Efficacy of Antibiotics in Children with Acute Sinusitis: Which Subgroups Benefit?

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STATEMENT OF COMPLIANCE

This trial will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, and 21 CFR Part 312);
- International Council for Harmonization (ICH) E6; 62 Federal Register 25691 (1997);
- The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule-Final Modification (45 CFR Parts 160 and 164);
- National Institutes of Health (NIH) Clinical Terms of Award;
- Approved protocol.

Compliance with these standards provides public assurance that the rights, safety and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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Title: Co-Principal Investigator

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Title: Co-Principal Investigator

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LIST OF ABBREVIATIONS

AAP	American Academy of Pediatrics
AE	Adverse Event
AOM	Acute Otitis Media
CFR	Code of Federal Regulations
CRHC	University of Pittsburgh Center for Research on Health Care
CHP of UPMC	Children's Hospital of Pittsburgh at the University of Pittsburgh Medical Center
CLSI	Clinical Laboratory Standards Institute
CRA	Clinical Research Associate
CRF	Case Report Form
DMSU	Data Management and Statistical Unit in the Division of General Academic Pediatrics at the Children's Hospital of Pittsburgh
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EHR	Electronic Health Record
FDAAA	Food and Drug Administration Amendments Act of 2007
FWA	Federalwide Assurance
GCP	Good Clinical Practice
GEE	Generalized Estimating Equations
H. influenzae	*Haemophilus influenzae*
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Coucil for Harmonization
ICMJE	International Committee of Medical Journal Editors
IDS	University of Pittsburgh Medical Center Investigational Drug Service
IDSA	Infectious Diseases Society of America
IRB	Institutional Review Board
ISM	Independent Safety Monitor
IT	Information Technology
M. catarrhalis	*Moraxella catarrhalis*
KPAR	Kentucky Pediatric/Adult Research
KY	Kentucky
MOP	Manual of Procedures
MT	Mid-Turbinate
N	Number (refers to number of subjects)

NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
NLM	National Library of Medicine
NNT	Number Needed to Treat
NP	Nasopharyngeal
OHRP	Office for Human Research Protections
PA	Pennsylvania
PC	Personal Computer
PCP	Primary Care Provider
PCV-13	Pneumococcal Conjugate 13-valent vaccine
PI	Principal Investigator
PittNet PBRN	PittNet Pediatric Practice Based Research Network
PRSS	Pediatric Rhinosinusitis Symptom Scale
QA	Quality Assurance
QC	Quality Control
S. pneumoniae	*Streptococcus pneumoniae*
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SPA	Study Product Administrator
URI	Upper Respiratory Infection
US	United States
WI	Wisconsin

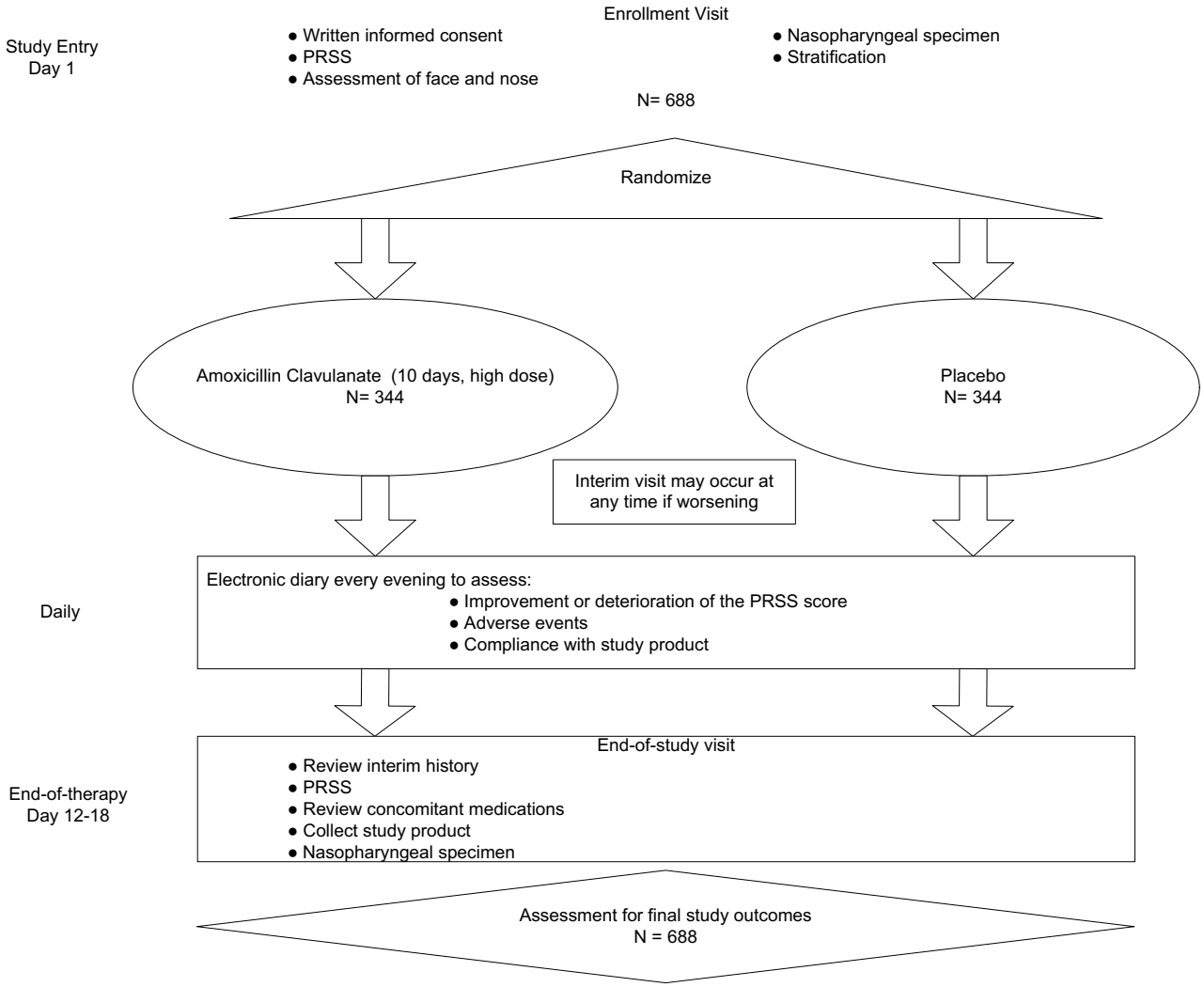
PROTOCOL SUMMARY

Title:	Efficacy of Antibiotics in Children with Acute Sinusitis: Which Subgroups Benefit?
Phase:	III
Objectives:	Primary • To determine whether the effect of antimicrobial treatment differs in predefined subgroups of children with acute sinusitis (i.e., to test for treatment subgroup interactions). Subgroups will be defined by the (1) presence vs. absence of nasopharyngeal (NP) colonization with respiratory pathogens (*Streptococcus pneumoniae, Haemophilus influenzae,* or *Moraxella catarrhalis),* and (2) presence vs. absence of colored (yellow or green) nasal discharge. Secondary • To determine whether antimicrobial therapy is superior to placebo (i.e., to test for the overall effect). Tertiary • To evaluate compliance with study product. • To assess adverse events associated with use of amoxicillin clavulanate, including the development of bacterial resistance. • To compare resource utilization according to treatment strategy.
Population:	688 children aged 2 to 12 years, who meet the current AAP criteria for sinusitis.
Inclusion Criteria:	2 -12 years of age (before 12th birthday);Persistent sinusitis: URI symptoms present for >10 days without improvement (11-30 days); Worsening sinusitis: URI symptoms worsening after a period of improvement (6-10 days); baseline score ≥9 on the Pediatric Rhinosinusitis Symptom Scale (PRSS), ≥2 doses of pneumococcal conjugate vaccine or appropriate for age.
Exclusion Criteria:	Sinusitis with severe presentation (≥3 days of colored nasal discharge and fever ≥39˚ C); asthma/allergic rhinitis explains symptoms; allergy to amoxicillin-clavulanate; immotile cilia syndrome; cystic fibrosis; immunodeficiency; parental/legal guardian inability to read/write English or Spanish; other concurrent infection (e.g., pneumonia, acute otitis media, streptococcal pharyngitis); systemic toxicity; wheezing on exam; antibiotic use within 15 days; prior sinus surgery;
Number of Sites:	5 sites (Pittsburgh will enroll 388 children, and Bardstown, and Madison will enroll 100 children each).. At each site, patients will be enrolled from primary care clinics.
Availability of Subjects:	Based on the preliminary data presented, we will be able to recruit at least 100 patients per year in Pittsburgh alone. Likewise, based on the strong track record of enrollment in clinical trials, other sites will be able to recruit at least 25 patients per year during the course of the study.
Consent Process:	Parents/legal guardians of children who meet criteria for persistent or worsening presentations of acute sinusitis will be approached for informed consent. Assent will be sought from older children who are believed to be developmentally capable.

Retention and Follow-up:	In a preliminary study, our retention rate was 94%. In this study, we have built in additional measures to improve retention (electronic daily diary, phone calls to patients with missing data, reimbursement for completing the diary, and home visits). We anticipate no changes in the approaches for retention during the course of the trial.
Study Duration:	5 years
Subject Duration:	12 to 18 days
Description of Agent and Rationale:	Amoxicillin-clavulanate (90/6.4 mg/kg/d in 2 divided doses for 10 days) or matching placebo will be used. Amoxicillin-clavulanate was chosen because of the increasing prevalence of *H. influenzae* in nasopharyngeal specimens of children with bacterial respiratory infections, and because it is the most effective available orally administered antimicrobial drug against the respiratory pathogens most commonly causing sinusitis. A high dose of amoxicillin will minimize the number of children experiencing treatment failure in the active treatment group. The use of an agent with suboptimal antibacterial coverage would also make it more difficult to determine whether treatment effect heterogeneity exists. Ten days was chosen because this is the duration most frequently used in practice.
Description of Study Design:	**Design**: Multicenter, randomized, double-blind, placebo-controlled, parallel group trial **Stratification variables**: presence/absence of colored (yellow or green) nasal discharge and site of enrollment **Duration of treatment**: 10 days **Primary outcome measure**: Pediatric Rhinosinusitis Symptom Scale (PRSS). The PRSS will be administered every evening as an electronic diary. PRSS scores on Days 1 to 11 will be the primary analysis variable (i.e., repeated measures over time will be used to measure disease burden). **Secondary efficacy outcome measures**: 1) Treatment failure will be defined as follows: a. Worsening at any time–PRSS score increased by >20% from entry. b. No change by 48 hours–PRSS score decreased by <2 points from entry (Day 1) to Day 3. c. Failure to improve significantly by 72 hours–PRSS score decreased by <20% from entry (Day 1) to Day 4. d. PRSS decreased by <20% from enrollment on 2 consecutive occasions on Days 5-11 e. Still symptomatic (PRSS score ≥50% of entry score) at the time of the end-of-study follow-up visit (Days 12 to 18). 2) Development of AOM on Days 1 to 11. 3) Receipt of a systemic antibiotic on Days 1 to 11 for any indication. **Tertiary outcome measures**:

	1) Proportion with adverse events (including emergence of bacterial resistance). 2) Proportion who are compliant with study product (took ≥70% of the doses). **Flow of patients:** We will review each child's PRSS scores every morning and will contact parents/legal guardians of children whose PRSS scores are not improving at the expected rate (see definition of treatment failure above). These children will be seen by the study team and rescue medication will be prescribed, as clinically indicated and without breaking the blind, but they will be continued to be followed in the same way (electronic daily diary and routine end-of-study follow-up visit). **Statistical methods**: The primary efficacy analyses will be: • To determine whether the effect of treatment differs in children with and without nasopharyngeal colonization with respiratory pathogens (i.e., we will test for interaction). • To determine whether the effect of treatment differs in children with and without colored nasal discharge (i.e., we will test for interaction). Generalized estimating equations will be used for these analyses. The primary analysis will be based on the intention-to-treat principle and will use two-sided tests. The variables chosen to define the subgroups were based on extensive preliminary data indicating likely heterogeneity of treatment effect in subpopulations defined by the presence/absence of these variables. This sample size will allow us to test these 2 hypotheses simultaneously.
Laboratory Tests:	A nasopharyngeal swab (or mid-turbinate nasal swab if a nasalpharyngeal swab is unable to be obtained)will be obtained at the baseline and final visit from all participants, when possible We will use the presence of respiratory pathogens as one of the subgrouping variables. These swabs will be shipped to the Microbiology Lab at the Children's Hospital of Pittsburgh (CHP) on ice within 48 hours. According to the preliminary data presented, shipping of swabs does not adversely affect the ability to recover the respiratory pathogens being investigated. The Microbiology Lab will identify *S. pneumoniae*, *H. influenzae,* and *M. catarrhalis* using standard microbiological techniques.
Data Management and Monitoring Plan:	Data will be electronically captured using (21 CFR Part 11-compliant) electronic case report forms designed by the University of Pittsburgh Center for Research on Health Care (CRHC). Data will be saved on the secured CRHC servers which are backed-up daily and archived weekly. Quality and completeness of data collection will be monitored on an ongoing basis by the data manager at the Data Management and Statistical Unit in the Division of General Academic Pediatrics at the Children's Hospital of Pittsburgh (DMSU). Independent clinical study site monitoring will be conducted as detailed in the clinical monitoring plan. Monitoring visits will include, but are not limited to review of regulatory files, accountability records, eCRFs, informed consent forms, medical and laboratory reports, and protocol compliance.
Time to Complete Enrollment:	4.5 years

Schematic of Study Design:



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Please refer to the protocol-specific communication plan in the Manual of Procedures (MOP) for other contact information.

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

2.1.1 Sinusitis

The current clinical practice guideline from the American Academy of Pediatrics for the Diagnosis and Management of Acute Bacterial Sinusitis recommends that the diagnosis of acute sinusitis is made when symptoms of an upper respiratory infection (URI) persist beyond 10 days without showing signs of improvement (persistent presentation), when symptoms appear to worsen (on the 6th to 10th day) after a period of improvement (worsening presentation), or when both high fever and purulent nasal discharge are present concurrently for at least 3 consecutive days (severe presentation).[1] In studies to date, children with persistent and worsening presentations comprise >95% of cases.[2] Our preliminary data and the available literature suggest that only a subset of children being diagnosed with acute sinusitis on the basis of current criteria are likely to have bacterial disease. This is not entirely surprising because current criteria rely solely on the duration and the quality of respiratory tract symptoms (which are both common and non-specific). Accordingly, it seems likely that many children currently being diagnosed as having acute sinusitis actually have an uncomplicated URI. This is important because acute sinusitis is one of the most common diagnoses for which antimicrobials are prescribed for children in the US, accounting for 7.9 million prescriptions annually.[3] *A critical need* thus exists to establish which children, if any, actually benefit from antimicrobial therapy.

2.1.2 Antimicrobial therapy

Inappropriate use of antibiotics contributes to the emergence of bacterial resistance on both individual and population levels.[3] Sinusitis is the 5th most common reason for an antibiotic prescription for children in the US,[4] and in contrast with most other frequently occurring pediatric infections, antibiotic prescribing rates for children with acute sinusitis have not decreased in the last 15 years.[3] Yet, available literature and our preliminary data suggest that only a subset of children diagnosed as having acute sinusitis based on the current clinical criteria are likely to have bacterial disease. This is not entirely surprising because current criteria[1] rely solely on the duration and the quality of respiratory tract symptoms. Because of the large overlap between symptoms of a viral upper respiratory tract infection (URI) and acute sinusitis, current criteria are insufficiently specific to identify children most likely to have bacterial disease.

2.1.3 Preliminary studies

In preparation for this trial, we prospectively enrolled 276 consecutive children aged 2 to 12 years with persistent or worsening presentations of acute sinusitis from 6 outpatient clinics in Pittsburgh (NIH R21AI076677, N. Shaikh, PI). The aims of this observational study were to (1) develop and validate a symptom severity scale; (2) identify important prognostic factors that could be used to define subgroups in the present study; and (3) determine signs and symptoms associated with likely bacterial sinusitis, which could then be used to define subgroups for the present study. We screened 2023 children with URI symptoms for eligibility. A total of 355 (18%)

children met clinical criteria for the diagnosis of persistent or worsening presentations of acute sinusitis, and parents/legal guardians of 276 children agreed to enroll their children in our observational study. The mean age (standard deviation) of children enrolled was 6.4 (2.9) years. Almost all children (n=267) had sinus radiographs performed on the day of diagnosis and most (n=204) had a nasopharyngeal swab collected for bacterial culture (for reasons explained below). A large majority of children received antimicrobial therapy (n=227). Seventy six percent of children had abnormal sinus radiographs and 49% had pathogens (*S. pneumoniae, H. influenzae,* or *M. catarrhalis)* isolated from their nasopharynx.[25-27]

Development and validation of the Pediatric Rhinosinusitis Scale (PRSS). Development of the pilot version of the scale was based on well-established methods of scale development.[28-30] Detailed semi-structured interviews with children with acute sinusitis and their parents/legal guardians guided us in the selection of items most important to them. Based on these data, we selected, from a larger pool of items, 10 items for the pilot version of the scale. Each item on the pilot version of the scale was rated on a 3-point Likert scale (none = 0, a little = 1, a lot = 2) and the total score was obtained by summing the scores on 10 equally-weighted questions. The 276 parents/legal guardians of children enrolled in the preliminary study were asked to complete the pilot version of the scale as a once-a-day paper diary (in the evening) for 8 to 10 days (i.e., from enrollment to the end-of-study follow-up visit). Two items (headache, fever) in the pilot version proved to have poor psychometric properties and were therefore dropped. Table 1 summarizes the psychometric properties of the remaining 8-item scale. These data support the validity and responsiveness of the PRSS; the scale appears to effectively measure severity of symptoms and overall functional status in young children with acute sinusitis. Changes in score over the first few days of illness were substantial and generally matched the assessments both of parents/legal guardians and of clinicians.

Table 1. Psychometric properties of the PRSS scale

Scale Property	Measurement	Result (Interpretation)
Missing Data	% scales with missing data	2% had missing data (acceptable)
Test-retest reliability	Intraclass correlation coefficient in clinically stable children	ICC = 0.52 (0.4-0.75 = fair/good).[31,32]
Construct validity (evidence that the scale measures the construct it intends to)	Association of PRSS with: 1. Radiographic diagnosis (p<.05*) 2. Functional status Questionnaire[33] (r=0.6*) 3. Parental/legal guardian overall assessment (r=0.4*) 4. Physician assessment of severity (r=0.4*)	 1. p=.0003 (strong association) 2. r = 0.53, p<.05 (c/w predicted) 3. r = 0.38, p<.05 (c/w predicted) 4. r = 0.28, p<.05 (c/w predicted)
Responsiveness (an index of how well scale measures change)	Standardized response mean	SRM = 2.07 (>0.7 = excellent responsiveness)[28,34,35]
Minimally important difference (the smallest degree of change that is clinically meaningful)	MID calculated using distribution-based methods (i.e., using Standard Error of Measurement and half SD).[30,35-40]	MID = 20% (i.e., a decrease of 20% from baseline = improvement)

*Results predicted *a priori*

Modification of the PRSS – During the analysis of the data from the PRSS validation study, we realized that expanding the number of response options would likely improve the psychometric properties of the scale. In particular, we were concerned about the possibility of a ceiling effect; patients with entering “a lot” of a certain symptom (the most severe response option available) would not be able to use the scale to indicate worsening. Accordingly we modified the PRSS by

increasing the number of response options from 3 to 6 (from “None”, “A Little”, “A lot” to “None”, “Almost None”, “A little”, “Some”, “A lot”, and “An Extreme Amount”) and administered it as an electronic diary to 65 children with acute sinusitis diagnosed at the Primary Care Center in Pittsburgh during the 2014-2015 respiratory season. Before administering the scale, however, we performed in-depth cognitive interviews with 75 patients regarding the wording of the individual questions, the new response options, the instructions, and modified the wording of some of the questions on the PRSS (see Supplement B below). The psychometric properties of the modified version of the PRSS (version 2.0) improved significantly. Specifically, (1) the proportion of child at the ceiling value was reduced by half for most items (e.g., 64% vs. 35% at ceiling for night time cough), (2) the responsiveness of the scale improved from 2.07 to 2.48, and (3) the test-reliability of the scale improved from 0.52 to 0.82. The MID of the scale remained stable at 20%. The modification of the scale does not change the sample size estimates; the new version has finer ratings for each of the eight items comprising the score (total maximum score increased from 16 to 40). Assuming these two discrete scales divide the underlying continuous scale into equal intervals, the standard deviation and the mean on the new scale should differ from those on the old scale by a factor of 2.5, which in fact they do (the baseline score and the average standard deviation across treatment and time both increased by 2.5). Because the new version of the scale appears to result in primary summary statistics that are a multiple of those resulting from the old scale, and the tests being used are scale invariant, the original sample size estimates can be used.

Identification of important prognostic factors

We compared median time to resolution of symptoms (defined as reaching a score of ≤ 2 on the PRSS on two successive occasions) according to the levels of the potential prognostic factors (variables measured at baseline) using a proportional-hazards model in children receiving antimicrobial therapy for acute sinusitis. The only variable that remained independently associated with time to resolution after adjustment for baseline severity of symptoms was nasopharyngeal colonization with pathogens (*S. pneumoniae, H. influenzae, M. catarrhalis)* at baseline. Median time to symptom resolution in those with and without nasopharyngeal colonization with pathogens was 7.5 and 8.5 days, respectively (p=.008). In contrast, in two previous studies of children with URI who were not receiving antimicrobial therapy, the presence of pathogens predicted *slower* resolution of symptoms.[27] Together, these findings suggest that in this trial, children who are colonized with pathogens will respond differently to treatment than those who are not colonized with pathogens (i.e., heterogeneity of treatment effect). Our preliminary data, which are similar to the data from Kaiser,[19,20] suggest that testing for bacteria in the nasopharynx may assist greatly in identifying children who will respond to treatment with antibiotics. If we find that only those children colonized with pathogens benefit from antimicrobial therapy, then the management of children with suspected sinusitis could be similar to the management of children with streptococcal pharyngitis. A rapid antigen test for *S. pneumoniae* is commercially available, can be performed at the bedside, and has good accuracy (sensitivity 88 to 92%, specificity 95 to 97%).[41,42] Similar PCR-based tests for *H. influenzae* and *M. catarrhalis* have also been developed. By prescribing antimicrobials only to those with pathogens, antimicrobial prescribing could be sharply reduced. Of note, in our preliminary dataset, results were driven largely by the subgroup of children colonized with *S. pneumoniae*.[27] We suspect that this was due to the smaller number of children colonized with *H. influenzae* and *M. catarrhalis*. The ability of the PRSS scale to discern differences in time to resolution according to the presence or absence of pathogens in the nasopharynx further supporting its utility and validity. In summary, our preliminary study supports using the presence of pathogens

in the nasopharynx to define subgroups and using the PRSS scale as the primary outcome measure.

Identification of important diagnostic factors

Relatively little data exist regarding the accuracy of individual signs and symptoms of sinusitis in children. Accordingly, one of the goals of our preliminary study was to identify signs and symptoms that could discriminate children with true bacterial sinusitis from children with an uncomplicated URI. However, because no practical gold standard exists for the diagnosis of bacterial sinusitis, we proposed to use radiography and nasopharyngeal culture results as reference standards. We reasoned that it would be very unlikely for children with no pathogens in their nasopharynx to have bacterial sinusitis. Similarly, although radiographs have are frequently positive in children with URI, normal radiographs are very unlikely in children with significant sinusitis.[43] Thus, we reasoned that use of both tests together could be used to divide children into two groups: those with "likely URI" (negative NP swabs OR negative X-rays) vs. those with "possible bacterial sinusitis" (positive NP swabs AND positive X-rays). This approach is admittedly less accurate than sinus aspiration; some children with a positive swab and a positive X-ray will have viral URI (because the positive predictive value of these findings is low). Nevertheless, because our goal is restricting antibiotic use, not perfect prediction, using these 2 tests could serve as a reasonable "silver standard" against which the accuracy of signs and symptoms commonly attributed to sinusitis could be assessed. *Although all children enrolled in our preliminary study met the diagnostic criteria set forth in the American Academy of Pediatrics (AAP) guidelines, only 79/204 (39%) were classified as having "possible bacterial sinusitis"*. Of the signs and symptoms investigated, colored nasal discharge, was the only finding associated with "possible bacterial sinusitis". Colored discharge was independently associated with the presence of NP pathogens ($p<.003$) and with abnormal sinus radiographs ($p<.001$) even after controlling for other variables (e.g., age). Thus, our results support using colored discharge to define the subgroups in this trial.

Survey of current practice supports equipoise. Genuine uncertainty exists among practicing clinicians regarding the need for routine antimicrobial treatment of children with acute sinusitis. In a survey of 68 community pediatricians affiliated with Children's Hospital of Pittsburgh of UPMC (response rate 86%), only 56% and 32%, respectively, reported routinely prescribing antibiotics for children meeting criteria for persistent and worsening presentations of acute sinusitis. The AAP sinusitis guideline committee was divided between those who favored immediate antimicrobial treatment and those who favored initial observation for children with persistent symptoms. Thus, in recognition of the substantial rate of spontaneous resolution among children diagnosed as having acute sinusitis,[6] the guideline[1] includes an option for initial observation for children with persistent symptoms (who constitute at least 85% of all children diagnosed with acute sinusitis).[2] Given the current uncertainty among practicing pediatricians and the observation-only option offered by the guideline, a placebo-controlled trial is appropriate and warranted.

2.2 Scientific Rationale

2.2.1 Rationale for the trial

2.2.1.1 Inadequate data on efficacy of antibiotics

Despite the large numbers of children who are treated with antibiotics for acute sinusitis, surprisingly little evidence exists to support antibiotic treatment. Only 3 placebo-controlled, randomized clinical trials have assessed the benefit of antimicrobial therapy for acute sinusitis (Table 2). A fourth study was excluded from the discussion below because no minimum duration of symptoms was required for inclusion;[5] thus, the majority of children included had what would be today classified as uncomplicated viral upper respiratory tract infections (URIs). The numbers of children enrolled in these trials were relatively small (111 children received placebo in the three trials combined),[2,6,7] and the inclusion criteria differed from trial to trial, and from diagnostic criteria for sinusitis set forth in current guidelines. The earliest trial[7] used signs and symptoms of sinusitis plus abnormal imaging of the sinuses to select children for enrollment, thus its results are not directly applicable. The results of the two more recent trials[2,6] were contradictory: the smaller trial supported antimicrobial treatment whereas the larger trial supported observation only. It seems questionable to recommend antimicrobial treatment based on the results of a trial in which only 28 children received placebo in light of a previous study twice as large that had contrary results. Similarly, it seems questionable to routinely recommend observation when clear evidence exists that some children improve more rapidly with antibiotics than without. Accordingly, the 3 randomized controlled trials conducted to date do not allow meaningful conclusions to be reached about the efficacy of antimicrobials. This is reflected in the contradictory recommendations proposed by different guideline committees.[1,8-10] A critical need exists for a placebo-controlled trial large enough to determine not only whether antimicrobial therapy is beneficial overall, but also whether there are definable subgroups of children for whom antibiotics are, or are not, sufficiently beneficial to justify their use. By addressing some of the limitations of previous trials, this study will provide data regarding the efficacy of antimicrobial therapy in children with acute sinusitis.

Table 2. Summary of Randomized Controlled Trials to Date and of the Current Trial

	Wald et al., 1986[7]	Garbutt et al., 2001[6]	Wald et al., 2009[2]	Current trial
N	93 (35 on placebo)	188 (55 on placebo)	58 (28 on placebo)	688 (344 on placebo)
Age	2-16 years	1-18 years	1-10 years	2-12 years
Inclusion criteria	Persistent symptoms and positive X-ray	Persistent symptoms	Persistent, worsening, or severe symptoms	Persistent or worsening symptoms
Treatment arms	Amox, Amox-clav, placebo	Amox, Amox-clav, placebo	Amox-clav, placebo	Amox-clav, placebo
Primary Outcome	Fewer than 2 symptoms present on Day 10 on a 10-item questionnaire (not validated)	Change in score from baseline to Day 14 on a 5-item scale with questionable validity	Fewer than 2 symptoms present on Day 14 on a 10-item questionnaire (not validated)	Symptom score over the first 10 days using a validated scale (i.e., repeated measures over time)
Result	66% vs. 43% cure with antibiotics vs. placebo	No difference on Day 14	50% vs. 14% cure with Amox-clav vs. placebo	To be determined
Major limitations	• 1˚ outcome dichotomous • 1˚ outcome assed on one particular day	• Change in score not ideal for measures with high variability	• 1˚ outcome dichotomous • 1˚ outcome assed on one particular day	• 1˚ outcome will measure symptom burden over time

	• Excluded children with normal radiographs or with history of asthma • Analysis not per intention-to-treat principle	• Dose of amoxicillin likely not effective for children with resistant *S. pneumoniae*	• Not powered to detect whether treatment effect differed in children with the 3 included presentations • Fewer children enrolled than expected	• Adequate doses of an effective antibiotic will be used • Analysis per intention-to-treat principle • Power calculation based on reliable preliminary data

2.2.1.2 Deficient methods used in previous trials

1) None of the previous trials tracked symptoms on a daily basis. Instead symptoms were assessed by telephone interview at fixed time points. Comparing symptoms on any given day is likely to be less sensitive than comparison of the burden of disease over time.
2) The primary outcome in all 3 studies to date was assessed on day 10 or 14. Because symptoms of sinusitis resolve spontaneously over time, comparison of symptoms this late in the course of disease is not ideal.
3) None of the previous trials used a properly validated symptom severity scale to measure response to therapy. The scale developed by Garbutt et al.[11] was psychometrically evaluated, but its construct validity appears questionable because no data were reported regarding the scale's correlation with other measures of functional status or with measures of sinusitis severity. Furthermore, parents/legal guardians/children did not provide any input regarding the importance of the items included in the scale. The questionnaire developed by Wald et al.[2] was not psychometrically evaluated.

2.2.1.3 Current diagnostic criteria lack specificity for bacterial disease

The current conventional approach in the US is to diagnose acute sinusitis in children with a URI whose clinical course is atypical, characterized by prolonged and/or worsening symptoms. Although this approach has had some success in reducing the number of children treated inappropriately with antibiotics, it needs to be refined for several reasons. First, because persistent or worsening upper respiratory symptoms may be due to causes other than bacterial superinfection (e.g., closely spaced sequential viral infections, asthma, allergic rhinitis). And second, because some uncomplicated viral infections may nonetheless be persistent or biphasic. A recent meta-analysis of studies of children with URI reported that 50% of children were still symptomatic at 10 days.[12] Although the majority of uncomplicated viral URIs are improving by 10 days, many children will continue to have residual respiratory symptoms which may be over interpreted by their parents/legal guardians or physicians. All of these factors may lead to the over diagnosis of sinusitis and to the prescription of unnecessary antibiotics. Accordingly, it is likely that many children diagnosed with acute sinusitis using the current criteria actually derive no benefit from antimicrobial therapy.

2.2.1.4 This trial may allow us to make diagnostic criteria more specific for bacterial disease.

Development of accurate diagnostic criteria would ideally require a cohort of children with clinically suspected sinusitis to undergo aspiration of the maxillary antrum. Signs and symptoms associated with the recovery of bacteria from the sinus could then be used to accurately identify those with bacterial disease. Unfortunately, sinus aspiration is invasive, often requires sedation, is technically difficult, and is recommended only for children who have severe disease, are

immunocompromised, or have infections that are unresponsive to antibiotic treatment. Accordingly, by necessity, the current diagnostic criteria were developed on the basis of clinical observations of the course of typical viral URIs, with acute sinusitis assumed when the duration or quality of children's symptoms differed significantly from the typical presentation. To our knowledge, no other infectious disease for which antibiotics are so frequently prescribed is diagnosed based simply on the duration or course of symptoms; diagnosis usually rests upon reliable findings on examination (as in acute otitis media) or direct testing for presence of bacteria (as in streptococcal pharyngitis). Because of the inaccuracies inherent in the current criteria, refinements are needed that would make the criteria more specific for bacterial disease. Instead of using sinus aspiration or imaging, we will use differential response to antibiotic therapy as a means of identifying children with bacterial disease. In other words, ***examination of response to treatment in various subgroups (defined a priori) in this large randomized, placebo-controlled trial represents a unique and innovative approach to refining the diagnostic criteria for acute bacterial sinusitis in children.***

2.2.2 Rationale for using NP colonization to identify the subgroups

2.2.2.1 Bacterial superinfection more likely when pathogens present

Like Acute Otitis Media (AOM), acute bacterial sinusitis is a superinfection that originates from bacteria in the nasopharynx. The negative predictive value of a nasopharyngeal culture for isolating the same organism from the middle ear is consistently >90%.[14-18] Thus, when pathogens are absent from the nasopharynx, bacterial superinfection of the middle ear is highly unlikely. No similar recent studies exist for acute sinusitis, presumably because sinus aspiration is considerably more invasive. Nevertheless, sinusitis and otitis are similar conditions. It seems reasonable to suppose that acute bacterial sinusitis will also be highly unlikely when no pathogens are present in the nasopharynx. Even if the negative predictive value of the NP culture is in the 75-90% range, it may nonetheless prove useful in practice because unlike AOM, where the diagnosis can be readily and accurately accomplished through direct–i.e. otoscopic–examination, the diagnosis of sinusitis cannot.

2.2.2.2 Children with pathogens in NP benefit more from antimicrobials

In two trials comparing antibiotics to placebo, Kaiser compared the resolution of symptoms in adults with URI or sinusitis according to the presence of pathogens in the nasopharynx.[19,20] In patients with no pathogen recovered from the nasopharynx, there was no difference between treatment arms in terms of symptom resolution (i.e., no benefit of therapy). In contrast, in those with pathogens recovered from their nasopharynx, symptoms resolved significantly more rapidly in the antibiotic arm. This study in adults suggests that the presence of pathogens in the nasopharynx holds promise also as a method of selecting children who are likely to benefit from antimicrobial therapy.

2.2.3 Rationale for using colored nasal discharge to define subgroups

In both children and adults, the presence of colored nasal discharge has been associated with the presence of *S. pneumoniae, H. influenzae,* and *M. catarrhalis* in the nasopharynx.[20,21] In a preliminary study, we found a robust association between the presence of nasopharyngeal pathogens and the presence of colored (green/yellow) nasal discharge (P<.003, see below).

Colored nasal discharge has been associated with response to antibiotics in adults with sinusitis; a recent individual patient data meta-analysis compared the number to the needed to treat (NNT) in the subgroup of adults with visible purulent discharge in the pharynx with the NNT for the overall group with acute rhinosinusitis. Compared to the overall group, those with visible discharge were more likely to benefit from antimicrobial therapy (NNT 8 and 15, respectively).[22] European and Canadian sinusitis guidelines use purulent nasal discharge to select children for antimicrobial treatment.[8,23] Most (86%) pediatricians in the US consider the presence of colored nasal discharge as “very important” or “moderately important” in their decision to diagnose acute sinusitis, and second in importance only to duration of symptoms.[24] Thus, it appears necessary to establish whether or not this finding is useful in selecting children who may benefit from antimicrobial therapy. Assessing for colored nasal discharge as a proxy for bacterial disease is appealing because it does not require microbiologic testing.

2.2.4 Rationale for placebo

A placebo arm is necessary to identify subgroups of children who do not require treatment. This will also help establish the natural history of the disease. A comparative trial comparing one antibiotic with another or a short vs. long course of an antibiotic would be premature at this time.

2.2.5 Rationale for the use of clavulanate

In our preliminary data, 48% of *H. influenzae* isolates and 100% of *M. catarrhalis* isolates produced ß-lactamase. Furthermore, the incidence of disease caused by *H. influenzae* may be increasing secondary to routine vaccination with pneumococcal conjugate vaccine.[14,44] Thus, the use of amoxicillin-clavulanate potassium instead of amoxicillin alone seems prudent. The most recent guideline from the Infectious Diseases Society of America (IDSA) recommends amoxicillin-clavulanate potassium as the preferred agent for sinusitis in children.[45] The AAP guideline recommends using amoxicillin with or without clavulanate potassium as the first-line agent.[1]

2.2.6 Rationale for using the high-dose amoxicillin-clavulanate potassium

In our preliminary study, 23% of the *S. pneumoniae* isolates were penicillin-nonsusceptible. In addition, 6% of the non ß-lactamase producing *H. influenzae* isolates were ampicillin-nonsusceptible. A higher dose of amoxicillin would be needed to treat these ampicillin/penicillin-resistant isolates of *S. pneumoniae* and *H. influenzae*. Furthermore, data collected after widespread use of Pneumococcal Conjugate 13-valent vaccine (PCV-13) indicate[46] that many of the emerging serotypes appear to be resistant to penicillin. The rates of diarrhea are no higher when using the high-dose formulation of amoxicillin-clavulanate (because it contains relatively less clavulanate).[47,48]

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

1) Amoxicillin clavulanate potassium - The most common side effect of amoxicillin clavulanate is diarrhea. Diarrhea is reported by about one third to one half of children who take this medication. Infrequently, children may develop vomiting, nausea, diaper rash, or abdominal pain. Rarely, anaphylaxis (a severe allergic reaction) may occur. The use of antibiotics has been linked to the development of resistant bacteria, both in the child receiving antibiotics and in the community at large. Finally, there is a risk that the child will not respond to amoxicillin clavulanate, and thus require a different treatment. Most of the reported side effects of amoxicillin clavulanate are mild to moderate and resolve when the medication is stopped.

2) Placebo - There is a theoretical risk that children receiving placebo may be symptomatic for a longer period of time or have more complications than children receiving antibiotics. None of the studies to date, however, have borne this out. The largest study to date found no difference in the time-to-resolution of symptoms in children on antibiotics. Similarly, there is no evidence that immediate treatment with antibiotics is more effective at preventing complications of sinusitis. Most complications of sinusitis seem to occur in older children (who are not included in this study) and occur during the first few days of an upper respiratory tract infection (before sinusitis is usually diagnosed). Placebo contains no active medications and an allergic reaction is very rare.

3) Nasopharyngeal swab - The NP swab may cause minor transient discomfort.

4) Loss of confidentiality - There is a rare risk of breach of confidentiality. Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subjects' PHI. All records will be kept in a locked file cabinet or maintained in a locked room at the participating clinical study sites. Electronic files will be password protected. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Any publications from this study will not use information that will identify subjects by name. Organizations that may inspect and/or copy research records maintained at the participating clinical study sites for quality assurance and data analysis include groups, such as the National Institute of Allergy and Infectious Diseases (NIAID) and Food and Drug Administration (FDA). A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US Law. This web site will not include information that can identify subjects. At most, this web site will include a summary of the results.

5) Internet Communication/Text Messaging- Although every reasonable effort has been taken, confidentiality during Internet communication activities cannot be guaranteed and it is possible that additional information beyond that collected for research purposes may be captured and used by others not associated with this study. Text message are not

encrypted or secure during their transmission. Text messages could be intercepted and used by others not associated with this study.

6) Mid-Turbinate Nasal Swab. The mid-turbinate (MT) nasal swab may cause some discomfort.

The risk to children receiving placebo will be negligible for several reasons. First, in the context of this trial, placebo is not equivalent to "no treatment". We will be monitoring changes in the PRSS score on a daily basis and those whose scores are worsening or not improving as expected will be evaluated without delay and treated with rescue antibiotics, as clinically indicated. Parents/legal guardians without reliable phone service will not be enrolled. In addition, parents/legal guardians will have 24-hour access to the study physicians who will arrange a study visit, usually within 24 hours, if indicated. Close follow-up and early treatment of children who appear to be worsening–the strategy proposed here–may be equally or more effective at preventing suppurative complications than routine prescription of antibiotics with no planned active follow-up, which is the standard of care. As such, our study will be similar to a study comparing immediate antimicrobial treatment with delayed prescription, the only difference being that parents/legal guardians and children can be more easily blinded using the design proposed here. We have an excellent track record of ensuring the safety of children in placebo-controlled trials. We recently completed a placebo-controlled trial in which we followed 147 children under 2 years of age with AOM who had been randomized to receive placebo.[49] Children in this study will be relatively less vulnerable because they will be older and many will be verbal. Second, we are excluding children at risk for complications of sinusitis (i.e., those with a severe presentation, systemic toxicity, immunodeficiency, and comorbid conditions). Most children enrolled will be well-appearing. In our preliminary dataset, only 3% of children had a temperature ≥38˚C at presentation. Third, suppurative complications of acute sinusitis are rare,[50] occur most often in adolescents[51] (whom we are excluding), and often occur unexpectedly within the first few days of the onset of URI symptoms,[52] well before the diagnosis of sinusitis would likely have been made. The routine use of pneumococcal conjugate vaccine is likely to further reduce the incidence of complications. Finally, although the rationale for antimicrobial therapy is faster resolution of symptoms, we do not believe that children receiving placebo will experience disproportionate suffering; no differences in time-to-resolution of symptoms was found in studies to date.[6] On the other hand, the potential harms associated with antimicrobial therapy (diarrhea, diaper dermatitis, risk of hypersensitivity reaction, potential to induce resistance) are well-documented and quite prevalent. Including children with "worsening" symptoms poses no undue risk to their safety; in our preliminary study, these children were no more likely than children with persistent symptoms to have either nasopharyngeal colonization with respiratory pathogens (45% vs 48%, p=0.85) or positive radiographs (p=78% vs 80%, p=0.75). Further, only 32% of pediatricians surveyed treat children with this presentation routinely. Accordingly, for children with the "worsening" presentation, the risks of withholding antibiotics, if any, would be lower in this trial than in usual practice.

There may be other unknown risks, discomforts, or side effects.

2.3.2 Known Potential Benefits

Children receiving placebo may benefit from participation in this trial because they will not be exposed to the side effects of antimicrobial therapy (diarrhea, diaper rash, development of resistant bacteria, anaphylaxis). This trial will also generate generalizable knowledge about the treatment of acute sinusitis in children.

3 OBJECTIVES

3.1 Study Objectives

Primary

- To determine whether the effect of antimicrobial treatment differs in predefined subgroups of children with acute sinusitis (i.e., to test for treatment subgroup interactions). Subgroups will be defined by the (1) presence vs. absence of nasopharyngeal (NP) colonization with respiratory pathogens (*Streptococcus pneumoniae, Haemophilus influenzae,* or *Moraxella catarrhalis),* and (2) presence vs. absence of colored (yellow or green) nasal discharge.

Secondary

- To determine whether antimicrobial therapy is superior to placebo (i.e., to test for the overall effect)

Tertiary

- To evaluate compliance with study product
- To assess adverse events associated with use of amoxicillin clavulanate, including the development of bacterial resistance
- To compare resource utilization according to treatment strategy

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

The PRSS scale (Supplement B) will be completed on a daily basis (in the evenings) from the day of enrollment (Day 1) to Day 11. PRSS scores over the first 10 days of therapy will be the primary outcome variable (i.e., repeated measures over time will be used to measure disease burden).

3.2.2 Secondary Outcome Measures

Secondary Efficacy Outcomes

1) Treatment failure – Children who are not improving at the expected rate will be identified through daily monitoring of PRSS scores. These children will be seen by the study team and rescue medication will be prescribed as clinically indicated. We will define treatment failure as follows:
    a. Worsening at any time–PRSS score increased by >20% from entry.
    b. No change by 48 hours–PRSS score decreased by <2 points from entry (Day 1) to Day 3.
    c. Failure to improve significantly by 72 hours–PRSS score decreased by <20% from entry (Day 1) to Day 4.
    d. PRSS decreased by <20% from enrollment on 2 consecutive occasions Days 5-11
    e. Still symptomatic (PRSS score ≥50% of entry score) at the time of the end-of-study follow-up visit (Days 12 to 18).

This definition is similar to that used by clinicians in practice. A similar composite outcome was used successfully in previous studies by Dr. Wald.[2,7] Days 3 and 4 were chosen as decision points because most (>90%) treatment failures are expected to occur around that time.[2] A 20% change was chosen because this represents the smallest change that appears to be clinically meaningful (see Table 1). Using these definitions, we estimate, based on our preliminary data and on the failure rates observed in previous studies using the same antibiotic,[2,7,49,53] that the rate of treatment failure in the antibiotic arm will be approximately 15%.

2) Development of AOM (acute symptoms and a bulging tympanic membrane) on Days 1 to 11.
3) Receipt of an antibiotic (other than the assigned study medication) on Days 1 to 11 for any indication.

3.2.3 Tertiary outcomes

Safety Outcomes

1) Adverse events - The proportions of children experiencing adverse events will be compared. We will also track the duration of each reported adverse event. This will include a comparison of the number of children at the follow-up visit who have resistance organisms. Diarrhea will be defined as the occurrence of ≥3 watery stools in 1 day or 2 watery stools per day for 2 consecutive days, and will be tracked in the daily diary.
2) Compliance - In the daily diary, we will ask parents/legal guardians to record whether they administered the doses of study product. Administration of ≥70% of the doses will be considered compliant.

Other outcomes

1) Resource utilization
    a. Direct medical costs (costs of visits to healthcare providers plus cost of medications). At the end-of-study follow-up visit, we will ask parents/legal guardians about the number and type of encounters with healthcare providers since enrollment. Similarly the number and types of medication used will be ascertained.
    b. Indirect costs: At the end-of-study follow-up visit, information will be collected on the indirect costs associated with the diagnosis of acute sinusitis, including travel expenses, alternate child care expenses for the patient and/or siblings, as well as time costs (e.g., for missed work).

4 STUDY DESIGN

This is a large, multi-center, randomized, double-blind, placebo-controlled, parallel group trial comparing antimicrobial treatment with amoxicillin-clavulanate potassium with matching placebo in children aged 2 years through 12 years of age, who meet the current AAP criteria for sinusitis. (See Schematic of Study Design).

Participants will be recruited from the primary care clinics at 5 sites: (1) Children's Hospital of Pittsburgh of UPMC and its affiliated Pediatric PittNet Practice Based Research Network (PBRN), CCP South Hills Pediatric Associates and CCP HealthQuest Hampton, Pittsburgh (Site PI and study Co-PI: Nader Shaikh); (2) Kentucky Pediatric and Adult Research, Bardstown, KY (Site PI: Stanley Block); (3) University of Wisconsin, Madison, WI (Site PI and Study Co-PI: Ellen Wald) and (4) Cyn3rgy Research (Site PI: Frank Calcagno).

Children will be randomized 1:1 to receive treatment for 10 days with either twice daily amoxicillin-clavulanate or matching placebo. Randomization will occur in blocks of 4 and study participants and study personnel (except the research pharmacist) will be masked to treatment allocation. Stratification will be based on the presence/absence of colored (yellow or green) nasal discharge and site of enrollment. Randomization codes will not be broken until completion of the trial unless there is a medical emergency that necessitates unmasking. A total of 688 children (approximately 344 in each treatment group), who meet the current AAP criteria for sinusitis will be enrolled over a 5-year period. Each participant will be followed for 12 to 18 days. Antimicrobial therapy will consist of amoxicillin-clavulanate suspension, 90 mg/kg/day divided into two equal doses. The placebo will be nearly identical in color, taste, and consistency to amoxicillin clavulanate. Amoxicillin clavulanate suspension will be purchased (Augmentin® Pediatric Suspension from Teva Pharmaceutical Industries Ltd.) and rebottled by the University of Pittsburgh Medical Center Investigational Drug Service (IDS). Both Amoxicillin clavulanate and placebo will be similarly labeled with a code number that masks site investigators, site staff, parents/legal guardians and children to the formulation. Study medication will be distributed to clinical sites by the IDS.

Treatment effect will be measured primarily using the validated Pediatric Rhinosinusitis Symptom Scale (PRSS) which will be administered every evening as an electronic diary. Once a day, we will send parents/legal guardians a text message and/or an email with a link to a secure website where they will be able to complete the PRSS. Versions for both a personal computer and a smart phone will be available. We will ensure that parents/legal guardians understand the process of completing the diary by having them complete a mock entry either on their personal cell phones or on the research personal computer (PC) or tablet at the enrollment visit. We will reimburse parents/legal guardians $5 for every diary entry completed on the day the alert was sent. Parents/guardians, who complete all diary entries, will be reimbursed an additional $30. Parents/legal guardians who do not have access to the internet will be loaned a tablet (with limited functionality) which they can use to complete the entries. We will design the electronic diary so as to prohibit incomplete forms from being submitted. If the parent/legal guardian does not complete the diary for a given day, we will call or text them the next morning to collect this information and to encourage them to complete the diaries for the following days.

Every morning (including weekends), we will call or text parents/legal guardians whose evening PRSS score is missing. If the PRSS score is missing, this information will be collected over the

phone. If a child's PRSS score is not improving as expected, an interim evaluation will be scheduled, usually on the same day. A study team member will be available 24 hours/day, 7 days/week via cellular phone. Children failing study product will be treated with clindamycin plus cefixime, amoxicillin-clavulanate potassium, or levofloxacin, or a similar antibiotic, as clinically indicated and without breaking the blind. The results of the nasopharyngeal (NP) culture (growth of *S. pneumoniae, H. influenzae*, and/or *M. catarhallis*) may be used to guide therapy. Although growth of Group A. Streptococcus will be ascertained, this will not be used for patient management (because the absence of pharyngitis on exam indicates that the patient is a carrier, which does not require intervention).

An end-of-study follow-up clinic visit will be held once during Days 12 to 18. If the parent/legal guardian is unable or unwilling to return for the end-of-study follow-up visit, we will offer to visit the patient's home.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Subject Inclusion Criteria

Children 2 to 12 years of age with persistent and worsening presentations of acute bacterial sinusitis, as defined in the latest AAP guideline,[1] will be included. *Persistent symptoms* will be defined as 11 to 30 days of nasal symptoms and/or cough (not exclusively nocturnal), that is not improving. *Worsening symptoms* will be defined as worsening nasal symptoms or worsening daytime cough or a new fever in children who were apparently recovering from a viral URI. These two presentations constitute a large majority of children with sinusitis (>95%).[2] Because resolution of symptoms (as measured by the PRSS) is our primary outcome, a score of ≥9 on the PRSS will be required.

Table 3. Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
• 2 -12 years of age (before 12th birthday) • Persistent sinusitis: URI symptoms present for >10 days without improvement (11-30 days) • Worsening sinusitis: URI symptoms worsening after a period of improvement (6-10 days) • PRSS score ≥9 • ≥2 doses of pneumococcal conjugate vaccine or appropriate for age.	• Sinusitis with severe presentation (≥3 days of colored nasal discharge and fever ≥ 39˚ C) • Immotile cilia syndrome, cystic fibrosis, immunodeficiency • Parental/legal guardian inability to read/write English or Spanish • Allergy to Amoxicillin-clavulanate • Other concurrent infection (e.g., pneumonia, acute otitis media, streptococcal pharyngitis) • Asthma/allergic rhinitis explains symptoms • Not reachable by phone • Systemic toxicity • Wheezing on exam • Systemic antibiotic use within 15 days • Prior Sinus surgery

5.2 Subject Exclusion Criteria

We will exclude children with a history of asthma who are actively wheezing or who have cough as the sole presenting symptom, and children with a history of allergic rhinitis whose respiratory symptoms have not acutely worsened. Other exclusion criteria are summarized in the Table 3.

5.3 Treatment Assignment Procedures

Children will be randomized centrally in a 1:1 ratio to receive either oral amoxicillin-clavulanate or placebo, each administered twice daily for 10 days. Ten days was chosen because this is the duration most frequently used in practice.[24]

5.3.1 Randomization Procedures

Randomization will occur in blocks of 4 and investigators and participants will be masked to treatment allocation. Stratification will be based on the presence/absence of colored (yellow or green) nasal discharge and site of enrollment.

High-dose amoxicillin-clavulanate potassium (90/6.4 mg/kg/day, maximal dose: 4 g/day, Teva Pharmaceutical Industries LTD., see Other Attachments section for product insert) or placebo

will be administered twice daily for 10 days. Placebo for all study sites will be prepared centrally by a research pharmacist at the University of Pittsburgh Medical Center Investigational Drug Service (IDS). The IDS is well suited to this task because it is currently preparing the same placebo (for amoxicillin-clavulanate) for our multicenter NIAID-sponsored AOM study (BAA-NIAID-DMID-NIHAI2009058). All study medications will be packaged in containers of identical appearance and will be labeled with a unique number. The IDS will maintain drug accountability records for all participating sites.

Per International Council for Harmonization (ICH) guidelines, screening records will be kept at each participating clinical study site to document the reason why an individual was screened but failed trial entry criteria.

All study personnel except the research pharmacist at the UPMC Investigational Drug Service will be masked to treatment group assignment. The subjects and parents/legal guardians of study subjects will also be masked to treatment group assignment. Randomization codes will not be broken until completion of the trial. Only in the event of a medical emergency and if unmasking would change the selection of treatment, will subject treatment assignment be revealed. The ISM or PI may unmask the treatment for a subject by contacting the Research Pharmacist at the UPMC Investigational Drug Service. Unmasked subjects will complete any remaining protocol assessments (diaries and routine end-of-study follow-up visit). When considering unmasking treatment for a subject, the investigator should consider whether knowing the identity of the treatment would change the selection of treatment. If knowledge of the subjects' treatment assignment would not affect treatment decisions, unmasking will not occur.

5.3.2 Reasons for Withdrawal

The following events are to be considered sufficient reason for discontinuation of a subject from the study product:

- Parents/legal guardians request; subjects are free to withdraw from participating in the study at any time upon request.
- Parents/legal guardians who do fail to complete any of the diaries during the first 4 days of the study will be withdrawn for non-compliance.

5.3.3 Handling of Withdrawals

If a parent/legal guardian is unwilling to continue follow-up through scheduled study visits, the subject will be referred back to their primary care provider (PCP) for continued antibiotic treatment and follow-up. Subjects withdrawn due to non-compliance will be replaced.

5.3.4 Termination of Study

The study will be completed when all enrolled subjects have completed follow-up or when the DSMB or DMID determines that the study needs to be terminated.

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 Study Product Description

6.1.1 Acquisition

The amoxicillin-clavulanate used in this study is amoxicillin-clavulanate potassium suspension, administered at a dosage of 90/6.4 mg/kg/day in 2 divided doses for 10 days, manufactured by Teva Pharmaceutical Industries Ltd. This drug is currently licensed for use in children with sinusitis (see Other Attachments section for product insert). It will be rebottled centrally at the IDS and reconstituted at each site.

The placebo used in this study, administered in 2 divided doses for 10 days, will be developed by the IDS using a formula which has been extensively tested to ensure similarity of taste, thickness (texture), odor and appearance (color) with the active product. It will be prepared centrally at the IDS and will be reconstituted at each site. The IDS at the University of Pittsburgh is well suited to this task because it is currently preparing the same placebo (for amoxicillin/clavulanate) for our multicenter NIAID-sponsored AOM study (BAA-NIAID-DMID-NIHAI2009058).

6.1.2 Formulation, Packaging, and Labeling

All study product (whether active treatment or placebo) will be presented in identical prescription bottles with safety caps. Further details regarding formulation, packaging and labeling are included in the protocol-specific Manual of Procedures.

6.1.3 Product Storage and Stability

The research pharmacist at IDS will ensure that all study product is stored in a secured (locked) area at a temperature of 15-30°C (monitored on a daily basis). At the participating clinical study sites, study product will be stored at this temperature in a dedicated locked storage area with logs to track temperature stability. The temperature will be recorded once daily when the study nurse is working. When the nurse is not working (weekends, holidays, vacation, sick days, etc.) the temperature will be recorded in a minimum/maximum style. In the event of documentation of ambient temperature outside the above range, study product will not be administered and the participating clinical study site investigator or coordinator will contact the sponsor and research pharmacist at the IDS for further instructions. No stability studies on the un-reconstituted active or placebo are necessary or will be conducted after transfer to the study bottles. The active product will not be changed in any way. Study product will be given a one-year expiration after transfer (or earlier if the product has an earlier expiration).

6.2 Dosage, Preparation and Administration of Study Intervention/Investigational Product

See the protocol-specific MOP for detailed information regarding the reconstitution of study product.

A designated study product administrator (SPA) at each of the participating clinical study sites will reconstitute the study product and provide parents/legal guardians with sufficient study product for 10 days.

- Active Treatment Group: Parents/legal guardians will be provided with amoxicillin-clavulanate potassium at 90/6.4 mg/kg/day in 2 divided doses for 10 days.
- Placebo Group: Parents/legal guardians will be provided with placebo in 2 divided doses for 10 days.

Parents/legal guardians will be instructed to record each dose of study product given to the subject in the daily electronic diary. Parents/legal guardians will be instructed on proper measurement and handling and storage of reconstituted study product. Suggested times for administration of study product will be 7:00 AM and 7:00 PM with a meal or a snack. Subjects enrolled prior to 1:00 PM will be given the first dose of study product at the time of enrollment and a second dose at 7:00 PM that day. Subjects enrolled in the afternoon (after 1:00 PM) will receive the first dose at the time of enrollment and the second dose the next morning. Subsequently, some children will receive the final dose of study production in the morning of Day 11.

6.3 Modification of Study Intervention/Investigational Product for a Participant

Children failing study product and children in whom study product is discontinued because of adverse events will be treated with clindamycin plus cefixime, amoxicillin-clavulanate potassium, or levofloxacin, or a similar antibiotic, as clinically indicated and without breaking the blind. The results of the NP culture may be used to guide therapy.

6.4 Accountability Procedures for the Study Intervention/Investigational Product(s)

Study product will be supplied by the IDS to all participating clinical sites. The SPA at each site will inventory, record and acknowledge receipt of all shipments of the study product. All study product will be accounted for in the electronic case report form and study product accountability inventory forms. The randomization assignment system will be generated by the Data Management and Statistical Unit in the Division of General Academic Pediatrics at the Children's Hospital of Pittsburgh. For each subject, the SPA will document the specific bottle number and volume of study product to be administered per day in the Investigational Product Accountability Log. Parents/legal guardians will be required to return the bottle containing study product to the investigator. Returned study product will be destroyed by the SPA according to the standard operating procedure (SOP) once its return has been documented. The study monitor will periodically check the amount of study product held by the investigator or pharmacist to verify accountability of all investigational products used, or unused.

6.5 Assessment of Subject Compliance with Study Intervention/Investigational Product

Parents/legal guardians will be instructed to track and record study product administration on the electronic diary and to return the study product bottle at the end-of-study follow-up visit. Subjects will be considered to have been compliant with study product if they have taken 70% of the intended regimen.

6.6 Concomitant Medications/Treatments

Medication history will be obtained by interview of the parents/legal guardians. We will ask about previous antihistamines, decongestant, albuterol, or corticosteroid use during the past 7 days and antibiotics use up to 3 months before enrollment.

Use of select oral or nasal concomitant medications (antihistamines, decongestants, albuterol, antibiotics, corticosteroids, and analgesics) taken by the subject from the time of consent through the end-of-study follow-up visit or early termination, whichever occurs first, will be ascertained by parent/legal guardian interview at the end-of-study follow-up visit or early termination, whichever occurs first. Receipt of a systemic antibiotic while taking study medication will be recorded as this constitutes a secondary endpoint of the study.

Medications that might interfere with the evaluation of the investigational product should not be used unless absolutely necessary. Medications in this category include: systemic corticosteroids, nasally administered decongestants or corticosteroids, and systemic medications containing decongestants, antihistamines, or corticosteroids. During participation in this study, subjects should not participate in any other clinical trial and should not receive any investigational drug or vaccine. The use of ibuprofen and acetaminophen is permitted. In the event of an allergic reaction to the assigned study product, subjects will be treated with clindamycin plus cefixime, or levofloxacin or a similar antibiotic, as clinically indicated using the results of the NP culture to guide therapy and without breaking the blind.

7 STUDY SCHEDULE

See Supplement A for the Schedule of Events table.

7.1 Screening – Day 1

Parents/legal guardians of children presenting to a participating center with URI symptoms will be introduced to study staff by office personnel. The research staff will question the parent regarding the presence and characteristics of their child's symptoms [duration of symptoms, course of symptoms (e.g., improving, staying the same, worsening), severity of symptoms (PRSS), history of allergic rhinitis, history of asthma]. If the provider's clinical assessment does not then reveal another etiology that would exclude the child from participating (e.g., AOM, pneumonia, streptococcal pharyngitis, wheezing) informed consent will be sought from the parent/legal guardian. We will attempt to enroll consecutive children meeting eligibility criteria. We will maintain logs of eligible children who are not enrolled.

7.2 Enrollment/Baseline Visit (Entry Visit) – Day 1

After obtaining written informed consent from the parent/legal guardian, we will gather information on the following potential predictors and confounders: demographic characteristics, risk factors (day care attendance, previous systemic antimicrobial use, exposure to household cigarette smoke), symptoms (type and duration, including some symptoms not included on the PRSS), past medical history (sinusitis, AOM, allergic rhinitis, asthma, pneumococcal vaccination), temperature and weight measurement (if not already taken for clinical care), and concomitant medications. Temperature will be measured using appropriate method according to the child's age and parental preference (oral, rectal, axially, temporal, or tympanic). We will assess the nose and throat for facial tenderness and swelling. A nasopharyngeal swab will be obtained, when possible, and placed in transport media and sent to the Microbiology Laboratory-CHP for processing. In the event a nasopharyngeal swab is unable to be obtained, the study team will attempt to obtain a mid-turbinate nasal swab.When possible,the first dose of the study product will be given at the time of enrollment following randomization and monitoring of adverse events will begin. This will reduce variability due to delay in the initiation of therapy. We will ask parents/legal guardians to refrain from administering intranasal medications (e.g., corticosteroids, decongestants), and systemic medications containing antihistamines, decongestants or corticosteroids to their child for the duration of the study. We will assess whether the nasal discharge is colored. In our preliminary study (n=276), we showed that asking parents/legal guardians directly about the color of the nasal discharge (In the last 24 hours, was your child's nasal discharge (mucus) yellow or green?) yielded information that was predictive of both the bacteria cultured from the nasopharynx (p=.006) and the findings of sinus radiographs (p=.003). Parental/legal guardian report of "white" discharge or physician examination of the anterior nares or nasal turbinates for colored discharge was not similarly informative. As an additional method of assessing color, we will utilize a color chart (with 4 colors: green, yellow, white, clear) and ask parents/legal guardians to identify the color that most closely resembles their child's nasal discharge. Nevertheless, based on our strong preliminary data, and based on the fact that the assessment of nasal discharge using a color chart is unlikely to be practical in a busy clinical practice, asking parents/legal guardians whether their

child's nasal discharge was yellow or green will remain the primary method of defining "colored nasal discharge".

7.3 Follow-up eVisits – Days 2-11

Diary – Parents/legal guardians will be asked to complete the PRSS electronically once daily–at the time of the evening dose of the study product and when their child is able to provide active input–from the day of enrollment (Day 1) to Day 11. Parents/legal guardians will be instructed to record each dose of study product given to the subject in the daily electronic diary. Suggested times for administration of study product will be 7:00 AM and 7:00 PM with a meal or a snack. Parents/legal guardians will be instructed on proper measurement and handling and storage of reconstituted study product. Once a day, we will send parents/legal guardians a text message or an email with a link to a secure website where they will be able to complete the PRSS. Versions for both a personal computer and a smart phone or tablet will be available. We will ensure that parents/legal guardians understand the process of completing the diary by having them complete a mock entry either on their personal cell phones or on the research PC or tablet at the enrollment visit. We will reimburse parents/legal guardians $5 for every diary entry completed on the day the alert was sent ($55 total).Parents/guardians, who complete all diary entries, will be reimbursed an additional $30. Parents/legal guardians who do not have access to the internet will be loaned a phone or tablet (with limited functionality) which they can use to complete the entries. We will reimburse parents/legal guardians $50 at the time of the end-of-study follow-up visit and to encourage the return of the study phone or tablet if one was loaned The diary will also ask about medication compliance (adherence assessment), adverse events, and the overall degree of change from the previous day (on a 7-point scale) (symptom assessment). In a survey of 108 parents/legal guardians attending our inner-city clinic, 85% reported having a cell phone with a data plan. The proportion of parents/legal guardians with access to the internet will likely be higher at the other study sites.

Phone calls – Every morning (including weekends), we will call or text parents/legal guardians whose evening PRSS score is missing. If the PRSS score is missing, this information will be collected over the phone or the parents/legal guardians will be provided a text with a link to complete the missing diary entry.

7.4 Final Study Visit (End-of-Study Follow-up Visit) – Days 12 to 18

Parents/legal guardians and their children will be asked to return once during Days 12 to 18 for a routine follow-up evaluation. At this visit, the PRSS will be completed and parents will be questioned regarding the child quality of life. A nasopharyngeal swab will be obtained,when possible, and placed in transport media and sent to the Microbiology Laboratory-CHP for processing. In the event a nasopharyngeal swab is unable to be obtained, the study team will obtain a mid-turbinate nasal swab. We will ask about adverse events, interim medical history including visits to other health care providers, and concomitant medications. A phone call, email or text message will be sent 1 to 2 days before the end-of-study follow-up visit to confirm the time of the appointment. If the patient is unable to come to the end-of-study follow-up visit, a visit to the home will be offered. If this is not possible, we will, to the extent possible, obtain information that was to be gathered at the Final Study Visit by phone or email.

7.5 Unscheduled Visit (Interim (Sick) Visit)

If a child's PRSS score is not improving as expected, or if a parent is concerned about their child, an interim evaluation will be scheduled, usually on the same day. If the parent/legal guardian is unable to come to the office, a home visit may be offered. If the child cannot be seen and assessment of the child's symptoms by phone indicate that the child is not acutely worsening and no new symptoms are reported, an antibiotic may be started without an evaluation. A study team member will be available 24 hours/day, 7 days/week via cellular phone. Children failing study product will be treated with clindamycin plus cefixime, amoxicillin-clavulanate potassium, levofloxacin, or a similar antibiotic, as clinically indicated and without breaking the blind. The results of the nasopharyngeal culture may be used to guide therapy. The following procedures may be performed at this visit: interim medical history including visits to other health care providers and concomitant medications collection, temperature measurement, face/nose assessment, PRSS score, and adverse events monitoring. Temperature will be measured using appropriate method according to the child's age and parental preference (oral, rectal, axially, temporal, or tympanic).

8 STUDY PROCEDURES/EVALUATIONS

8.1 Clinical Evaluations

Medical History: Will be obtained by interview of the parents/legal guardians. Parents/legal guardians will be queried regarding demographic characteristics, risk factors (day care attendance, exposure to smokers in the house), symptoms (type and duration, including some symptoms not included on the PRSS), and past medical history since birth (sinusitis, allergic rhinitis, asthma, and medications used to treat these) at the baseline visit. We will also ask parents/legal guardians to assess the severity of their child's symptoms using a visual analog scale anchored at "very mild" and "very severe". At the final end-of-study follow-up visit, we will ask parents to complete the PRSS, to answer question about visits to other providers, missed work, quality of life, and the need to make alternate daycare arrangements, and about adverse events.

Medication History: Will be obtained by interview of the parents/legal guardians. We will ask about previous antihistamines, decongestant, albuterol, or corticosteroid use during the past 7 days and antibiotics use up to 3 months before enrollment. We also track the use of these same medications along with analgesic medication through the end-of-study follow-up visit or early termination, whichever occurs first. Receipt of a systemic antibiotic while taking study medication will be recorded as this constitutes a secondary endpoint of the study. The use of these medications will be ascertained by parent/legal guardian interview at the end-of-study follow-up visit or early termination, whichever occurs first.

Vital Signs: Temperature and weight will be measured at enrollment/baseline visit and the interim (sick) visit (if not already taken for clinical care). Temperature will be measured using appropriate method according to the child's age and parental preference (oral, rectal, axially, temporal, or tympanic).

Limited assessment of face and nose: At the baseline and unscheduled interim (sick) visit, a targeted assessment of the face and nose using standardized methods will be performed by appropriate study personnel.

Diary: The PRSS will be administered by parents/legal guardians every evening as an electronic diary. In addition to the PRSS score, the diary will track compliance with study product, the frequency and the consistency of bowel movements, and a global assessment of health. The critical data for symptom resolution is during days 2-11, but we have given parents the opportunity to record the information from day 1 in order to establish the habit of recording in the diary.

8.2 Laboratory Evaluations

8.2.1 Clinical Laboratory Evaluations

At the enrollment/baseline and final study visit, a nasopharyngeal sample may be obtained from one nostril using a sterile, flexible, thin, flocked swab. Compared to Dacron swabs, flocked swabs are better tolerated and have a higher yield for bacteria[54,55] and viruses.[56-58] The tip of the nose

will be raised and the swab introduced gently along the floor of the nasal cavity, close to the nasal septum, until the pharyngeal wall is reached. If any obstruction is encountered, the sample will be taken from the other nostril. All investigators will be trained on this procedure before to the onset of the study (see protocol-specific Manual of Procedures). We will cut the tip of the swab with a pair of sterile scissors into a cryovial containing RLT and this will be stored for future studies of RNA expression. The remainder of the swab will be placed into Amies and will be refrigerated (2-8˚ C) until it can be transported (on ice) to the Microbiology Laboratory at Children's Hospital of Pittsburgh (within 48 hours). Two types of culture plates will be used initially: trypticase soy 5% sheep blood agar and chocolate agar. Cultures will be incubated overnight at 37°C with 5% CO_2. If no growth is present after overnight incubation, the culture will be re-incubated for an additional 24 hours. Identification of *S. pneumoniae*, *H. influenzae, M. catarrhalis and Streptococcus pyogenes* will be performed using standard semiquantitative techniques. For isolates thought to be *H. influenza* that will be subcultured on a *Haemophilus* ID Quad plate. These isolates will be typed and if found to be non typeable, confirmed to be *H. influenza* by PCR. In addition, we will test for β-lactamase production using a cefinase test on selective agar. Isolates considered to be *M. catarrhalis* will undergo subculture and identification will be confirmed using the Remel Catarrhalis Test Disk. Isolates considered to be *S. pneumoniae* will undergo subculture on a TSA blood agar plate. Susceptibility testing will be done on all isolates using the Vitek system. Isolates will be considered nonsusceptible to penicillin according to the most current guidelines from the Clinical Laboratory Standards Institute (CLSI). Microdilutional broth susceptibility testing will be performed on all penicillin non susceptible isolates. All pneumococcal isolates will be typed using gene-based typing methods.

8.2.2 Special Assays or Procedures

Not applicable.

8.2.3 Specimen Preparation, Handling, and Shipping

8.2.3.1 Instructions for Specimen Preparation, Handling, and Storage

All clinical microbiological samples (NP swab and MT swab specimens) obtained from all study participants enrolled at all participating clinical study sites will be processed at CHP according to guidelines established by the Microbiology Laboratory. This laboratory will identify all organisms cultured from the samples. Instructions for specimen preparation, handling, and storage are included in the Laboratory Plan.

8.2.3.2 Specimen Shipment

NP swab (or MT swab) specimens may be collected at the entry visit (Day 1) and the follow-up visit (Day 12-18). Specimens will be placed in a transport tube with a study label. Specimens are transported to the Microbiology Laboratory at CHP at intervals of every 3 hours for CHP of UPMC sites. Specimens from PittNet PBRN sites will be refrigerated and sent via courier to the Microbiology Laboratory at CHP within 48 hours. Specimens from all other sites will be mailed on the day of collection to the Microbiology Laboratory at CHP. Specimen shipments will be recorded in a specimen-tracking log.

The NP or MT swab specimens will be sent to:

Children's Hospital of Pittsburgh
Microbiology Laboratory B228
4401 Penn Avenue
Pittsburgh, PA 15224

Instructions for specimen shipment are included in the Laboratory Plan.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

We will track common and important adverse events linked with the study product [i.e., Protocol-Defined Diarrhea (PDD), generalized rash, and bacterial resistance], any adverse event, which requires more than minimal medical intervention (see below for definitions), and all serious adverse events.

Because the study product is approved for use for children with sinusitis, we will only track 1) common or important adverse events linked with the study product (PDD, generalized rash), 2) severe adverse event (AEs which require more than minimal medical intervention, Table 4, below), and 3) serious adverse events (see section 9.2.3). PDD will be defined by the occurrence of three or more watery stools in 1 day or two watery stools daily for at least 2 days.

The occurrence of these AEs will be recorded from the first study intervention, Day 1 (enrollment), through the end-of-study follow-up visit.

9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1 Adverse Events

Adverse Event (AE): ICH E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor. FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

AEs not meeting the protocol-defined criteria for SAEs will be captured on the appropriate electronic case report form (eCRF). Information to be collected for non-serious AEs includes event description, date of onset, licensed study physician's assessment of severity and relationship to study product and alternate etiology (if not related to study product) (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator), date of resolution of the event, seriousness and outcome. AEs occurring during the collection and reporting period will be documented appropriately regardless of their relationship to the study product. All recorded AEs will be followed to adequate resolution. Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases at any time during the study, it will be recorded as an AE. AEs must be graded for severity and assessed for relationship to study product (see definitions below). Adverse events characterized as intermittent require

documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate eCRF. Bacterial resistance will be reported based on the report from the laboratory.

Severity of Event: AEs will be assessed by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or appropriate sub-investigator. The severity of non-serious AEs will be assessed according to the scale below:

- Mild: events require minimal or no treatment and do not interfere with the subject's daily activities.
- Moderate: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe: events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Examples of the types of non-serious AEs that will be collected (contained within the heavy lines) and AEs that will not be collected (gray font and marked by an asterisk) are shown in the Table below.

Table 4. Procedure for Recording of Non-Serious Adverse Events

Non-Serious Adverse Events			
	Mild	**Moderate**	**Severe**
Rash	*Localized	Generalized and moderate	Generalized and severe (e.g., severe urticaria; serum sickness; Stevens-Johnson Syndrome)
Diarrhea	*Loose stools	3 or more watery stools in 1 day or 2 watery stool daily for at least 2 days (i.e., PDD)	Diarrhea requiring rehydration therapy and is incapacitating
All other Adverse Events	*Requires minimal or no treatment and does not interfere with daily activities	*Requires some treatment and may interfere with daily activities	Requires systemic drug therapy and is clearly incapacitating
Bacterial resistance	N/A	N/A	All bacterial resistance will be collected

*AEs that will not be collected

Relationship to Study Products: The study physician's assessment of an AE's relationship to the study product is required prior to unblinding and is part of the documentation process, but it

is not a factor in determining what is or is not reported in the study. Factors to consider in determining a causal relationship include whether: (1) the event is described in the product insert; (2) a temporal relationship exists between the event and administration of study product; (3) a possible alternative etiology has been identified; and (4) it is biologically plausible that the event may be related to the product. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. In a clinical trial, the study product must always be suspect. The relationship to study product must be assessed for AEs using the terms: related or not related. The following guidelines will be used in this assessment:

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.

- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

9.2.2 Reactogenicity

Not applicable.

9.2.3 Serious Adverse Events

Serious Adverse Event (SAE): An adverse event or suspected adverse reaction is considered "serious" if it results in any of the following outcomes:

- Death,

- a life-threatening adverse event*,

- inpatient hospitalization or prolongation of existing hospitalization,

- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or

- a congenital anomaly/birth defect.

- Important medical events that may not result in death, be life threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

* Life-threatening adverse event. An adverse event is considered "life-threatening" if, in the view of either the site principal investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

All SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or appropriate sub-investigator.
- Recorded on the appropriate SAE form and eCRF
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Reviewed and evaluated by the Independent Safety Monitor (ISM), Data and Safety Monitoring Board (DSMB), DMID, and the Institutional Review Board (IRB).

9.2.4 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

NP specimens will be obtained for culture at baseline and follow-up for the identification of *S. pneumoniae, H. influenzae,* and *M. catarrhalis*. Detection of *S. pneumoniae, H. influenzae,* and *M. catarrhalis* in the nasopharynx will be considered a normal finding.

Study product may need to be discontinued in subjects with a clinical adverse event, laboratory abnormality, intercurrent illness, or other medical condition such that continuation of study product would not be in their best interest. Randomization codes will not be broken at any time in the event of treatment failure unless deemed necessary for medical /emergency/safety reasons. These subjects will be asked to continue to record their symptoms on the PRSS on a daily basis and to return to the clinic for a routine end-of-study follow-up visit to be held once during Days 12 to 18.

9.3 Reporting Procedures

Non-serious AEs occurring throughout the study-reporting period will be documented from the first study intervention, Day 1 (enrollment), through the end-of-study follow-up visit (Day 12-18) using the eCRF.

SAEs occurring throughout the study-reporting period will be documented from the first study intervention, Day 1 (enrollment), through the end-of-study follow-up visit (Day 12-18) using the appropriate SAE form and eCRF.

SAEs related to the study product will be reported to the principal investigators and IRBs immediately (within 24 hours of site awareness). Unexpected severe adverse reactions related to study product will be reported to the IRBs per local IRB guidelines and subsequently reported to the principal investigators. Line-item reports of all SAEs and a report of all recorded AEs will be submitted to the DSMB and DMID according to the frequency established in the DSMB charter.

9.3.1 Serious Adverse Events

Any AE that meets a protocol-defined serious criterion will be submitted immediately (within 24 hours of site awareness) on a SAE form to the DMID Pharmacovigilance Group, at the following address:

DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Dr. Suite 650
Bethesda, MD 20814, USA
SAE Hot Line: 1-800-537-9979 (US)
SAE FAX Phone Number: 1-800-275-7619 (US)
SAE Email Address: PVG@dmidcroms.com

In addition to the SAE form, selected SAE data fields must also be entered into the central database. Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible.

The site will send a copy of the SAE report(s) to the ISM when they are provided to the DMID Pharmacovigilance Group. The DMID medical monitor and clinical protocol manager will be notified of the SAE by the DMID Pharmacovigilance Group. The DMID medical monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

At any time after completion of the trial, if the investigator becomes aware of an SAE that is suspected to be related to study product, the investigator will report the event to the DMID Pharmacovigilance Group.

9.3.2 Regulatory Reporting for Studies Conducted Under IND

In consultation with DMID, the principal investigators will report any suspected adverse reaction that is both serious and unexpected. The principal investigators will report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event. The principal investigators will notify FDA and all participating site principal investigators (i.e., all principal investigators to whom the sponsor is providing drug under its IND(s) or under any principal investigator's IND(s)) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. The principal investigators will also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. Relevant follow up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, the principal investigators will submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request. All serious events designated as "not related" to study product, will be reported to the FDA at least annually in a summary format.

9.3.3 Reporting of Pregnancy

Not applicable.

9.4 Type and Duration of Follow-up of Subjects after Adverse Events

AEs will be collected, assessed, and followed through resolution throughout the study-reporting period.

SAEs will be collected, assessed, and followed through resolution even if this extends beyond the study-reporting period.

Resolution of an AE/SAE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Follow-up procedures, evaluations, and outcomes will be recorded on the appropriate form and/or eCRF.

9.5 Halting Rules

Further enrollment and study product administration will be halted for DSMB review/recommendation if any of the following are reported:

- Any death occurs following study product administration that was not the result of trauma or accident.
- Any subject develops brain abscess or bacterial meningitis.
- Two subjects develop complications of sinusitis (e.g., orbital cellulitis, frontal bone subperiosteal abscess).

If any of the halting rules are met following any subject receipt of study product, the trial will not proceed with the remaining enrollments or study product administration without a review by and recommendation from the DSMB to proceed. The University of Pittsburgh, IRBs and DMID retain the authority to suspend enrollment and/or study product administration during the entire trial, as applicable.

9.6 Safety Oversight (ISM plus DSMB)

Safety oversight will be conducted by an external DSMB, which is an independent group of experts that reviews study data, monitors subject safety and advises DMID and the principal investigators. The DSMB will consist of at least three voting members with appropriate expertise to contribute to the interpretation of the data from this trial including a biostatistician experienced in statistical methods for clinical trials and a clinician with relevant expertise.

The DSMB members will be separate and independent of study personnel participating in this trial and should not have scientific, financial or other conflict of interest related to this trial. To avoid any appearance of conflict of interest, it is critical that DSMB members not be involved in the study, have no vested interest in its outcome, have no ties to the study investigators and have no financial ties to any commercial concerns likely to be affected by the study's outcome.

The DSMB will review study progress and participant, clinical, efficacy, laboratory, and safety data at the following time points:

- At specified times during the course of this trial as defined in the DSMB Charter.
- At the time of the interim analysis (conducted after 344 subjects have been enrolled and completed follow-up).
- Ad hoc when a halting rule is met, for immediate concerns regarding observations during this trial, or as needed.

The DSMB will meet regularly to monitor the cumulative safety data during the period when participants are receiving study product and during the participant follow-up period. The DSMB will monitor the study according to the guidelines specified in the study protocol and the charter established at their initial meeting, unless the DSMB determines during the course of the trial that modification of the guidelines is in the best interest of this trial and its participants. Such a decision may be based on new information that emerges during the course of this trial (e.g., publication of the results of a similar trial), realization of inappropriate initial study assumptions, or the occurrence of an unanticipated scenario.

The DSMB will operate under the rules of a DMID-approved charter that will be written at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. Procedures for DSMB reviews and meetings will be defined in the charter. Procedural issues include: the board's meeting frequency; the types and formats of reports it will receive from the DMSU, the policy on whether and how the members may be unblinded; what interim data (if any) may be released to the study investigators (e.g., overall AE rate); and how minutes will be taken and distributed.

Before initiation of this trial, the DSMB will review the study protocol (particularly the specific outcome definitions), halting rules, the interim and final analysis plan, the procedures for recording and reporting SAEs, and the data and safety monitoring plan (including draft shells of safety reports and tables). The informed consent document/process also will be inspected to ensure that all required elements have been included in language understandable to parents/legal guardians of children to be enrolled in this trial.

Study data will be reviewed by the DSMB per the charter for this study. The DSMB will review applicable data to include but not limited to study progress, enrollment, demographic, clinical, efficacy outcomes, laboratory and safety data which includes AE/SAEs, medical history, physical assessments, concomitant medications, compliance, and laboratory results (NP cultures). Interim statistical reports will be generated when 50% of patients have completed the study. Comparative results are presented to the DSMB in closed sessions attended only by voting members of the DSMB and by a representative of DMID. Additional data may be requested by the DSMB, and additional interim statistical reports may be generated as deemed necessary and appropriate by DMID. The DSMB may receive data in aggregate and presented by group. The DSMB may also be provided with expected and observed rates of the expected AEs in an unblinded fashion, and may request treatment assignment be unblinded for an individual subject if required for safety assessment. The DSMB will review grouped and unblinded data in the closed session only. As an outcome of each review or meeting, the DSMB

will make a recommendation as to the advisability of proceeding with enrollment and study product administration (as applicable), and to continue, modify, or terminate this trial.

DMID or the DSMB chair may convene the DSMB on an ad hoc basis according to protocol criteria or if there are immediate concerns regarding observations during the course of this trial. The DMID Medical Monitor is empowered to stop study enrollment and study product administration if adverse events that meet the halting criteria are reported. The DMID Medical Monitor and the ISM will be responsible for reviewing SAEs in real time. The DSMB will review SAEs on a regular basis and ad hoc during this trial.

Independent Safety Monitor (ISM)

ISMs are physicians with relevant pediatric expertise and whose primary responsibility is to provide timely independent safety monitoring. The ISM (one for each site) will not be directly involved in the trial, will not be under the investigators' supervision, and will have no financial, intellectual, proprietary or professional interest in the outcome of the trial. An ISM with relevant sinusitis and/or pediatric infectious diseases expertise is assigned to each participating clinical study site, is in close proximity to the site and has the authority to readily access study participant records. The ISM reviews any SAE in real time and other AEs as needed and provides an independent assessment to the investigators and DMID. The ISM will not contact the DSMB directly.

10 CLINICAL MONITORING

10.1 Site Monitoring Plan

Site monitoring will be conducted to ensure that human subject protections, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet DMID, University of Pittsburgh, and ICH E6 (GCP) guidelines and applicable regulations, and that this trial is conducted in accordance with the protocol, protocol-specific MOP, and applicable standard operating procedures.

Independent clinical study site monitoring will be conducted as detailed in the clinical monitoring plan. This will include on-site monitoring visits at standard intervals, or more frequently as necessary, throughout the study to oversee data collection, review source documentation, ensure GCP, protocol and regulatory compliance, and resolve data queries. Monitoring visits will include, but are not limited to review of regulatory files, accountability records, eCRFs, informed consent forms, medical and laboratory reports, and protocol compliance. The monitor's Clinical Research Associates (CRAs) will have reasonable access to the participating clinical study sites, study personnel, and all study documentation. CRAs will meet with participating clinical study site investigators to discuss any problems and actions to be taken and document visit finding and discussions. Clinical monitoring reports will be submitted to the principal investigators and DMID.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

Hypothesis 1: Children not colonized with respiratory pathogens are unlikely to benefit from antimicrobial therapy.
Hypothesis 2: Children without colored nasal discharge are unlikely to benefit from antimicrobial therapy.

11.2 Primary and Secondary Analyses

Primary

- To determine whether the effect of antimicrobial treatment differs in predefined subgroups of children with acute sinusitis (i.e., to test for treatment subgroup interactions). Subgroups will be defined by the (1) presence vs. absence of nasopharyngeal (NP) colonization with respiratory pathogens (*Streptococcus pneumoniae, Haemophilus influenzae,* or *Moraxella catarrhalis),* and (2) presence vs. absence of colored (yellow or green) nasal discharge.

Secondary

- To determine whether antimicrobial therapy is superior to placebo (i.e., to test for the overall effect)

Tertiary

- To evaluate compliance with study product
- To assess adverse events associated with use of amoxicillin clavulanate, including the development of bacterial resistance
- To compare resource utilization according to treatment strategy

11.3 Analysis Populations

11.3.1 Intent-to-Treat Population (ITT)

The ITT population will consist of all eligible randomized children with at least 1 diary entry. This population will form the basis for the primary and secondary efficacy analyses of study data as well as for the safety analyses.

11.3.2 Per Protocol Population

Children who receive 70% of the prescribed doses of study product (whether antibiotics or placebo) will comprise the per protocol population. This population will form the basis of secondary, supportive analyses of the efficacy and safety endpoints.

11.4 Efficacy Assessments

The daily PRSS score over the first 10 days of therapy (Day 1 to 11) will be recorded by parents/legal guardians using an electronic tablet or a personal computer, a cell phone, or a tablet every evening. A routine end-of-study follow-up clinic visit will be held once during Days 12 to 18 day. An interim visit will be scheduled if the PRSS score has not improved as expected, i.e. if child meets definition for treatment failure.

11.4.1 Primary Efficacy Variable

The PRSS score over the 10 days of therapy will serve as the primary efficacy variable because it represents the outcome that it is clinically most relevant. Clinicians prescribe antimicrobials for children with acute sinusitis under the assumption that it hastens the resolution of symptoms. Thus, to assess the degree of improvement and/or deterioration we chose a validated symptom score to serve as the primary efficacy variable.

The PRSS (See Supplement B) consists of eight discrete items: runny nose, stuffy nose, daytime cough, nighttime cough, sleeping difficulty, trouble breathing through the nose, irritability, and being tired. Parents/legal guardians are asked to rate these symptoms, as “none”, “almost none”, “a little”, “some”, “a lot”, or “an extreme amount” with corresponding scores of 0 to 5. PRSS scores may thus range from 0 to 40.

11.4.2 Secondary Efficacy Variables

The secondary efficacy variables include:

1) Treatment failure - Children who are not improving at the expected rate will be identified through daily monitoring of the PRSS scores by the study staff. These children will be seen by the study team and rescue medication will be prescribed, as clinically indicated. We will define treatment failure if any of the following conditions are met:
    a. Worsening at any time–total PRSS score increased by >20% from entry.
    b. No change by 48 hours–total PRSS score decreased by <2 points from entry (Day 1) to Day 3.
    c. Failure to improve significantly by 72 hours–total PRSS score decreased by <20% from entry (Day 1) to Day 4.
    d. PRSS decreased by <20% from enrollment on 2 consecutive occasions on Days 5-11
    e. Still symptomatic (total PRSS score ≥50% of entry score) at the time of the end-of-study follow-up visit (Days 12 to 18).
2) Development of AOM (acute symptoms and a bulging tympanic membrane) on Days 1 to 11.
3) Receipt of an antibiotic (other than the assigned study product) for any indication on Days 1 to 11.

11.5 Safety and Tolerability Assessments

Safety and tolerability assessments include:

1) Adverse events - The proportions of children experiencing certain adverse events will be compared. We will also track the duration of these adverse events. Diarrhea will be

defined as the occurrence of ≥3 watery stools in 1 day or 2 watery stools per day for 2 consecutive days. This will be tracked in the daily diary. Changes in bacterial resistance from baseline to follow-up will be tabulated.

2) Compliance - In the daily diary, we will ask parents/legal guardians to record whether they administered the doses of study product. Administration of ≥70% of the doses will be considered compliant.

11.6 Statistical Analyses

11.6.1 General Considerations

Study data will be monitored on an ongoing basis by the Data Management and Statistical Unit in the Division of General Academic Pediatrics at the Children's Hospital of Pittsburgh. Final cleaning and editing of the study database will be carried out after the last patient completes follow-up. Unblinding of treatment assignments will not be performed until the study data are cleaned, queries resolved, and database lock achieved. All changes to the study database will be documented. A permanent archive of the database will be maintained by the DMSU.

A 2x2 factorial design, adjusted for multiple testing, will be used to detect interactions for the longitudinal outcome, where Factor A will be antibiotic-treated vs. placebo and Factor B will be either colored nasal discharge (yellow or green vs. clear) or nasopharyngeal colonization (positive vs. negative).

All statistical tests will be two-tailed and conducted at global significance level of 0.05. For the primary efficacy analysis, the significance level for the final analysis will take into account the interim analysis. Sites with few children randomized may be pooled. Pooling of study sites will occur prior to unblinding. All programs used in the statistical analysis will be documented, tested, and archived. Archiving of statistical analyses at the DMSU includes the original written specifications for the analyses, any subsequent modifications, the computer program file, and the log, list and other output files produced by the program. The DMSU will use the most current version of SAS®.

11.6.2 Interim Analysis

Interim analysis will occur after 344 children have completed this trial. Type I error will be controlled using the method of Fleming, Harrington and O'Brien[59] and testing will be conducted at significance levels of 0.005 and 0.048 at the interim and final analyses, respectively. If at least one of the tests for interaction is significant (i.e., if there is unequivocal evidence of treatment effect heterogeneity), the DSMB may consider recommending stopping this trial early.

11.6.3 Subject Disposition

The number of patients screened, randomized, withdrawn, and included in each analysis population (ITT, Per Protocol) will be reported by treatment group and according to site. In addition, the number of patients completing this trial and the reasons for patient withdrawal will be tabulated by treatment group. These data will be used to prepare a CONSORT diagram.

11.6.4 Baseline (Pre-Treatment) Analyses

Demographic and baseline clinical characteristics will be presented by treatment group for all patients. For categorical variables we will report frequencies and percentages. For continuous variables we will report means and standard deviations.

11.6.5 Concomitant Medication Use

We will report the incidence of concomitant medication use according to treatment group using the ITT population.

11.7 Efficacy Analyses

11.7.1 Primary Efficacy Analysis of the Primary Efficacy Endpoint

We present compelling preliminary data and extensive literature suggesting that the effect of antimicrobial therapy is likely to differ in certain subgroups of children with acute sinusitis. Accordingly,[60-65] the primary efficacy analysis will assess the heterogeneity of treatment effect in subpopulations defined by presence of nasopharyngeal colonization and by the presence of colored nasal discharge (i.e., to test for interaction between treatment and subgroup effects).

Interactions between treatment group and each subgrouping variable will be tested simultaneously. A Generalized Estimating Equations (GEE) model will be fit by including treatment by subpopulation interaction terms (adjusted for the baseline PRSS score) using the ITT dataset (see Section 6.8 for detailed multiple testing procedure).[66] The regression analysis will be adjusted for clinical site as a potential confounding factor.

Assumptions required for the validity of GEE will be assessed. These will include (i) the marginal mean of the response depends on a link function, (ii) the marginal variance depends on the marginal mean, and (iii) the correlation within subject depends on the marginal mean and other parameters. Therefore an appropriate link function will be chosen for the primary outcome and the goodness of fit of the model will be assessed.

11.7.2 Secondary Efficacy Analysis of the Primary Efficacy Endpoint

The secondary efficacy analysis will compare the PRSS scores during the first 10 days of therapy in the two treatment groups. This analysis is considered secondary because reporting the average treatment effect in the entire sample is not appropriate if the treatment effect in the subgroups we are considering is heterogeneous. GEE will be used to compare the marginal means adjusted for the baseline PRSS score and stratification variables using the ITT population.

In addition, we will explore whether heterogeneous response to treatment is observed for other baseline variables, including worsening presentation, age, history of allergic rhinitis, and individual pathogens. We consider this investigation of the additional variables to be only

exploratory, possibly providing information that may prove important in conducting future studies.

11.7.3 Secondary Efficacy Analyses of the Secondary Endpoints

Secondary efficacy variables include treatment failure, development of AOM, and receipt of an antibiotic. All of these are dichotomous variables. We will use the Cochran-Mantel-Haenszel test[67-69] stratified by study site, using the ITT dataset.

Additional analyses of the dichotomous secondary efficacy variables will use logistic regression to adjust for baseline covariates and other prognostic variables.

11.8 Missing Data

For children with missing values for the primary endpoint (no diary data available for a particular day), we will use only the days with non-missing values, which can be accommodated by the GEE method. Children with no diary entries will be excluded from the analysis. If a patient has missing data for a dichotomous secondary outcome variable, we will perform a sensitivity analysis first assuming that all such patients had the deleterious outcome (for instance, treatment failure) and then assuming that all such patients had a favorable outcome.

The proportion of patients with missing data for each outcome variable will also be compared between treatment groups and the sensitivity to the missing data will be examined by reanalyzing the outcome using only the non-missing data. However, we are confident that the amount of missing data will be negligible because study procedures have been put in place to minimize missing data.

11.9 Handling of Data from Withdrawn Subjects

All such subjects who have at least 1 diary entry will be included in the intent-to-treat analysis population.

11.10 Safety and Tolerability Analyses

11.10.1 Compliance

Compliance will be assessed by parental/legal guardians report on the daily diary. Compliance with study product will be defined as receipt of at least 70% of the expected doses. The proportion of patients who are compliant will be reported by treatment group. Treatment group differences in compliance will be assessed using a Cochran-Mantel-Haenszel test stratified by study site.

11.10.2 Adverse Events

The number of patients with adverse events will be tabulated by treatment group. The number of patients experiencing each adverse event will also be summarized by severity and relationship to study drug. If an adverse event is reported more than once during the study period for a given patient, the greatest intensity will be presented in the tables. For summary tables, adverse events will be grouped by organ system. We will also track the duration of each reported adverse event. Diarrhea, a key and expected adverse event, will be defined as the occurrence of ≥3 watery stools in 1 day or 2 watery stools per day for 2 consecutive days, and will be tracked in the daily diary. The incidence of serious adverse events and study medication discontinuation due to adverse events will also be compared using Fisher's exact test.[70] Data listings and narratives will be provided for patients discontinuing treatment due to adverse events and patients with serious adverse events.

11.10.3 Resource utilization

We will collect data on direct costs (i.e., costs of visits to healthcare providers plus cost of medications) and indirect costs (e.g., travel costs). For direct costs, we will ask parents/legal guardians about the number and type of encounters with healthcare providers since enrollment. Similarly the types and duration of medication used will be ascertained. For indirect costs, we will ask parents/legal guardians about travel expenses, alternate child care expenses (for the patient and/or siblings), as well as time costs (e.g., for missed work). These assessments will be conducted at the time of the end-of-study follow-up visit.

11.11 Sample Size Justification

To estimate the sample size for this trial, we used estimates of within-subject correlation and grand variance from our preliminary data of children diagnosed with acute sinusitis. Because two simultaneous tests for interactions are being conducted, we used a two-sided significance level of 0.025 (50:50 split of the overall significance level of 0.05 for Bonferroni adjustment).

Assuming an α of 0.025 (two-sided test), 344 evaluable children per treatment group will provide statistical power of 80% to detect an interaction effect size of 2.5 points in the mean symptom score (as measured by the PRSS) over the 10-day period assuming, as per results presented in Leon and Heo,[71] that the required sample size to detect an interaction between treatment group and a subgroup would be four times that of a main effect of the same magnitude for a repeated measures outcome under a 2x2 factorial design.

Even though we have calculated the sample size using the simple Bonferroni procedure, for the final analysis we will use a modified Bonferroni procedure for multiple testing, which is not as conservative for highly correlated test statistics.[72] Under the Simes' procedure, the null hypothesis associated with the smallest p-value will be rejected if the p-value is smaller than or equal to $\alpha / 2$ and one associated with the second smallest p-value will be rejected if the p-value is smaller than or equal to $\alpha/2$. Here $\alpha/2$ is the appropriate significance level for the interim or definitive analysis. Specifically, the (ordered) observed p-values will be compared using 0.0025 and 0.005 for the interim analysis and using 0.024 and 0.048 for the definitive analysis.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating clinical study site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Each participating clinical study site will permit authorized representatives of DMID, University of Pittsburgh or its designee, and appropriate regulatory and monitoring agencies to examine (and when required by applicable law, to copy) clinical trial records for the purposes of quality assurance reviews, audits, monitoring and evaluation of the study safety and progress. These representatives will be permitted access to all source data. All sites use certified, comprehensive Electronic Health Record (EHR) systems requiring privacy and security compliance and HIPAA and institutional policies addressing unauthorized access to the EHR systems; these policies preclude external representatives listed in this protocol from accessing the EHR. However, paper copies of the respective EHR system documentation may be provided to the monitors for review.

Web-based electronic case report forms (eCRFs) will be the source documents for data collected during the study visits. These forms will be accessible from all study sites using a secure website managed by the DMSU. The data system includes features such as password protection, automatic time/date stamps, and automatic range checks that will identify data that appear inconsistent, incomplete or inaccurate. Electronic forms facilitate the generation of clean datasets by guiding investigators through the data collection process in such a manner as to display only questions and screens that are appropriate for the particular subject, thus minimizing the possibility of incorrect entries. An electronic audit trail of all changes will be maintained by the system (i.e., by recording old vs new value, date, time and reason for change). The database also performs an important tracking function by monitoring such parameters as missed follow-up appointments to ensure that the required data collection instruments are administered within the time constraints dictated by the study protocol. All files will be backed-up daily and archived weekly.

Additional source documents include the patient’s medical record (i.e., for children who are prescribed another antibiotic while on study product), and laboratory reports (entered into the eCRF by the staff at the Microbiology Laboratory at CHP).

13 QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DMID-accepted site quality management plan, the participating clinical study sites are responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance.

The principal investigators will provide direct access to all participating clinical study sites, source data/documents, and reports for the purpose of monitoring and auditing by DMID and University of Pittsburgh or its designee, and inspection by local and regulatory and authorities.

The principal investigator will ensure all study personnel are appropriately trained and applicable documentation is maintained on site.

The DMSU will implement quality control procedures beginning with the data management system and generate data quality control checks that will be run on the central database. Any missing data or data anomalies will be communicated to the participating clinical study site(s) for clarification and resolution. Monitoring of the day-to-day quality of the trial will be conducted by the Data Manager.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

The investigators will ensure that this trial is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46, 21 CFR 50 and 56, and the ICH E6; 62 Federal Regulations 25691 (1997), if applicable. Each investigator's institution will hold a current Federalwide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) for federally funded research.

14.2 Institutional Review Board

An IRB registered with OHRP will review and approve the protocol and informed consent form prior to commencement of subject recruitment at each site.

Prior to enrollment of subjects into this trial, the approved protocol and the informed consent form will be reviewed and approved by the appropriate IRBs listed on their FWA.

The responsible official for the IRB will sign the IRB letter of approval prior to the start of this trial and a copy will be provided to the University of Pittsburgh and DMID. The IRB FWA number will be provided to the University of Pittsburgh and DMID.

All amendments to the protocol or informed consent form will be written by the sponsor, approved before they are placed into use, provided to the investigators for submission to their IRBs, and a copy of the signed IRB letters of approval will be provided to the University of Pittsburgh and DMID.

14.3 Informed Consent Process

The participating clinical study site investigators will choose subjects in accordance with the eligibility criteria detailed in Section 5. The investigator will not exercise selectivity so that bias is prevented. Before any study procedures are performed, the subject's parent/legal guardian must sign an informed consent form that complies with the requirements of 21 CFR Part 50 and 45 CFR 46 and the local IRB.

Informed consent is a process that is initiated prior to the subject's parent/legal guardian agreeing to have their child participate in this trial and continuing throughout the subject's study participation. Before any study procedures are performed, the subject's parent/legal guardian will receive a comprehensive explanation of the study procedures and study interventions/products (antibiotics and placebo). This will include the nature and risks/benefits of this trial, alternate therapies, any known AEs, the investigational status of the components, and the other elements that are part of obtaining proper informed consent. The subject's parent/legal guardian will also receive a detailed explanation of the proposed use and disclosure of their protected health information. The subject's parent/legal guardian will be allowed sufficient time

to consider participation in this trial, after having the nature and risks of the study explained to them, and have the opportunity to discuss this trial with their family, friends or legally authorized representative or think about it prior to agreeing to participate.

Informed consent forms describing in detail the study interventions/products (antibiotics and placebo), study procedures, risks and possible benefits will be given to the subject's parent/legal guardian. The informed consent form will not include any exculpatory statements. Informed consent forms will be IRB-approved and the subject's parent/legal guardian will be asked to read and review the appropriate document. Upon reviewing the appropriate document, the participating clinical study site investigator (or designee) will explain the research study to the subject's parent/legal guardian and answer any questions that may arise. The subject's parent/legal guardian must sign the informed consent form, and written documentation of the informed consent process is required prior to starting any study procedures/interventions being done specifically for the study, including administering study product. The subject's parent/legal guardian will be given a copy of all informed consent forms that they sign.

By signing the informed consent form, the subject's parent/legal guardian agrees to have their child complete all evaluations required by this trial, unless the subject's parent/legal guardian withdraws their child voluntarily, or their child is withdrawn or terminated from this trial for any reason.

The rights and welfare of the subjects will be protected by emphasizing to the subject's parent/legal guardian that the quality of their child's medical care will not be adversely affected if they decline to have their child participate in or withdraw their child from this trial.

Some children in this trial may be developmentally capable of providing assent. If so, this will be documented on the informed consent document.

The University of Pittsburgh will provide the participating clinical study site investigators, in writing, any new information that significantly impacts the subjects' risk of receiving the investigational product. This new information will be communicated by the participating clinical study site investigators to the subject's parent/legal guardian who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated and the subject's parent/legal guardian will be re-consented per IRB requirements, if necessary.

Study personnel may employ IRB-approved recruitment efforts prior to obtaining the subject's parent/legal guardian consent if a patient-specific screening consent is on record or if the IRB has agreed that chart review is allowed without a fully executed screening consent. In cases where there is not a patient-specific screening consent on record, site clinical staff may pre-screen via chart review and refer potential subjects to the research staff; however, before any study procedures are performed to determine protocol eligibility an informed consent form must be signed.

14.4 Exclusion of Women, Minorities, and Children (Special Populations)

This trial will be conducted in children aged 2 to 12 years, an age group that experiences the highest incidence of acute sinusitis. Children who meet eligibility criteria will be entered in this

trial without regard to sex, religion, or ethnic background and it is anticipated that enrollees will be divided approximately equally between boys and girls. We will recruit and enroll children who are representative of the sex, racial, and ethnic distribution of patients with acute sinusitis at the participating clinical study sites. No subject will be included or excluded on the basis of sex, race or ethnicity. Self-reporting of ethnicity and race using two separate questions will be used to identify demographic information as required by OMB Directive 15.

14.5 Subject Confidentiality

Subjects will have code numbers and will not be identified by name. Subject confidentiality is strictly held in trust by the site principal investigator, their study personnel, the sponsor, and their agents. This confidentiality is extended to cover testing of biological samples, in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All information provided by the sponsor and all data and information generated by the participating clinical study sites as part of this trial (other than a subject's medical records) will be kept confidential by the investigators and their study personnel to the extent permitted by law. This information will not be used by the investigators or their study personnel for any purpose other than conducting this trial. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigators or their study personnel; (2) information which is necessary to disclose in confidence to an IRB solely for the evaluation of this trial; (3) information which is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in Section 16. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

The study monitor, applicable regulatory authorities, such as the FDA, or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigators, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The participating clinical study sites will permit access to such records.

All paper records containing identifying information will be kept in locked files accessible only to the investigators and their study personnel and unlocked only while study personnel are working with the files. To ensure that confidentiality is maintained, the study coordinator will conduct inspections of the relevant premises at random times, usually weekly. Information regarding individual subjects will be kept private and shared only with the IRB, DSMB, the investigators, their study personnel, and the sponsor(s) and their agents.

Clinical and laboratory data will be entered into a 21 CFR Part 11-compliant Internet eCRF provided by the University of Pittsburgh Center for Research on Health Care (CRHC). The data management system includes password protection, automatic time/date stamp and internal

quality checks, such as automatic range checks that occur in real time to identify data that appear inconsistent, incomplete or inaccurate.

The respective information technology (IT) departments at each site will take all necessary steps to protect the confidentiality, integrity, and availability of all information assets on the computer network from unauthorized access while providing the mechanisms to grant, monitor, modify and remove access as required. At CHP, for example, users are authorized to access CHP's IT resources based on roles and responsibilities necessary to perform the functions of their job. Access is granted based on what is minimally necessary for job completion. At all participating clinical study sites computer user accounts and passwords are used to uniquely identify and authenticate a user to a computer system or application. Accessing a computer application or system with a username and password is equivalent to the user's signature.

Additional efforts at the CRHC include limiting access to areas containing electronic confidential information. This includes monitoring the movement of people, equipment, and supplies into or out of the areas containing confidential information. The CRHC requires card access or pre-approved visitor sign-in. Physical controls for the data center include:

- Locked doors with restricted, logged, card key access
- Video surveillance monitored by security and public safety personnel
- Raised floor
- Heat, smoke, and water detection
- Environmental controls for heat and humidity
- Fire suppression
- Supporting utilities monitored by facilities personnel

Further, the CRHC's network is protected via an intrusion detection system (Solutionary) that protects against malicious code, denial of service attacks, and viruses. Interception of data transmission and electromagnetic interception are addressed by domain-based policies that manage data securely with security standards of IPsec, VPN, SSH, and PGP encryption.

Each participating clinical study site computer must be compliant with basic standards to be granted access to the system. All participating clinical study site computers must be protected by an institutional firewall or local firewall software. Each computer must also be protected by local anti-virus and anti-spam software. These standards are verified through an authorization process overseen by the CRHC. At each participating clinical study site, each protocol team member shall only be assigned one unique account for each computer system or application. Passwords shall consist of seven or more characters and contain characters from three of the following four categories: capital letters (A through Z); lowercase letters (a through z); numbers (0 through 9); and symbols (!, $, #, %, @). Computer systems or applications shall automatically inform the account holder when a password change is required. New computer accounts shall be created with a one-time password that requires the user to establish a unique password during the initial log on.

In the event that a breach is suspected, all potentially compromised account passwords will be immediately changed, and the appropriate help desk will be notified to investigate the potential security breach.

To protect against data loss, each participating clinical study site will adhere to the CRHC and CHP data backup and recovery plans, which include procedures for creating and maintaining retrievable exact copies of information, programs, and operating systems. The plan covers:

- Regular back-ups
- Secure off-site storage of tapes and documentation
- Regular testing of backup media
- Incident response procedures
- Disaster recovery plans with procedures for restoring lost information
- Emergency mode of operation plan that contains procedures protecting electronic information while operating in an emergency situation
- Testing and revision plan that contains procedures for periodic testing and revisions of the contingency plans.

Any publications or presentations resulting from this work will not identify participants by name, but will only present aggregate data.

14.6 Costs, Subject Compensation, and Research Related Injuries

There will be no costs to the subject or their parent/legal guardian for the participation in this trial. Subjects' parents/legal guardians may be compensated for the participation in this trial. Compensation will be in accordance with the local IRB's policies and procedures, and subject to IRB approval. Parents/legal guardians will be reimbursed at each visit for their time and expenses, according to the local standards and IRB approval.

We will reimburse parents/legal guardians $30 for the Enrollment/Baseline visit, and $5 for every diary entry completed on the day the alert was sent ($55 as well as an additional $30 if all diary entries are completed). Parents/legal guardians, who agreed to the nasal swab, will receive $20 at enrollment. Parents/legal guardians who do not have access to the internet will be loaned a phone or tablet (with limited functionality) which they can use to complete the entries. We will reimburse parents/legal guardians $30 at the time of the end-of-study follow-up visit and to encourage them to return the study phone or tablet if one was loaned to them. If a second NP swab (or MT swab)is obtained at the child's final study visit, we will reimburse the participant $20 for their time. In the event a subject is unable to return for their final study visit, the subject will be compensated $10 for completing the final study visit over the phone.

When needed, based on time of the year and climate conditions, taxicabs or “gas cards” may be used to facilitate transportation. Parents will receive free parking for each study visit, as applicable per site.

Parents/legal guardians will be encouraged to contact the Principal Investigator if they believe that the research procedures have resulted in an injury to the subject. Emergency medical treatment for injuries solely and directly related to participation in this research study will be provided to participants. The insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to the participant. If the research-related injury requires medical care beyond this emergency treatment, parents/legal guardians will be responsible for the costs of this follow-up care. No plan exists for any additional financial compensation.

14.7 Study Discontinuation

In the event that this trial is discontinued, enrolled subjects will continue to be followed until the end-of-study follow-up visit. Subjects with ongoing medical issues that require further follow-up will be referred to their physician. No further study products will be administered.

14.8 Future Use of Stored Specimens

Subjects or parent(s)/legal guardian(s) will have agreed to allow their NP sample and the organisms isolated from it to be used for future research studies including studies of bacterial genomics in the consent form. Samples will be stored indefinitely in the Microbiology Laboratory or at a central clinical storage facility and may be shared with investigators at the participating clinical study site and other investigators at other institutions.

The samples will not be sold or used directly for production of any commercial product. No human genetic tests will be performed on samples.

Each sample will be encoded (labeled) with a unique tracking number to protect subject confidentiality.

There are no benefits to subjects in the collection, storage and subsequent research use of specimens. Reports about future research done with subjects’ samples will NOT be kept in their health records.

If the subject or parent/legal guardian withdraws from the study, samples may still be used for this research.

15 DATA HANDLING AND RECORD KEEPING

The investigators are responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported.

The eCRF will be developed by the DMSU as the source document to record and maintain data for each subject enrolled in the trial. Data reported in the eCRF should also be consistent with other source documents (laboratory reports), or the discrepancies should be explained.

Any other source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, the original entry will be crossed with a single line, initialed and dated, without obliterating the original entry. The DMSU will provide guidance to investigators on making corrections to the eCRF or other source documents.

15.1 Data Management Responsibilities

All source documents will be reviewed by the clinical team and data entry personnel, who will ensure that they are accurate and complete. Adverse events must be assessed for severity and causality, and reviewed by the participating clinical study site investigator or designee.

Data collection is the responsibility of the study personnel at the participating clinical study site under the supervision of the site investigator. During the trial, the investigators must maintain complete and accurate documentation for the study.

The DMSU will be responsible for data management, quality review, analysis, and reporting of the trial data, including uploading results to the National Library of Medicine (NLM) database. The DMSU will manage data by developing checks on the central database for logical inconsistencies and reports for the participating clinical study sites, including recruitment, retention, missing forms, subject follow-up visit schedules, and treatment adherence.

The DMSU can generate reports, including data quality and compliance information. Information on form submission and completeness will be available through the central database. Information will also be available to chart protocol progress, including recruitment and retention, schedule of upcoming patient visits, and quality of the data obtained. Other specialized reports may also be developed.

Study personnel can query data from the central database in real-time and generate customized reports displaying current data for their clinical study site. DMID will be provided with read only access to the central database in real-time. If necessary, study and data entry and management personnel can view the same information simultaneously when troubleshooting a data issue.

15.2 Data Capture Methods

Screening logs of eligible and enrolled subjects will be maintained to detect the possibility of selection bias. The University of Pittsburgh Center for Research on Health Care eCRF will be accessible from participating clinical study sites using a secure Internet connection. The data

management system will present study site personnel with a readily available and comprehensive set of data management tools to perform data entry and routine processes by displaying information regarding forms that have been received, forms that are due, and forms that are late. The eCRF incorporates automatic edit checks that serve to prevent errors and substantially reduce time to clean data.

Data obtained during the study visits will be entered directly into the eCRF which makes the eDMS the source document for this information. These data include clinical data (including AE/SAEs, concomitant medications, physical assessments, and diaries) and laboratory data (NP results). These data will be entered into a 21 CFR Part 11-compliant Internet eCRF provided by the University of Pittsburgh Center for Research on Health Care. The data management system includes password protection, automatic time/date stamp and internal quality checks, such as automatic range checks that occur in real time to identify data that appear inconsistent, incomplete or inaccurate. This will allow for ongoing and rapid query resolution and locking of the database at the close of the trial.

Some limited additional information may need to be gathered from the EHR, in particular, as it relates to children who are seen by non-study providers and prescribed antibiotics while receiving study product. Clinical data from the off-site visits e.g., emergency department visits, participant primary care visit, etc., will be entered directly from the source documents. In this circumstance, the paper documents received from the provider will be considered the source documents.Types of Data

Data for this study will include clinical, efficacy, safety, and laboratory data gathered in the eCRF. We will also obtain records of medical encounters at other facilities (if needed to document reasons for subject receiving another antibiotic during the study).

15.3 Timing/Reports

Study data will be reviewed by the DSMB per the DSMB charter for this study. Safety summary reports may be generated for this purpose.

An Interim Report for DSMB review will be prepared by the DMSU after 344 subjects have been enrolled and completed follow-up. These reports will contain the most up-to-date data permitted by the timeframe necessary for the DMSU to prepare and review the analyses. Reports will usually consist of two parts, corresponding to the open and closed sessions of the DSMB meeting, and include an assessment of the progress of the trial, including recommendations on whether it should continue or be terminated or modified. Only the DSMB members (and designated representatives from DMID) will receive copies of the closed session report. The reports will be sent by the DMSU to the DMID for distribution to the DSMB members at least 14 business days prior to a scheduled meeting. Safety and efficacy results will be presented by treatment group using randomly-assigned labels for the two treatment groups.

The Clinical Study Report will be completed when all primary and secondary endpoint data are available.

15.4 Study Records Retention

Study documents (records and documents pertaining to the conduct of this trial, including eCRFs, informed consent forms (except for future use informed consent forms), laboratory test results, and study product inventory records) will be retained until the subject is 23 years of age. Records will not be destroyed without the permission of the University of Pittsburgh and DMID. Informed consent forms for future use will be maintained as long as the sample exists.

15.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the subject, the investigators, or their study personnel. As a result of deviations, corrective actions will be developed and implemented promptly.

These practices are consistent with ICH E6:

4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3

5.1 Quality Assurance and Quality Control, section 5.1.1

5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the participating clinical study site to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations will be reported to the University of Pittsburgh, DMID and DSMB. Protocol deviations must also be reported to the local IRBs per their guidelines. The investigators and their study personnel are responsible for knowing and adhering to their IRB requirements.

All deviations from the protocol will be addressed in study subject source documents. A completed copy of the Protocol Deviation Form will be maintained in the regulatory file, as well as in the subject’s source document.

16 PUBLICATION POLICY

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central (http://www.ncbi.nlm.nih.gov/pmc/) an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

Refer to:

- NIH Public Access Policy, http://publicaccess.nih.gov/
- NIH OER Grants and Funding, http://grants.nih.gov/grants/oer.htm

Following completion of this clinical trial, the lead principal investigator is expected to publish the results of this research in a scientific journal. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov* (http://clinicaltrials.gov/), which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies.

The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., Phase I trials), would be exempt from this policy.

For trials in which DMID is not the IND/IDE sponsor, or there is no IND/IDE, and DMID does not provide data management services, it is the responsibility of the investigator to register the trial and post results in compliance with Public Law 110-85, the Food and Drug Administration Amendments Act of 2007 (FDAAA). Any clinical trial starting enrollment after 01 July 2005 must be registered on or before subject enrollment. For trials that began enrollment prior to this date, the ICMJE member journals will require registration by 13 September 2005, before considering the results of the trial for publication.

Refer to:

- Public Law 110-85, Section 801, Clinical Trial Databases

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18 SUPPLEMENTS

18.1 Supplement A: Schedule of Events

Study Procedure	Screening/ Enrollment/ Baseline/Entry Visit (Day 1)	Follow-up eVisits (Days 2-11*)	Unscheduled/ Interim (Sick) Visit	Final End-of-Study Follow-up Visit (Days 12-18)
Informed Consent	**X**			
Randomization	**X**			
Study Product Administration	**X**	**X**		
Medical History	**X**		**X**	**X**
Assessment of Face/Nose	**X**		**X**	
PRSS Score	**X**	**X**	**X**	**X**
Nasopharyngeal Swab (or Mid-Turbinate) obtained when possible	**X**			**X**
Adherence Assessment		**X**		
Concomitant Medications	**X**		**X**	**X**
Monitoring of Adverse Events	**X**	**X**	**X**	**X**
Collect Unused Study Product				**X**

*Data collected using an electronic diary. Parents/legal guardians of subjects with missing diaries will be called.

18.2 Supplement B: Pediatric Rhinosinusitis Symptom Scale (PRSS)

How has your child been doing?

We are interested in finding out how your child has been doing over the last 24 hours. Please answer these questions with the help of your child. For each question, please place a check (✓) in the box corresponding to your child's symptoms. Please answer all questions.

Did your child…

	No	Almost None	A Little	Some	A Lot	An Extreme Amount
Have a **stuffy nose today**?	❒	❒	❒	❒	❒	❒
Have a **runny nose today**?	❒	❒	❒	❒	❒	❒
Cough during the day?	❒	❒	❒	❒	❒	❒
Act **more tired** than usual **today**?	❒	❒	❒	❒	❒	❒
Act **irritable or fussy today**?	❒	❒	❒	❒	❒	❒
Have **trouble breathing** through the nose **today**?	❒	❒	❒	❒	❒	❒
Cough last night?	❒	❒	❒	❒	❒	❒
Have **trouble sleeping last night**?	❒	❒	❒	❒	❒	❒

Thank you