Protocol Synopsis

I. Protocol title:

Evaluate the efficacy of RespireAid^{TM} in patient with externally contracted seasonal epidemic

II. Objectives:

The main objective of this study is to evaluate the clinical efficacy of the RespireAid^{TM} (Tai-wan-Qing-Guan-Yi-Hao) to ease the symptoms of fever, sore throat, and cough, and the safety after treatment.

III. Test drug

1. Name: RespireAid^{TM} (Tai-wan-Qing-Guan-Yi-Hao) (NRICM101)
2. Dosage form: oral granule
3. Strength: 5g/sachet
4. Packing type: sachet
5. Dosage and administration:
   Take 1 sachet(5g) 4 times daily
6. Mechanism of action (if known):
   RespireAid^{TM} have three targeting potential pathways in externally contracted seasonal epidemic: binding of viral spike protein to human angiotensin-converting enzyme 2 (ACE2), 3CL protease that facilitates virus replication, production of pro-inflammatory cytokines interleukin (IL)-6 and tumor necrosis factor (TNF)-α.

IV. Developmental phase: ☐First in human Phase ☐I ☐II ■III ☐IV

V. Study design:

1. ■Control: ■placebo
   ☐active (please specify name and dosage)
   ☐other
   ☐Uncontrolled
2. Blinding: ☐open label ☐evaluator blind ☐ single blind ■ double blind
   ☐double dummy ☐other
3. Randomized: ■yes ☐no
4. ■Parallel ☐Cross over ☐Other
5. Duration of treatment: 5 days
6. Titration: ☐forced ☐optional ■none
7. ☐Single national ■Multi center(Taiwan) ☐Multi center

VI. Endpoints

1. Primary endpoint(s):
   <u>Efficacy endpoint</u>
   - Time to symptom-free for fever.

Safety endpoint

- Treatment-emergent adverse events (TEAEs)

2. Secondary endpoints:

Efficacy endpoint

- Time to symptom-free for sore throat.
- The change from baseline in the severity of cough during treatment period.

Safety endpoint

- Physical examination
- Vital sign

VII. Selection criteria

1. Main inclusion criteria:
   (1) Male or unpregnant female patients ≥ 18 years to ≤ 79 years of age, who have the symptoms of fever, sore throat, and cough (match the definition in table 1 to 2 in protocol), by investigator's judgement, with mild to severe symptoms (> 20 mm in each VAS).
   (2) With BMI between 18 to 30 kg/m².
   (3) Without a history for alcohol or drug abuse, or other significant organic diseases.
   (4) No history of cancer. Unless no signs of relapse occurred for over 5 years which no anticancer therapies are needed.
   (5) Ability to read and write Chinese, and provide data through questionnaire.
   (6) Ability to understand and comply all procedures of the study, and provide written consent.
2. Main exclusion criteria:
   (1) Confirmed diagnosis of pneumonia or other disease by chest X ray which would impact on study evaluations.
   (2) Must require long-term use of NASIDs, corticosteroids or other immunosuppressive agents.
   (3) Pregnant female.
   (4) Subjects are not suitable for the conduct of the study for any other reasons, determined by the investigator. For example, subjects who require to use antibiotics, COVID-19 or influenza antiviral drugs.

VIII. Study procedures:

This is a multicenter, parallel, double-blind, randomized, placebo-controlled study. A total of 258 male or unpregnant female outpatient subjects ≥ 18 years to ≤ 79 years of age will be enrolled into this study (dropout rate 10%). There will be 2 visits in this study. In Visit 1 (Day 1), subjects who have the symptoms of fever, sore throat, and cough (match the definition in table 1 to 3 in protocol), by investigator's judgement will be recruited into the study.

Subjects will be randomized into the RespireAid^{TM} group or placebo group with allocation rate 2:1.

Following to the clinical guideline of NRICM101, subjects in RespireAid^{TM} group will take drug four times daily with 20g oral granule, administered for 5 days. The subjects in placebo group received study drug with the same dose frequency. Other than study drugs, the rescue drug, acetaminophen, will be administered. If subjects have moderate or severe fever, sore throat, he/she could receive one rescue medication (500mg) per 4 hours, up to 6 tablets in total in one day.
Subjects will be educated how to use e-dairy. The dairy will be recorded the severity of fever, sore throat, and cough from baseline (Day 1, before use of study drug) to Day 5. The efficacy endpoint will be the improvement of fever, sore throat, and cough, and the safety endpoint will be adverse events after treatment. The study and rescue drugs will be dispensed to subjects and the study staff will teach them how to receive medications. If subjects have persistent fever, unscheduled visits will be arranged to check whether or not they would be suitable to participate into this study.
Adverse events will be recorded at Visit 2(Day 8), and the dairy with drug record will be checked.

IX. Concomitant treatment:

1. During study period, the drugs which may impact the efficacy evaluation (i.e. fever, sore throat, and cough) will be prohibited, including
   (1) Chinese medication other than study drug
   (2) Western medication other than study drug
      - NSAIDs
      - Acetaminophen
   (3) Expectorant cough medicines
      - Mucolytics, such as Bromhexine
      - Antitussives, including Opioids (e.g. Codeine, Ethylmorphine, Pholcodine), nonopioids (e.g. Noscapine, Dextromethorphan, Chlophedianol), antihistaminics and Prenoxdiazine
      - Adjuvant antitussives, such as bronchodilators
2. During study period, long-term use of NASIDs, corticosteroids or other immunosuppressive agents will be prohibited.
3. During study period, antibiotics, COVID-19 or influenza antiviral drugs will be prohibited.
4. During study period, subject could receive other treatments/therapies that are not otherwise prohibited and, in the judgment of the Investigator, are required for proper medical care.

X. Statistics

1. Primary hypothesis: ■superiority □non inferiority
□equivalence □other

2. Sample size: enrolled 258 subjects
evaluable 231 subjects

3. Efficacy population: ■ITT ■PP □other
Safety population: □ITT □PP ■other: Safety Population

4. Statistical method(s) for efficacy/safety evaluations:

Efficacy Evaluation

The primary efficacy endpoint is the "time to symptom-free for fever" which is the days of the symptom-free for fever based on the diary record. The primary endpoint will be analyzed by weighted log-rank test for comparison between RespireAid^{TM} and placebo groups. Kaplan-Meier plot will be drew to present the time to event data. The secondary efficacy endpoint of the "time to symptom-free for sore throat" will be analyzed as the analysis of the primary efficacy endpoint. The change from baseline in the severity of cough during treatment period will be summarized as categorical data with frequency and percentage and analyzed by Chi-square test.

Safety Evaluation

All safety assessments, including AEs, physical examinations (PEs), and vital signs (VS), where indicated, will be presented using descriptive statistics by study groups and time points.

5. Planned interim analysis: □yes ■no

XI. Please attach flow chart and/or assessment schedule, if available.

Visit	**1**	**2**
	Screening/Strat of Treatment	**End of Treatment/End of Study/Early withdrawal**
Days	**1**	**8**
Windows		**±2**
Informed Consent	X	
Inclusion/Exclusion criteria	X	
Randomization	X	
Medical History	X	
Demographic data	X	
Physical Examination	X	X
Vital Signs	X	X
COVID-19 testing		
Chest X ray	X	
Urine Pregnancy test [a]	X	
Dispense study drug [b]	X	

Dispense rescue drug [c]	X	
Return study drug		X
Return rescue drug		X
e-diary [d]	X	X
Concomitant Medication	X	X
TEAE	X	X

a: If the result of urine pregnancy test is positive, the subject won't be enrolled into the study.

b: The study drugs will be given four times daily with 20g oral granule, administered for 5 days.

c: The rescue drugs could be given one tablet (500mg) per 4 hours, up to 6 tablets in total in one day.

d: E-Dairy card will be recorded before use of study drugs(baseline), Day 1 to Day 5.