▣ Protocol Synopsis

Protocol Title	A cluster-randomized, open, prospective, observational study to evaluate the treatment effectiveness and safety of N-acetylcysteine(NAC) inhalation compared with standard treatment in patients with symptomatic acute rhinosinusitis
Sponsor	Boryung Pharmaceutical Co., Ltd.
Participating Site(s) and Investigator(s)	Approximately 12 sites
Study duration	Entire study duration: (enrollment of the first subject to end of observation for the last subject): Around 1 year and 7 months - Enrollment period: Around 1 year and 6 months - Follow-up period: 14 days (±3 days)
Indication	For patients with symptomatic acute rhinosinusitis (including recurrent acute rhinosinusitis and symptomatic acute-on-chronic rhinosinusitis)
Study Objectives	N-acetylcysteine (NAC), known to have mucolytic and antioxidant effects, is widely used to treat respiratory diseases and manage post-surgery pulmonary complications. It is also administered as a treatment for acetaminophen addiction and a preventive measure for contrast-induced nephropathy (CIN). While NAC inhalation is commonly used for mucolytic purpose for various respiratory disease because it has relatively less side effects compared to oral or injection administrations, it is more used as a part of allopathy than as a major therapy. As a result, there is neither enough relevant clinical data nor specific reference in treatment guidelines. Therefore, this study aims to evaluate the overall treatment effectiveness and safety of NAC inhalation compared with standard treatment, and to perform follow-up observations on administration cases, patient characteristics, and adverse events of NAC inhalation used in real clinical settings.
Phase and Design	A Cluster (study center)-randomized, prospective, observational study.
Investigational Drug	Not applicable
Sample Size and Rationale	Approximately 300 subjects : Re-enrollment is not allowed. - According to similar study results in the past, the difference between N-acetylcysteine (NAC) inhalation and standard treatment in the total score of the investigator's symptomatic severity assessment can be judged as 0.3. In this study, the assumed difference was 1 and the assumed standard deviation was 2.6, conservatively taking the highest value. With the assumed intraclass correlation coefficient (ICC) of 0.005, significance level of 5%, and test power of 80%, the study was to have 6 clusters (study centers) per treatment arm with a total of 12 clusters and 20 subjects in each cluster. it is calculated, as a result, that 120 subjects will be required per treatment arm and 240 subjects in total. Withdrawal is estimated at 20%; therefore, the plan is to recruit 300 subjects in total to have 150 subjects per arm and 25 subjects in each cluster.
Cluster (study center) Selection criteria	① Medical institutions in Korea at the general hospital level ② An otolaryngologist should be available to conduct the study.

Eligibility Criteria – Inclusion Criteria	① Patients are explained about the study objectives and methodologies, and shall express their consent by signing a written agreement for the use of their personal information. ② Male and female patients who are ≥ 18 years old. ③ Symptomatic acute rhinosinusitis patients whose symptoms have been present for more than 1 week and less than 12 weeks; recurrent acute rhinosinusitis patients (acute rhinosinusitis relapsed 3 times or more within 6 months, sub-clinical symptoms between the relapses); or, symptomatic acute-on-chronic (12 weeks or more) rhinosinusitis patients. ➢ Patients display 2 or more symptoms that imply rhinosinusitis infection. The displayed symptoms should include at least one or more cardinal symptoms (nasal congestion or nasal/postnasal discharge). In addition, facial pain/sense of facial pressure, or reduction/loss of smell can also be accepted as relevant symptoms. ④ The total score of the investigator's symptomatic severity assessment for a patient is 4 or above, and four symptomatic aspects (nasal congestion, nasal/postnasal discharge, facial pain/sense of facial pressure, reduction/loss of smell) are rated in four categories (0=no symptom, 1=mild, 2=moderate, 3=severe). ⑤ Patients have anterior rhinoscopy or nasal endoscopy results, and one or more of the following are observed: ➢ Redness ➢ Edema or mucosal obstruction (mostly in the middle nasal) ➢ Mucopurulent discharge (mostly in the middle nasal) ➢ Nasal polyps
Eligibility Criteria – Exclusion Criteria	① Patients with rhinosinusitis of dental origin. ② Patients with a known chronic pulmonary symptoms including bronchial asthma and chronic bronchitis. ③ Patients with nasal obstruction to the extent that drug administration is difficult. ④ Patients who have received endoscopic sinus surgery within the last 3 months. ⑤ Patients who have shown hypersensitivity or are likely to show hypersensitivity to N-acetylcysteine inhalation components (for the test sites) ⑥ Pregnant or breast-feeding patients. ⑦ Patients who are currently participating in other clinical trials (clinical trials for drugs or medical devices) or are planning to participate in other clinical trials during the duration of this study. ⑧ Patients who are not suitable for study participation upon the investigator's judgment.
Rhinosinusitis treatment	Patients are randomized to test sites and control sites at the cluster (study center) level. Study centers that are randomized as control sites apply standard treatments for rhinosinusitis excluding NAC inhalation, whereas study groups that are randomized as test sites apply NAC inhalation in addition to standard treatments for rhinosinusitis. This study is an observational study; therefore, the protocol does not present details of the standard treatments or NAC inhalation including dose per administration, number of doses, or administration methods. This study relies on the investigators' daily medical practices and the patients' conditions for appropriate decisions to be made. However, NAC can be diluted in sodium chloride or sterile distilled water and no other drugs (for example, bronchodilator) are to be mixed.
Study Methodology	<Overview>

12 medical institutions in Korea that meet the inclusion criteria are cluster-randomized (test sites : control sites =1:1). Information about randomization is disclosed to both investigators and subjects. This means both study center investigators and subjects will be aware of the purpose of this study as well as the result of randomization (whether the subjects will receive NAC inhalation or not) from the beginning of the study.

Investigators shall obtain voluntary consent for participation in this research from patients who visit their medical institutions with symptomatic acute rhinosinusitis within the study duration. Patients who provided a written consent for the use of their personal information and who satisfy inclusion/exclusion criteria will be given a study enrollment number and available data on these patients will be collected among the predefined study relevant data in the case reports until Day 14 (±3 days) from the starting day of treatment.

<Follow-up observation schedule and the scope of data collection>

Data created during subjects' visit to study centers for treatment shall be collected in the case report form. Follow-up observation time points defined below refer to data collection time points. That is, investigators can freely determine patient visit schedules based on the subjects' medical conditions regardless of the follow-up time points defined in this protocol. However, all the data created during the study period and judged to be necessary in relation to this study can be collected in the case report form.

In case of various tests including laboratory tests, no separate tests are conducted for this observational research and only those with test results are collected. Following data shall be collected during the study period.

- Demographics of the subjects.
- Disease information: diagnosis and start date of symptoms; indications on acute bacterial rhinosinusitis; anterior rhinoscopy/nasal endoscopy test results (for follow-up observation: if available); radiological test results (if available); and, infection source test results (if available).
- Past medical history and intercurrent diseases: Examination on intercurrent diseases such as immune deficiency-inducing diseases, chronic diseases including diabetes, lower respiratory diseases, and asthma. Review on anatomical anomaly (if available) that increases the risk of rhinosinusitis, history of sinusitis surgery, and smoking preference.
- Recent drug administration: Medication status for use of systemic antibiotics/antifungal agents, immunosuppressants, antihistamine drugs, or steroid for the past 4 weeks.
- Body temperature, body weight, height (Enrollment data only for height and weight)
- Rhinosinusitis treatment information: information on standard treatment and/or NAC inhalation, surgical procedures (if performed, for example: sinus irrigation or sinuscopy)
- Co-medication/procedures: information on other drug administration and surgical procedures during the study period.
- VAS assessment: to be indicated on 100mm VAS by subject for overall symptomatic severity.
- SNOT-20 (Sino-Nasal Outcome Test) assessment: to be filled-out by subjects.
- Investigator's symptom assessment: investigator's assessment for treatment response where each symptom's severity is rated by the investigator.

	・ Existence of rhinosinusitis complications. ・ Adverse drug reaction related to NAC inhalation. ・ Serious adverse events ·adverse drug reactions.
Endpoints	Primary Endpoint • Change in the total score of the investigator's symptomatic severity assessment (Day 0, Day 14) (Assessed symptoms: nasal congestion, nasal/postnasal discharge, facial pain/sense of facial pressure, reduction/loss of smell are rated in four categories [0=no symptom, 1=mild, 2=moderate, 3=severe]) Secondary Endpoint • Change in the total score of the investigator's symptomatic severity assessment (Day 0, Day 7) • Change in the score of the investigator's symptomatic severity assessment (Day 0, Day 7, Day 14) • Change in SNOT-20 score (Day 0, Day 14) Safety Assessment Parameters • Adverse drug reaction (ADR) related to NAC inhalation and incidences/profiles of serious adverse events and ADRs. • Rate of subjects who discontinued the study due to ADR and relevant ADR profiles.
Statistical Analysis Methods	Analysis of primary endpoints Obtain descriptive statistics (average, standard deviation, median, minimum, quartile, and maximum) for the change in the total score* of the investigator's symptomatic severity assessment by treatment group on Day 14 compared with each time point and baseline (Day 0). Paired t-test shall be used to check intra-group change difference and Two sample t-test shall be used to check inter-group change difference. Also, the same analytic methods shall be used for each cluster (study center). Present ICC, and the Mixed model shall be used to check inter-group difference of the change in the total score of the investigator's symptomatic severity assessment in consideration of clusters. * The total sum of the investigator's symptomatic assessment scores (on nasal congestion, nasal/postnasal discharge, facial pain/sense of facial pressure, and reduction/loss of smell). Analysis of secondary endpoints ・ Change in the total score of the investigator's symptomatic severity assessment (Day 0, Day 7) Obtain descriptive statistics (average, standard deviation, median, minimum, quartile, and maximum) for the change in the total score of the investigator's symptomatic severity assessment by treatment group on Day 7 compared with each time point and baseline (Day 0). Paired t-test shall be used to check intra-group change difference and Two sample t-test shall be used to check inter-group change difference.

	If necessary, in addition, Repeated Measures ANOVA can be conducted to check inter-group difference taking into account of changes in the total score of the investigator's symptomatic severity assessment on baseline (Day 0), Day 7 and Day 14. Multiple regression analysis can also be performed to check factors that influence the change in the total score of the investigator's symptomatic severity assessment. For this, independent parameters may include demographics, baseline characteristics and clinical factors that can be selected in consideration of collected data or clinical characteristics. • Change in SNOT-20 scores (Day 0, Day 14) Obtain descriptive statistics (average, standard deviation, median, minimum, quartile, and maximum) for individual and total SNOT-20 scores by group on Day 14 compared with each time point and baseline (Day 0). Paired t-test shall be used to check intra-group change difference and Two sample t-test shall be used to check inter-group change difference. <u>Analyses of safety data</u> • Adverse drug reaction (ADR) incidence Present the number of subjects with ADR related to NAC inhalation, ADR incidence, 95% confidence interval for the incidence, and the number of ADR cases. Also, present the number of ADR cases by characteristic (severity, measures taken, progress, and etc.) • Serious adverse event/adverse drug reaction incidence Present the number of subjects with serious adverse event(s) and serious adverse drug reaction(s), their incidence, 95% confidence interval for the incidence, and the number of cases.