and progressive lung damage. Abnormalities in innate and adaptive immunity may predispose to bronchiectasis at both stages. Progressive lung damage results from a 'vicious cycle' of recurrent bacterial infection and a poorly regulated inflammatory response. Respiratory exacerbations in people with bronchiectasis are associated with reduced quality of life, accelerated decline in pulmonary function associated with physical disability, hospitalisation and even death. Nonenteric Gram-negative bacteria commonly infect areas of bronchiectasis, though *Staphylococcus aureus* and NTM are also commonly encountered as well (see below Table for a summary of the bacteriology of bronchiectasis).

**Table 2—*Bacteriology of Bronchiectasis***

| | Study/Year, % | | |
|---|---|---|---|
| Organisms | Nicotra et al[34]/1995 (n = 123) | Pasteur et al[38]/2000 (n = 150) | King et al[51]/2007 (n = 89) |
| *H influenzae* | 30 | 35 | 47 |
| *P aeruginosa* (including mucoid) | 31 | 31 | 12 |
| *Moraxella catarrhalis* | 2.4 | 20 | 8 |
| *Streptococcus pneumoniae* | 10.6 | 13 | 7 |
| *S aureus* | 7.3 | 14 | 4 |
| No organism | Not specified | 23 | 21 |
| Mycobacterium | 17 | 0 | 2 |

**O'Donnel AE. CHEST 2008, 134: 815–23**

Management of bronchiectasis is unsatisfactory with only very trials and there are no disease-modifying drugs or treatment guidelines. Immunomodulating agent such as low-dose macrolides have also been shown to have some efficacy although more data are needed to advocate their long-term usage. Antibiotic therapy is complex and limited in bronchiectasis, including short-term empirical treatment for acute exacerbation and long-term maintenance of oral, nebulized and i.v. therapy. Patients with bronchiectasis have some variants of IgG deficiency, often associated with a functional impairment of specific antibody response. Conjugate pneumococcal vaccine is part of the routine infant immunisation schedule in many countries. Current recommendations for additional pneumococcal vaccination include children and adults with chronic suppurative disease. However, current but limited evidence supports the use of 23-valent pneumococcal vaccine as routine management in adults with bronchiectasis. There is no data on the efficacy of pneumococcal vaccine on pulmonary decline. And there is neither evidence for, nor against, routine annual influenza vaccination for children and adults with bronchiectasis. This long-neglected illness should receive more research attention in order that we can have better understanding of its aetiology, pathogenesis and treatment.

Immunostimulants represent a heterogeneous group of drugs which includes agents such as vaccines, interferons, chemical compounds and agents derived from bacteria. A detoxified example of this latter class is OM-85, an extract from 8 bacteria frequently responsible for respiratory tract infections *(Haemophilus influenzae, Klebsiella pneumoniae* and *ozaenae, Staphylococcus aureus, Streptococcus pneumoniae, pyogenes* and *viridans, Moraxella catarrhalis),* which has been shown to significantly improve COPD exacerbation and other associated-conditions in elderly patients.

**Our encouraging preliminary data from 25 patients with non-cystic fibrosis broniectasis showed that in 6 months' administration, OM-85 significantly decreased the numbers of acute exacerbation of bronchiectasis (from 4.2 ±2.5 to 2.8 ± 1.3, p=0.05), prolonged the first time to exacerbation**

**(from 56.4 ± 28.6 days to 93.7 ± 43.8 days, p<0.05), and decreased suptum purulence and volume, improved the severity of cough and life quality.**

# 2 STUDY TYPE AND PHASE

**STUDY TYPE:** This is a multicenter, randomized, double blind, placebo-controlled trial. The study will be approved by the Institutional Review Board at each of the study sites. Written informed consent will be obtained from each of the study participants.

**PHASE III**

# 3 STUDY OBJECTIVES

**Primary**

- **Broncho-vaxom could prevent against the acute exacerbations of bronchiectasis.**

**Secondary:** broncho-vaxom could:

- **prolong the first time to acute exacerbation;**
- improve signs and symptoms and healthy life quality;
- decrease the use of antibiotics;
- improve lung ventilatory function (Forced expiartory volume in 1 s % predicted (FEV1%, FEV1/forced expiratory volume (FVC);

# 4 STUDY VARIABLES

## 4.1 Efficacy variables

### 4.1.1 Primary efficacy variable

- The numbers of acute exacerbation.

### 4.1.2 Secondary efficacy variables

- The time to the first time of exacerbation (An exacerbation was defined as a clinical deterioration with all of the following: increasing cough, increasing sputum volume, worsening sputum purulence, and hempotysis).

### 4.1.3 Other efficacy variables

- St George's Respiratory Questionnaire (SGRQ);
- Leicester Cough Questionnaire (LCQ) ;
- kinds of antibiotics ;
- FEV1, FVC, FEV1/FVC.

## 4.2 Laboratory variables

- Levels of pro-inflammatory cytokines in blood and sputum (as feasible).
- C-reactive protein in serum
- Serum Ig level
- Bacterial culture of sputum

## 4.3 Safety variables

The safety and tolerability of OM-85 will be evaluated by recording adverse events during the study and safety laboratory parameters at trial inclusion and end.

### 4.3.1 Primary safety variable

- Adverse events including severe adverse events

### 4.3.2 Secondary safety variables

- laboratory test

### 4.3.3 Other safety variable(s)

Not applicable

# 5 STUDY DESIGN

This is a multicenter, randomized, double blind, placebo-controlled trial in Chinese patients with non-cystic fibrosis bronchiectasis

# 6 STUDY DURATION PER SUBJECT

- 12 months of duration per patient and 12 visits totally.
- Two courses of Broncho-vaxom®, (OM-85), one oral capsule of OM-85 (7mg) or placebo per day for 10 days a month for 3 consecutive months at the beginning of the study, then 6 months later with the same schedule.

# 7 PLANNED NUMBER OF SUBJECTS, SITES, AND STUDY MILESTONES

- The target enrollment is **244** patients with non-cyctic fibrosis bronchiecatsis, and **122** patients will be allocated to each arm.
- Estimated start: March 2015
- Estimated end: March 2017

# 8 ANTICIPATED REGIONS AND COUNTRIES

- 10 institutions from Beijing, Tianjin, Hangzhaou, Shenyang. All sites are with mainland China.

# 9 SELECTION AND WITHDRAWAL OF SUBJECTS

## 9.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC)approved written Informed Consent form is signed and dated by the subject or by the parent(s) or legal representative. The Informed Consent form or a specific Assent form, where required, will be signed and dated by minors.
2. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule or medication intake according to the judgment of the investigator.

3. Subject with both genders is adult patients (>18 years) **diagnosed with brochiectasis by high-resolution computer tomography** (HRCT) having acute exacerbation, defined by increased sputum, color sputum, fever, and hemoptysis, when recuiting.

## 9.2 Exclusion criteria

Subjects are not permitted to enroll in the study if any of the following criteria is met:

1. Subject has previously participated in this study or subject has previously been assigned to treatment in a study of the medication under investigation in this study.
2. Subject has participated in another study of an investigational medicinal product (IMP) or a medical device within the last 30 days or is currently participating in another study of an IMP or a medical device.
3. Subject has a history of chronic alcohol or drug abuse within the last 6 months).
4. Subject has any medical or psychiatric condition that, in the opinion of the investigator, could jeopardize or would compromise the subject's ability to participate in this study.
5. Subject has a known hypersensitivity to any components of the IMP or comparative drugs as stated in this protocol.
6. Recent immunostimulant in last 3 months, cancer, stroke, severe cardiovascular disease, hepatic/kidney impairment, immuno-related diseases.

## 9.3 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care.

Subjects should be withdrawn from the study if any of the following events occurs:

1. Subject develops an illness that would interfere with his/her continued participation.
2. Subject is noncompliant with the study procedures or medications in the opinion of the investigator.

3. Subject takes prohibited concomitant medications as defined in this protocol.
4. Subject withdraws his/her consent.
5. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
6. The sponsor or a regulatory agency requests withdrawal of the subject.

Investigators should attempt to obtain information on subjects, in the case of withdrawal or discontinuation. For subjects considered as lost to follow-up the investigator should make an effort (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents) to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. The case report form must document the primary reason for withdrawal or discontinuation.

Investigators should contact the Medical Monitor whenever possible to discuss the withdrawal of a subject in advance.

# 10 INVESTIGATIONAL MEDICINAL PRODUCT(S)

- Two courses of Broncho-vaxom®, (OM-85), one oral capsule of OM-85 (7mg) or placebo per day for 10 days a month for 3 consecutive months at the beginning of the study, then 6 months later with the same schedule.

# 11 STATISTICS

## 11.1 Definition of analysis sets

There are three analysis populations in the study: Full Analysis Set, Per Protocol Set and Safety Set. The primary endpoint will be analyzed on Full Analysis Set, which is the primary population and will be supported by Per Protocol Set. The secondary endpoint and baseline information will be analyzed on Full Analysis Set. Safety analyses will be performed on Safety Set.

**Full Analysis Set (FAS):** FAS is defined as all randomized subjects who took at least one dose of either trial medications and had at least one efficacy evaluation after treatment.

**Per Protocol Set (PPS):** PPS is a subset of FAS which complied with the protocol sufficiently. It's all subjects in the FAS who:

- are in compliance with treatment, with study drug exposure more than 80%, and
- provide the primary endpoint evaluation , and
- have no major protocol violation

**Safety Set:** All the subjects who have been randomized and taken at least one dose of either trial medications.

## 11.2 Planned efficacy analyses

### 11.2.1 Analysis of the primary efficacy variable

The primary efficacy variable is the numbers of acute exacerbation during the treatment. It will be analyzed on FAS population and supported by PPS population. Statistical description and Statistical inference will be conducted. Mean, standard deviation, median, maximum and minimum will be presented as a statistical description by study group.

Statistical inference consists of parameter estimation and hypothesis test. Comparison between two groups will be performed using student-t test or Wilcoxon test depending on data distribution. 2-tailed 95% confidence interval of the difference between groups will also be presented.

### 11.2.2 Other efficacy analyses

The secondary objective will be analyzed based on full analysis set.
The data analysis includes statistical description and statistical inference. Mean, standard deviation, median, maximum and minimum will be presented in each visit by group for continuous variables as a statistical description. For categorical variables, frequency and proportion will be summarized by group.

Comparison between groups will be performed. For continuous variables, student-t test will be performed according to the distribution of data analyzed. The categorical data will be analyzed by Pearson chi-square test or Fisher exact test. The change after and before treatment within each group will be described and tested by paired t test or signed- ranks test.

The time to the first time of acute exacerbation will be analyzed as survival data. Kaplan-Meier curve of two groups will be presented and Log-rank test will be used to test the difference between two groups.

## 11.3 Planned safety and other analyses

Analysis on safety will be done using safety set.

### 11.3.1 Safety analyses

Analysis on safety will be done using safety set. All adverse events will be coded using the last version of MedDRA.

- Adverse Events(AEs) and Serious Adverse Events (SAEs)

Total frequency and incidence of AE and SAE will be described. The frequency of AE in each group will be tabulated by system organ class and the preferred term. The severity and relationship with the study will be summarized by each group.

Adverse events related (definitely related, probably related and possibly related) will be described and listed separately by the two groups. Adverse events (AE) led to withdrawal from the study will be described and summarized separately by the two groups.

- Laboratory tests

Clinical significant changes of Laboratory tests will be described and summarized separately by the two groups.

Clinical significant change is defined as a change from normal or no -clinical significant abnormal at baseline to clinical significant abnormal after dosing.

### 11.3.2 Other analyses

The baseline and demographic data will be described by group using the Full Analysis Set.

## 11.4 Planned interim analysis and data monitoring

No interim analysis is planned.

## 11.5 Determination of sample size

The sample size is determined by the numbers of acute exacerbation. According ton the pilot data of 25 patients, assuming the average numbers of acute exacerbation is 2.8 for OM-85 group and 3.5 for control group after 12 months. The standard deviation is supposed to 1.5 conservatively.

Group sample sizes of 97 and 97 can achieve 90% power to detect a difference of 0.7 between the null hypothesis that both group means are 3.5 and the alternative hypothesis that the mean of test group is 2.8 with known group standard deviations of 1.5 and 1.5 and with a significance level (alpha) of 0.05 using a two-sided two-sample t-test. Considering the possibility of dropout, 244 subjects are needed (122 subjects per group).

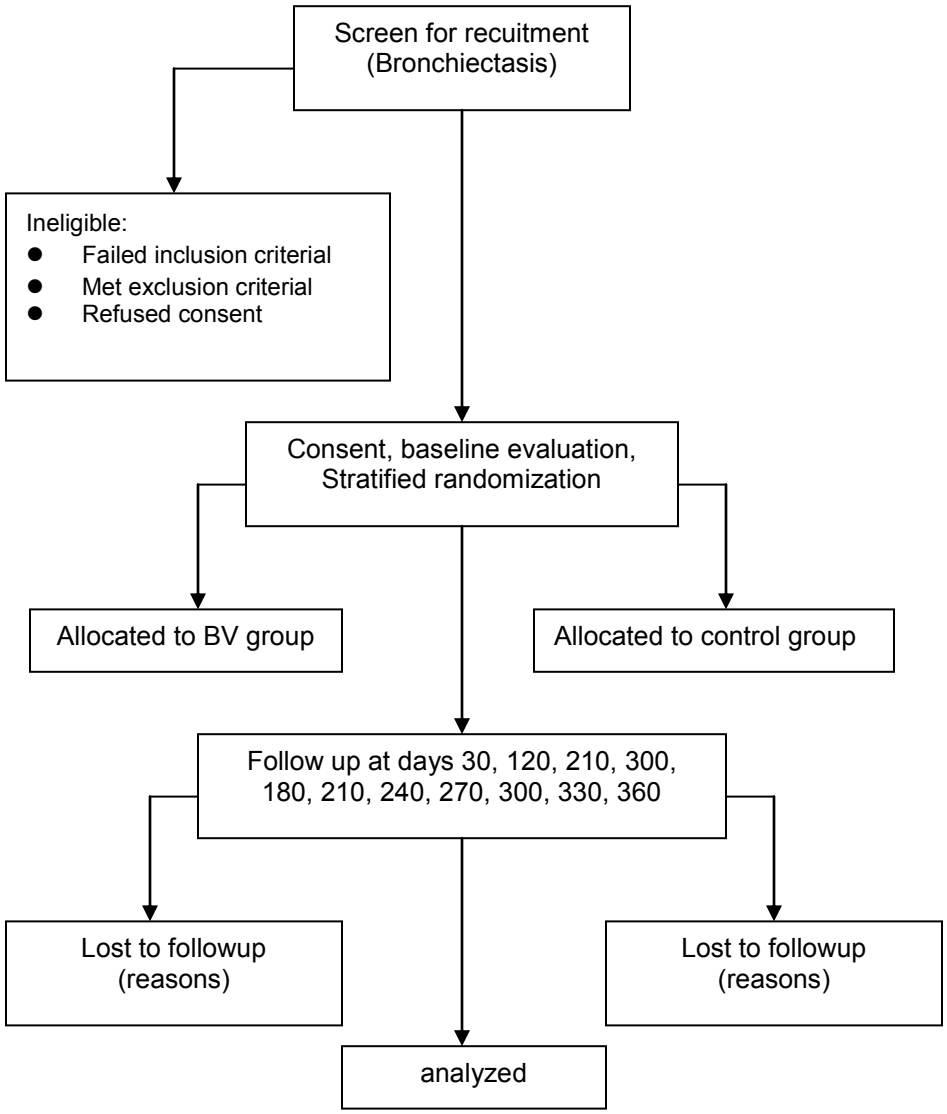
# 12 SCHEDULE OF STUDY ASSESSMENTS

**Table 12:1. Schedule of study assessments**

| Assessments (add day, month etc. if appropriate) | Screening and Randomization visit | Treatment Period | | | Follow-Up/ Discharge |
|---|---|---|---|---|---|
| | V1-2 | V3-V11 | | | V12 |
| | Day-3 and Day 1 | V3-V11 (days 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330) | | | Day 360 |
| Written informed consent | X | | | | |
| Demographic data | X | | | | |
| Verification of inclusion/exclusion criteria | X | | | | |
| Withdrawal criteria | | X | X | | |
| General medical/procedures history | X | | | | |
| Habits and lifestyle | X | | | | |
| Physical examination | X | | | | X |
| Vital signs | X | X | X | X | X |
| Recording of medication and procedures | | X | X | X | X |
| Recording of adverse events | X | X | X | X | X |
| Study drug dispensing and return | | X | X | X | X |

# 13 SCHEMATIC DIAGRAM

**Flow of patients through the study.**



- We will document the baseline data including the number of acute exacerbation in the previous year, lung function measures, sputum volume and color. On every visit, we will record the change in the baseline data. We will compare the difference between the baseline data and the data from the last visit in the two groups. (see the flow chart)

## ● Scientific communication plan:

| | | |
|---|---|---|
| **Type of scientific communication:** | Clinical Trial | |
| **Journal:** | Respiratory Medicine | not applicable ☐ |
| **Meeting/conference:** | European Respiratory Society Conference | not applicable ☐ |
| **Anticipated dates:** | 2014 | |

## ● Relevant literature:

(1) Sprenkle MD, et al. Clinical efficacy of OM-85 BV in COPD and chronic bronchitis: a systematic review. COPD. 2005, 2:167-75.

(2) Solèr M, et al. Double-blind study of OM-85 in patients with chronic bronchitis or mild chronic obstructive pulmonary disease. Respiration. 2007, 74: 26-32.

(3) Collet JP, et al. Economic impact of using an immunostimulating agent to prevent severe acute exacerbations in patients with chronic obstructive pulmonary disease. Can Respir J. 2001, 8: 27-33.

(4) Pasteur MC, et al. British Thoracic Society guideline for non-CF bronchiectasis. Thorax. 2010, 65: 577.

## ● Requested support:

| | |
|---|---|
| **Clinical supply:** | **No:** ☐ **Yes:** ☐ |
| • **Estimated Quantity:** | |
| **Financial support:** | **No:** ☐ **Yes:** √☐ |
| • **Estimated costs for the whole project, itemized budget + requested budget support** [ in US $ or €] | € 100,000 |
| • **Other sources of funding** | **No:** ☐ **Yes:** ☐ if Yes, please specify: |