Contents

2.1 Acute Asthma Assessment Questionnaire

The Acute Asthma Assessment Questionnaire (AAAQ) has been developed by AsthmaNet investigators in an effort to better characterize asthma exacerbations. Participants are asked to report the primary precipitating factor for the exacerbation (common cold, allergies, pollution or chemical irritants, too little asthma maintenance medication and/or lack of adherence, or exercise). They are also asked to review their activity impairment due to asthma, asthma symptoms, rescue bronchodilator use, asthma awakenings, general amount of impairment, and stress level caused by asthma over a 3-day (72 hour) period. This tool will help evaluate exacerbation severity with the goal of establishing correlation between acute scores and the risk of subsequent adverse events.

This questionnaire appears as Appendix 2 in the SIENA protocol. It will be administered to all SIENA participants at Visit 3, the day he/she starts prednisone for treatment of an asthma exacerbation (Day 0), as well as at the participant's exacerbation visit (Day 3), and Day 10, 14, and 21 phone contacts after exacerbation. This tool will allow us to assess impairment associated with exacerbations and the extent to which recovery has occurred over time.

Visit 3, 90-92, 90A-92A, 90B-92B, 90C-92C, 90D-92D
Administer Acute Asthma Assessment Questionnaire (AAAQ)

To introduce the AAAQ and to establish a baseline, this questionnaire will be administered to participants at the randomization visit (Visit 3). The administration of the AAAQ is one of the early procedures performed at Visit 3, in conjunction with the administration of the other asthma outcome questionnaires. Study coordinators should observe the order of procedures as they are laid out on the visit procedure checklists.

If the participant experiences an exacerbation between study visits after randomization, he/she should complete the copy of the AAAQ that resides in the Asthma Exacerbation kit that he/she has at home (see the discussion of the Asthma Exacerbation Kit in this section for further details) on the day he/she starts prednisone. This form should be returned to the performance site at the participant's Exacerbation Visit, and the visit ID should correspond to the appropriate Asthma Exacerbation visit ID. A participant's first Asthma Exacerbation will have visit ID 90, second 91, and third 92. The visit date should match the date the participant supplied in the source documentation box at the time of completion. At the Exacerbation Visit, the AAAQ should be completed again (as follow-up to the event), and the visit ID on this form should correspond to the Exacerbation visit ID followed by "A". Note that these instructions also apply if the participant is seen at the performance site for exacerbation conditions between visits and he/she will start a prednisone course the same day. In that case the form should be completed and turned in to study personnel the same day.

If an exacerbation is identified at the time of a regular study visit and prednisone is prescribed and will be started the same day, then the participant should complete the AAAQ at the time of the visit (rather than waiting to complete it at home). The visit ID on this form should correspond to the appropriate Asthma Exacerbation visit ID. At the participant's Asthma Exacerbation study visit (3-7 days following start of prednisone), he/she should complete the AAAQ again (as follow-up to the event), and the visit ID on this form should correspond to the Exacerbation visit ID followed by "A".

The AAAQ will also be completed at Asthma Exacerbation phone contacts 10, 14, and 21 days following start of prednisone. The visit IDs on this form at Day 10, 14 and 21 should correspond to the Exacerbation visit ID followed by "B", "C" and "D", respectively.

See Section 4 of this MOP for data management instructions for handling AAAQ forms completed at various times during the trial.

Administration Instructions

The AAAQ is completed by the participant. When administering the questionnaire, request that the participant complete the entire form and provide answers as completely and as accurately as possible. No stated or implied time limit should be set.

Participants should use a black or blue pen to complete the questionnaire. If the participant wishes to change a response, the original response should be crossed out with a single line and then dated and initialed by the participant. The final response should be circled for clarification. No changes to the participant-completed form may be made by study personnel; changes may only be made by the participant.

When the participant is finished with the questionnaire, collect it and review it for completeness before proceeding with the visit. If a question has been left blank, ask the participant to do his/her best to answer it. The answers to all of the questions are necessary to score the instrument. Check that the participant's responses are clearly marked.

The participant should provide source documentation on the AAAQ form by providing his/her initials and the date/time in the source documentation box. Review the source documentation provided by the participant to ensure that the date and time are accurate before collecting the form.

2.2 Adherence Issues

Participants enrolled in the SIENA protocol are involved in study activities throughout the trial. A great deal is asked of participants, and the quality of the study results is a function of the participants' level of protocol adherence. Each participant must be given every opportunity to be compliant and successful.

Factors That Affect Adherence
It is important to be aware of factors that may affect a participant's adherence level.

Participant Characteristics
- ability to comprehend and recall instructions
- support of family members for study participation
- satisfaction with care and caregivers
- degree of concern about health
- perception of disease severity
- perceived costs and benefits of treatment

Performance Site Personnel Characteristics
- consistency of AsthmaNet personnel with whom participants have contact during the study
- demonstration of interest and genuine concern for the participant's health
- warm and caring demeanor; approachable
- engagement in social conversation and active interchange
- presentation of clear instructions
- proficiency in clinical activities
- accessibility when the participant has questions, concerns or emergency needs

Clinic Characteristics
- positive and warm environment (unhurried and comfortable)
- timely appointments
- organized and efficient

Characteristics of Regimen (determined by the protocol)
- most important determinant of adherence
- should not be too complex
- side effects of study drug should not be a big problem/concern
- regimen should be adaptable to participant's life and work, not the other way around

Improving Adherence
A number of approaches can be used to improve adherence in the SIENA trial:

- Associate the regimen with daily activities

  Encourage the participant to associate the required study activities with his/her daily routine to help make these steps automatic. This point can be reinforced while reviewing the Daily Activities handouts at each visit (P6_DAILYACT0A, P6_DAILYACT0B, P6_DAILYACT1, P6_DAILYACT3_2).

- Educate the participant

  - Make sure the study activities are understood
  - Demonstrate the activities and have the participant do the same
  - Present instructions as clearly as possible
  - Have the participant repeat instructions
  - 'Quiz' the participant on the instructions
  - Teach the regimen in a stepwise fashion (i.e., step 1, step 2, step 3 for AM and PM activities)
  - Review 1 or 2 of the participant handouts at each visit
  - Use phone contacts to reinforce instructions and to ensure that the participant is performing activities correctly

- Provide positive reinforcement for excellent participant adherence

- Encourage support of family and friends during study participation

- Prepare participants for what will happen at upcoming visits

- Run the clinic on schedule and make good use of the participant's time

- Make sure the clinic is accessible with flexible hours and ample, convenient parking

- Avoid no-shows with a reminder phone call in advance of the visit date. Call the participant’s residence and cell phone immediately if there is a no-show

- Ensure that clinic personnel are easily accessible by phone, pager, and e-mail

- Develop a friendly and caring relationship with the participant

  An integral part of the visit is interacting with the study personnel. A feeling of attachment or obligation to an individual improves adherence and reduces withdrawals.

Tools for Monitoring and Improving Adherence during the SIENA Trial
The following tools are in place to improve and/or monitor adherence (form name is given in parentheses, where applicable):

Visit Scheduler Reports
Missed visits and poorly timed visits are forms of non-adherence. In order to allow the participant and the performance site to plan for upcoming visits, visit scheduler reports have been programmed that list the ideal dates and lower and upper regular and extended windows for upcoming visits per the protocol.

See the Visit Scheduler discussion in this section and Section 3 of this manual for further details on the creation of visit scheduler reports.

Visit Handouts and Study Folder
A series of handouts is presented and reviewed with the participant at Visit 1 (or Visit 0A for Supervised Washout participants) and at various subsequent visits as new procedures and concepts are introduced. Because it may be difficult to comprehend and execute all instructions initially, and because activities may change during the study depending on the study phase, participants are asked to bring this folder to each visit for review and replacement of certain materials. A description of each of the SIENA handouts follows can be found in the Study Handout Folder discussion in this section.

Daily Activities Handouts
SIENA Daily Activities: Visit 0A – 1-Step (P6_DAILYACT0A_1STEP)
SIENA Daily Activities: Visit 0A – 2-Step (P6_DAILYACT0A_2STEP)
SIENA Daily Activities: Visit 0B (P6_DAILYACT0B)
SIENA Daily Activities: Visit 1 (P6_DAILYACT1)
SIENA Daily Activities: Visit 3 (P6_DAILYACT3/P6_DAILYACT3_2)

These handouts contain simple summaries of the study activities that must be carried out each day, including dosing with the Respimat® during the run-in and Scheduled Respimat® and Twisthaler®/MDI during the randomized treatment phase. These handouts also provide the participant a quick reference for criteria for determination of treatment failure and significant exacerbation conditions. See the Daily Activities Handout discussion in this section for further details.

P6_DAILYACT3 is for participants randomized to Twisthaler; P6_DAILYACT3_2 is for participants randomized to MDI.

How to Use Your spirotel® Electronic Diary and Peak Flow Meter (HTSPIROTEL)
This handout provides instructions for home use of the spirotel® device. The spirotel® device and handout are introduced at Visit 1 (or Visit 0A) when the participant begins the run-in period. Participants must demonstrate the ability to use proper peak flow technique and to coordinate use of the spirotel® device for entering diary information before leaving the performance site. These skills are assessed using the spirotel® Performance Checklist (SPIROTEL_PERF). This form should be filed in the participant's

study folder at the performance site. A performance check is required at Visit 1 (or Visit 0A) as part of eligibility assessment. See the Spirotel® discussion in this section for further details.

How to Use Your Metered Dose Inhaler (HTMDI)
This handout provides general instructions for proper inhalation technique for home use of the MDI inhaler.

Participants must demonstrate proper metered-dose inhaler (MDI) inhalation technique as assessed through the MDI Inhalation Technique Checklist (No Spacer) (P6_TECH_MDI_NOSP) before leaving Visit 1. For participants randomized to mometasone MDI at Visit 3, MDI inhalation technique will also be assessed through the MDI Inhalation Technique Checklist (No Spacer) (P6_TECH_MDI_NOSP) at Visits 3, 5, 7 and 9. In SIENA, completed P6_TECH_MDI_NOSP form(s) will be data entered. See the Inhalation Technique Assessment discussion in this section for further details.

How to Use Your Respimat® (HTRESP)
This handout provides general instructions for proper inhalation technique for home use of the Respimat®.

Participants must demonstrate proper Respimat® inhalation technique as assessed through the Respimat® Inhalation Technique Checklist (P6_TECH_RESP) before leaving Visit 1. Respimat® inhalation technique will also be assessed through the Respimat® Inhalation Technique Checklist (P6_TECH_RESP) at Visits 3, 5, 7 and 9. In SIENA, completed P6_TECH_RESP form(s) will be data entered. See the Inhalation Technique Assessment discussion in this section for further details.

How to Use Your Twisthaler (HTTWIST)
This handout provides general instructions for proper inhalation technique for home use of the Twisthaler®.

For participants randomized to mometasone Twisthaler® at Visit 3, they must demonstrate proper Twisthaler® inhalation technique as assessed through the Twisthaler Inhalation Technique Checklist (P6_TECH_TWIST) before leaving Visit 3. Twisthaler® inhalation technique will also be assessed through the Twisthaler® Inhalation Technique Checklist (P6_TECH_TWIST) at Visit 1, 5, 7 and 9. In SIENA, completed P6_TECH_TWIST form(s) will be data entered. See the Inhalation Technique Assessment discussion in this section for further details.

SIENA Inhalers: Key Differences (P6_INHALE_KEY_DIF/P6_INHALE_KEY_DIF_2)
This handout has been developed as a quick reference for the participant to ensure that he/she knows some of the slight differences on how to use an MDI, Respimat®, and Twisthaler® at home.

P6_INHALE_KEY_DIF is for participants randomized to Twisthaler;
P6_INHALE_KEY_DIF_2 is for participants randomized to MDI.

SIENA Participant Identification Card (P6_ID/P6_ID_2)
The SIENA Participant Identification Card (P6_ID/P6_ID_2) facilitates the identification, treatment, and handling of worsening asthma symptoms by the participant and by healthcare providers. Baseline peak flow, 65% baseline peak flow, baseline rescue use, and weekly high rescue use values are completed on the ID card at Visit 1. For those not taking part in the Supervised Washout, these values will be updated at Visit 2. See the Participant Identification Card discussion in this section for further details.

P6_ID is for participants randomized to Twisthaler; P6_ ID_2 is for participants randomized to MDI.

If Your Asthma Gets Worse (P6_ASWORSE_SUP)
This handout contains instructions for recognizing and treating asthma attacks for Supervised Washout participants. It outlines proper use of the ProAir® RESCUE inhaler in detail. It is important for the integrity of the study for the participant to understand how to use this inhaler as outlined in the protocol. This handout should be thoroughly covered at Visit 0A and reviewed at Visit 0B. For further information regarding treatment of asthma exacerbations, see the Significant Asthma Exacerbation and Study Medications discussions in this section.

If Your Asthma Gets Worse (P6_ASWORSE)
This handout contains instructions for recognizing and treating treatment failure and asthma attacks starting at Visit 1. It outlines proper use of the ProAir® RESCUE inhaler and open-label Asmanex® (YELLOW) inhaler in detail. It is important for the integrity of the study for the participant to understand how to recognize treatment failure and asthma attacks, and to use these inhalers as outlined in the protocol. This handout should be thoroughly covered at Visit 1 and reviewed at subsequent visits. For further information regarding treatment of asthma exacerbations and treatment failures, see the Significant Asthma Exacerbation, Treatment Failure and Study Medications discussions in this section.

SIENA Visit Preparation Checklist (P6_VISPRP/P6_VISPRP_2)
This handout is a tool for improving adherence with respect to the participant's preparation for each visit. The P6_VISPRP handout contains a checklist to help participants to remember to bring all necessary medications, and materials to each visit. It also includes reminders to ensure that the participant refrains from using certain medications, foods, and beverages within protocol-specified periods prior to each visit. Clinic personnel should review this handout with the participant before he/she leaves each visit to be sure the information in the checklist is understood.

P6_VISPRP is for participants randomized to Twisthaler; P6_ VISPRP_2 is for participants randomized to MDI.

spirotel® device: The spirotel® device is an electronic diary (e-diary) and peak flow monitor in one unit that stores all measurements the participant provides between visits

in its memory. The device has been customized for AsthmaNet to provide a participant-friendly screen and flow of procedures. Participants will have defined windows during which they can do their morning and evening assessments, including answering their diary questions and performing their peak flow maneuvers. This device will not allow 'backfilling' or 'recall' of data; it must be used on schedule twice daily. This customization requires participants to be conscientious about their home activities in order to meet the compliance thresholds required for the study. Data from the spirotel® device are downloaded at each visit and reports are generated for review with the participant. The Spirotel® Participant Visit Report shows the dates and times associated with each AM and PM session, along with the diary data the participant entered and his/her PEF measurements. The Spirotel® Participant Compliance Report (P6_COMPLY_RPT) provides metrics on how frequently the participant carried out all required home procedures between visits. Knowing that e-diary data will be reviewed at the next visit will encourage participants to be more compliant.

Daily diary records help participants assume more responsibility for their own care. Recall bias is minimized, as the e-diary device requires participants to complete their AM and PM diary assessments each day.

Specific SIENA 'alerts' have been programmed into the spirotel® device. These alerts will prompt participants to take their morning and evening medications, start open-label Asmanex® (YELLOW) inhaler for treatment failure, and call the clinic. These alerts should improve adherence with several aspects of the protocol.

See the spirotel® discussion in this section and the spirotel® Manual of Operations in Appendix 6 of the AsthmaNet General Manual of Operations for further details.

Spirotel® Performance Check (SPIROTEL_PERF): Peak flow measurement and diary question completion are important daily activities. Regular measurement of lung function and assessment of symptoms and rescue inhaler use will help the participant identify when he/she is trending towards exacerbation and will increase adherence with the onset of appropriate treatment and reporting of these events.

Improper peak flow technique is a form of non-adherence. Coaching the participant on the proper technique early in the study and reviewing this technique throughout the study improve adherence. The Spirotel® Performance Checklist (SPIROTEL_PERF) is used at Visit 1 (or Visit 0A for Supervised Washout participants) to document that each participant has achieved proper peak flow technique.

Failure to complete diary assessments twice a day is another form of non-adherence. Instructing the participant in the proper way to use the spirotel® device for entry of diary information improves adherence. The SPIROTEL_PERF checklist is used at Visit 1 (or Visit 0A for Supervised Washout participants) to document that each participant has achieved an understanding of how to use the spirotel® device correctly.

See the spirotel® discussion in this section and the spirotel® Manual of Operations in Appendix 6 of the AsthmaNet General Manual of Operations for further details.

Inhalation Technique Assessment

MDI Inhalation Technique Checklist (Without Spacer) (P6_TECH_MDI_NOSP)

Proper inhalation technique using a metered-dose inhaler (MDI) (e.g., study mometasone or placebo MDI, rescue ProAir®) is important to the study. Improper technique is a form of non-adherence with study procedures. Instruction in proper technique and continual coaching serve to improve adherence. The MDI Inhalation Technique Checklist (Without Spacer) (P6_TECH_MDI_NOSP) is used to document that each participant has achieved proper MDI inhalation technique at Visit 1. For participants randomized to the mometasone MDI device at Visit 3, MDI inhalation technique will also be assessed through the MDI Inhalation Technique Checklist (Without Spacer) (P6_TECH_MDI_NOSP) at Visit 3, 5, 7 and 9. Documentation of proper technique is required to satisfy the eligibility criteria assessed at this visit. See the Inhalation Technique Assessment discussion in this section for further details.

Respimat Inhalation Technique Checklist (P6_TECH_RESP)

Proper inhalation technique using the Respimat (e.g., study tiotropium or placebo Respimat®) is important to the study. Improper technique is a form of non-adherence with study procedures. Instruction in proper technique and continual coaching serve to improve adherence. The Respimat Inhalation Technique Checklist (P6_TECH_RESP) is used to document that each participant has achieved proper Respimat inhalation technique at Visits 1, 3, 5, 7 and 9, and review as necessary. Proper inhalation technique is an eligibility criterion assessed at Visit 1. See the Inhalation Technique Assessment discussion in this section for further details.

Twisthaler Inhalation Technique Checklist (P6_TECH_TWIST)

Proper inhalation technique using the Twisthaler (e.g., study mometasone or placebo Twisthaler®) is important to the study. Improper technique is a form of non-adherence with study procedures. Instruction in proper technique and continual coaching serve to improve adherence. For participants randomized to the mometasone Twisthaler® device at Visit 3, Twisthaler Inhalation Technique Checklist (P6_TECH_TWIST) is used to document that each participant has achieved proper Twisthaler inhalation technique at Visits 1, 3, 5, 7 and 9, and review as necessary. Proper inhalation technique is an eligibility criterion assessed at Visit 3. See the Inhalation Technique Assessment discussion in this section for further details.

Counseling for Non-Adherence

At each visit the participant's level of adherence with study procedures must be assessed. Individuals who have maintained high levels of adherence should be applauded. If adherence levels are low, this should be addressed with the participant.

During each visit, review the necessity of correct study medication use and the importance of avoiding medications that are not allowed during the study. Discuss the importance of rescue use information that is collected at home. Remind the participant

that correctly following study procedures is crucial to the study; it is a part of the commitment he/she made when agreeing to participate.

When addressing problems, try to be constructive and helpful:

Acceptable: "I noticed that you have not been taking your WHITE study inhaler twice daily regularly. Is there anything we can do to help you?

Unacceptable: "You are not doing what you are supposed to do. What is your problem?"

When dealing with problems it is best to re-explain procedures slowly and thoroughly and to rationalize and persuade logically. Attribute lack of adherence to a misunderstanding between clinic personnel and the participant. Ensure that the participant is aware of the resources available to help him/her understand the study procedures, such as study handouts and the availability and willingness of clinic personnel to answer questions whenever they arise.

2.3 Adverse Events

Definition and Reporting
Adverse events include the following:

- Clinical Adverse Events:

  A clinical adverse event is any unintended worsening in structure or function of the body; any illness that occurs during the trial. These events are documented on the Clinical Adverse Events (AECLIN) form.

  The term 'study drug' on the AECLIN form should be interpreted to mean any drug dispensed as part of the study, including open-label Asmanex® and blinded Respimat® and Twisthaler®/MDI devices. If an adverse event is thought to be related to one of these medications, this fact should be documented in Q1080 on the AECLIN form. In addition, if the dose of the medication was altered as a result of the adverse event, this should be noted in Q1090. Following randomization, if a change in the status of the participant's blinded scheduled Respimat® and Twisthaler®/MDI occurred because of an adverse event, a SIENA Change in Scheduled Medications form (P6_CHANGE_MEDS) also should be completed.

  See Section 10 of the AsthmaNet General Manual of Operations for further details on AECLIN form completion and submission.

- Laboratory Adverse Events:

  A laboratory adverse event is the occurrence of abnormal laboratory tests or other test (e.g., lab) results. These events are documented on the Clinical Adverse Events (AECLIN) form.

- Significant Asthma Exacerbation:

  Significant asthma exacerbations should be recorded on the Significant Asthma Exacerbation form (P6_SIGEX). In addition, significant asthma exacerbations should be recorded on the AECLIN form using ICD-9 code 493.92. If a participant experiences a significant asthma exacerbation during the run-in phase, he/she is ineligible for randomization and should be terminated. See the Significant Asthma Exacerbation discussion in this section for further details.

- Treatment Failure:

  Treatment failure events should be recorded on the Treatment Failure Checklist (P6_TXFAIL_CHK), as well as Treatment Failure Information form (P6_TXFAIL) if treatment failure not as a result of significant asthma exacerbation. In addition, treatment failures should be recorded on the AECLIN form using ICD-9 code 000.00. If a participant experiences two or more treatment failures during the run-

in phase, he/she is ineligible for randomization and should be terminated. See the Treatment Failure discussion in this section for further details.

- Serious Adverse Events:

  Any experience that poses a significant hazard to a participant is considered a serious adverse event. With respect to human clinical experience, a serious adverse event includes any experience that meets at least one of the following criteria:

  1. Results in death
  2. Is life threatening (places the participant at immediate risk of death from the event as it occurred)
  3. Results in a significant or persistent disability/incapacity
  4. Requires inpatient hospitalization or prolongation of an existing hospitalization
  5. Results in a congenital anomaly/birth defect
  6. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. Examples include allergic bronchospasm requiring intensive treatment in an emergency department or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or abuse.

  Serious adverse events are reported on the Serious Adverse Events Reporting Form (SERIOUS) as well as on the Clinical Adverse Events (AECLIN) form.

  If an adverse event is deemed serious by the above definition, a SERIOUS form should be completed and faxed or e-mailed to the SIENA scientific coordinator at the DCC as soon as possible, preferably within 72 hours of clinic notification. Promptly faxing this form to the DCC expedites communicating the details of the adverse event to the Steering Committee, Data and Safety Monitoring Board (DSMB), and Institutional Review Boards (IRBs) if the event was deemed unexpected and possibly related to the study. If the documentation cannot be assembled within 72 hours due to the need for access to medical records or inability to contact the study participant, contact the SIENA scientific coordinator so that the DCC has communications on file and can follow up.

For detailed information on adverse events, see Section 4 in the AsthmaNet General Manual of Operations.

ICD-9 Codes

In general, ICD-9 codes describing an adverse event of any type should be obtained by searching the AsthmaNet ICD-9 Codes Excel spreadsheet. This spreadsheet can be accessed on the secure website in the Applications folder or through a link provided in concurrent forms entry. The spreadsheet includes the ICD-9 code for a particular

diagnosis, along with long and short text descriptions of the related diagnosis. Clinical personnel can search the spreadsheet for a specific condition to find an appropriate code. Codes and their associated descriptions were downloaded from the Department of Health & Human Services, Centers for Medicare & Medicaid Services (CMS) website. They are from version 27 of the full and abbreviated code titles of the ICD-9-CM codes effective October 1, 2009. This code library will be used for the duration of AsthmaNet to ensure standardization across trials. Note that no other ICD-9 code references are acceptable.

For AsthmaNet, reported ICD-9 codes should describe the underlying condition or disease that resulted in a particular adverse event. For example, if a participant is hospitalized for a hysterectomy that was necessitated by uterine fibroids, the ICD-9 code for uterine fibroids should be recorded on the Clinical Adverse Events (AECLIN) form. The procedure code for hysterectomy is unavailable in the master spreadsheet and should not be recorded. In general, procedure codes will not be reported.

Specific ICD-9 codes of interest for the SIENA study include:

- 000.00: Protocol-defined treatment failure event
- 493.92: Significant asthma exacerbation

Visit 1 (or Visit 0A for those in Supervised Washout)

Record any adverse events that have occurred since the participant signed the informed consent on the Clinical Adverse Events (AECLIN) form

If the participant experienced any adverse events between the date he/she (or his/her parent/guardian) signed the informed consent form (original signature date) and the date of Visit 1 (or Visit 0A for those in Supervised Washout), record the events on the Visit 1 (or Visit 0A) AECLIN form. If no adverse events are recorded for the participant at Visit 1 (or Visit 0A for those in Supervised Washout), check the 'None' box.

A comprehensive medical history is taken during Visit 1 for those not in the Supervised Washout, and at Visit 0A for those in the Supervised Washout. As part of this history it is important to probe for pre-existing conditions, both those related to asthma and those unrelated to asthma. This baseline knowledge is necessary to determine if conditions experienced during the SIENA study should be considered adverse events (i.e., worsening of a chronic condition or a condition that appears for the first time during the study). Pre-existing conditions should not be recorded on the Clinical Adverse Events (AECLIN) form, but they should be noted in the clinic notes that are stored in the participant's study folder.

Visits 2-8 (as well as Visits 0B, 1 for Supervised Washout participants)

Follow up clinical and laboratory adverse events from previous visit and record any new events (AECLIN)

The Clinical Adverse Events (AECLIN) form should be updated each time the clinic has contact with a participant, whether for a scheduled visit or phone contact, impromptu visit, or unexpected phone call.

In preparation for each contact, review the participant's file to determine if there were any ongoing adverse events at the last visit/contact. If an ending date for an ongoing adverse event becomes available, update the AECLIN form with this new information. Probe the participant for the occurrence of any new adverse events and record these on AECLIN.

An AECLIN form should be completed for each participant at each visit, even if the participant has not experienced any new adverse events since the previous visit. If no new adverse events are being recorded for the participant at a visit, check the 'None' box. If new information is available, record it and have the participant review it for accuracy.

Visit 9 or other early termination visit
Events that are ongoing at the time a participant leaves the study should be left open for stop dates (i.e., coded as 'ongoing at final visit'). The participant should be probed for any stop dates that are now known to close out previously-recorded events. All AECLIN forms for a given individual should be forwarded to the DCC following his/her study termination.

See Section 10 of the AsthmaNet General Manual of Operations for further details on AECLIN form completion and submission.

Serious Adverse Event Reporting to Boehringer-Ingelheim
Boehringer Ingelheim (BI), provider of the tiotropium Respimat® used in SIENA, requires that serious adverse events be reported. This applies to randomized participants, as well as non-randomized participants who are in the Supervised Washout or run-in. Serious Adverse Event(s) should be reported using the BI Investigator-Initiated Serious Adverse Event Reporting Form. A locked Word version of this form with fillable fields has been provided to ease reporting of events. This is located in the Protocols: SIENA: Documents folder. Form instructions and a brief PowerPoint overview of the form are also posted.

Completed forms should be emailed to Anne-Marie Dyer (adyer@psu.edu) and Ron Zimmerman (rzimmerm@phs.psu.edu). If no forms are forthcoming following a serious adverse event, queries will be sent.

2.4 Appointments: Confirming and Scheduling

Visits 0A, 0B, 1, 2A, 3
Run SIENA Visit Scheduler
Review planned visit schedule
Confirm/Schedule upcoming appointment(s) and review Visit Preparation handout (P6_VISPRP_2)

Visits 4, 5, 6, 7, 8
Run SIENA Visit Scheduler
Review planned visit schedule
Confirm/Schedule upcoming appointment(s) and review Visit Preparation handout (P6_VISPRP/P6_VISPRP_2)

Visit 2
Confirm/Schedule upcoming appointment and review Visit Preparation handout (P6_VISPRP_2)

Visits 90-92
Run Asthma Exacerbation Visit Scheduler
Review planned Asthma Exacerbation visit schedule, including visit and phone contacts
Confirm/schedule upcoming appointments, phone contact(s) and review Visit Preparation handout (P6_VISPRP/ P6_VISPRP_2)

Visits 90A-92A, 90B-92B, 90C-92C
Confirm/schedule upcoming Asthma Exacerbation phone contact(s) and /or appointment(s) and review Visit Preparation handout (P6_VISPRP/ P6_VISPRP_2)

Visits 90D-92D
Confirm/schedule upcoming appointment(s) and /or phone contact(s) and review Visit Preparation handout (P6_VISPRP/ P6_VISPRP_2) with reminder to bring completed AAAQ, WPAI_ASTHMA, and WURSS-21 forms to the next visit

At each visit, review the current SIENA Visit Scheduler Report and confirm the date of the next regular visit and any upcoming phone contacts. Write the scheduled date on the participant's copy of the Visit Scheduler Report for his/her reference, and enter the date into the clinic's appointment book or scheduling calendar.

Review the SIENA Visit Preparation handout (P6_VISPRP/ P6_VISPRP_2) with the participant. Remind him/her of the substances that must be avoided prior to each scheduled visit. Also remind the participant to bring his/her study medications (used and not used), SIENA Asthma Monitoring Log (P6_ASTHMA_LOG), spirotel® device, and handout folder to each visit. Review the checklist on side 2 of the handout.

Visits for a given participant should be scheduled for the same time of day as measured by the time that baseline spirometry takes place during a visit (+/- 3 hours of Visit 1 spirometry for run-in visits, +/- 3 hours of Visit 1 spirometry for post-randomization visits if randomized on or before September 8, 2015 OR +/- 3 hours of Visit 3 spirometry for post-randomization visits if randomized after September 8, 2015). This is done to avoid the introduction of circadian variability into the assessment of lung function. If a participant needs to be scheduled outside the 3-hour window, the SIENA scientific coordinator at the DCC should be contacted to obtain an exception.

See the Visit Scheduler and Visit Windows discussions in this section for further details.

2.5 Asthma Exacerbation Kit

Visit 3
Distribute asthma exacerbation kit and review instructions (WPAI_ASTHMA, AAAQ, WURSS-21, P6_ASTHMA_EXAC)

One of the exploratory aims of the SIENA trial is to evaluate the responsiveness of a range of tools to characterize the time-course (onset and resolution) and magnitude of morbidity associated with an asthma exacerbation and the use of systemic corticosteroids. The following questionnaires will be used:

- Asthma-Specific Work Productivity and Activity Impairment Questionnaire (WPAI_ASTHMA)

  This questionnaire measures the effect of the participant's asthma on his/her ability to work, attend classes, and/or perform regular daily activities in a 7-day timeframe. See the discussion of the Work Productivity and Activity Impairment Questionnaire in this section for further details.

- Acute Asthma Assessment Questionnaire (AAAQ)

  This questionnaire measures impairment level in terms of asthma symptoms, rescue bronchodilator use, nighttime awakenings, stress caused by asthma, and effects on usual activities in a 3-day timeframe. It also records the primary cause of the exacerbation. See the Acute Asthma Assessment Questionnaire discussion in this section for further details.

- Wisconsin Upper Respiratory Symptom Survey

  This questionnaire measures the severity and impact of the common cold. See the Wisconsin Upper Respiratory Symptom Survey discussion in this section for further details.

To facilitate collection of questionnaire data at the onset of an exacerbation, which may occur when the participant is at home or otherwise away from the performance site, an "Asthma Exacerbation Kit" will be given to each participant at Visit 3. This kit should be kept at home with the participant's study materials and rescue prednisone bottle. The kit includes:

- One copy of the WPAI_ASTHMA questionnaire. Complete the participant's SIENA ID, initials, and Asthma Exacerbation Visit ID (first Asthma Exacerbation will have visit ID 90, second 91, and third 92) in the header field prior to dispensing the kit.

- One copy of the AAAQ questionnaire. Complete the participant's SIENA ID, initials, and Asthma Exacerbation Visit ID in the header field prior to dispensing the kit.
- Twenty-one copies of the WURSS-21 questionnaire. Complete the participant's SIENA ID and initials in the header field prior to dispensing the kit.
- One copy of the "Asthma Exacerbation Kit Instructions" handout

Review the kit instructions with the participant. Emphasize that one copy of each of the questionnaires should be completed on the day he/she takes the first dose of prednisone when it is prescribed to treat an asthma exacerbation. The questionnaires should be completed if a medical practitioner outside of the study prescribes prednisone to treat asthma, as well as when someone at the study site prescribes it. The participant should record the date he/she completed the questionnaire as part of the source documentation on the questionnaire. It is also helpful if the participant notes the first day of prednisone on his/her Asthma Monitoring Log and notes completion of the kit there, as well. The completion date is very important for analysis. The participant should continue to complete one WURSS-21 survey per day until he/she answers "Not sick" to the question "How sick do you feel today?" for two days in a row.

If the participant forgets to complete the questionnaires on the first day of prednisone, the participant should complete them as soon as he/she remembers with the actual date he/she completed the questionnaires in the source documentation box on the questionnaires. This information will be matched to the prednisone course information recorded on the Concomitant Medications form (CMED) so that the timing of the responses relative to use of prednisone can be determined and accounted for.

Visits 90-92, 90A-92A, 90B-92B, 90C-92C, 90D-92D
Administer Acute Asthma Assessment Questionnaire (AAAQ)

Visits 90-92, 90B-92B, 90C-92C, 90D-92D
Administer Asthma-Specific Work Productivity and Activity Impairment Questionnaire (WPAI_ASTHMA)

If an asthma exacerbation occurs between regular visits, the participant should follow the instructions on the "Asthma Exacerbation Kit Instructions" handout (P6_ASTHMA_EXAC). He/she will complete WPAI_ASTHMA and AAAQ, and start completing the WURSS-21, at home on the day he/she starts prednisone. These completed forms should be returned to the performance site at the participant's Asthma Exacerbation Visit, and the visit ID should correspond to the appropriate Asthma Exacerbation visit ID. Day 0 forms for a participant's first Asthma Exacerbation will have visit ID 90, second 91, and third 92. The visit date should match the date the participant supplied in the source documentation box at the time of completion. At the Asthma Exacerbation Visit, the AAAQ should be completed again (as follow-up to the event), and the visit ID on this form should correspond to the Asthma Exacerbation visit ID followed by "A". Note that these instructions also apply if the participant is seen at the performance site for exacerbation conditions between visits and he/she will start a

prednisone course the same day. In that case the form should be completed and turned in to study personnel the same day.

If an asthma exacerbation is documented at the time of a regular visit and the participant will begin taking prednisone that day, he/she should complete the WPAI_ASTHMA and AAAQ questionnaires at the time of the visit (rather than waiting to do so at home). He/she should also be instructed to start completion of the WURSS-21. Clinic personnel should collect the WPAI_ASTHMA and AAAQ questionnaires at the visit and review them for completion. The visit ID on this form should correspond to the appropriate Asthma Exacerbation visit ID. Visit 9XA should be scheduled to take place in 3-7 days.

The AAAQ and WPAI_ASTHMA will also be completed at Asthma Exacerbation phone contacts 10, 14, and 21 days following start of prednisone. The visit IDs on this form at Day 10, 14 and 21 should correspond to the appropriate Asthma Exacerbation visit ID (first Asthma Exacerbation will have visit ID 90, second 91, third 92, etc.) followed by "B", "C" and "D", respectively.

Visits 90A-92A
Collect completed Asthma Exacerbation forms (AAAQ, WPAI_ASTHMA, WURSS-21)
Distribute Asthma Exacerbation forms to be completed at phone contacts, including extra copy to replenish kit

- ➔ Acute Asthma Assessment Questionnaire (AAAQ) (4 copies)
- ➔ Asthma-Specific Work Productivity and Activities Impairment Questionnaire (WPAI_ASTHMA) (4 copies)

If the participant experienced a significant asthma exacerbation between visits, the completed AAAQ and WPAI_ASTHMA forms should be collected at the time of the Asthma Exacerbation Visit. Four copies of the AAAQ and WPAI_ASTHMA should also be distributed for the phone contacts at Day 10, 14, and 21, as well as one copy to replenish the Asthma Exacerbation kit. Refer to Section 4 for how to complete returned forms.

2.6 Asthma Bother Profile

Visits 3, 5, 7, 9
Administer Asthma Bother Profile (ABP)

The Asthma Bother Profile[1] (ABP) is an asthma-specific tool for measuring quality of life. The instrument includes 15 questions that elicit information about various kinds of distress caused by asthma to which participants respond on a six-point scale ranging from 'no bother at all' to 'makes my life a misery.' This questionnaire is appropriate for adults, ages 18 and over, and includes questions regarding the impact of asthma on a person's paid work, leisure activities, and social life, as well as psychological distress questions. Parts one and five of the original questionnaire have been omitted from the AsthmaNet version, as they are unneeded for scoring the questionnaire and similar information is collected on other data collection forms used in the SIENA trial. Permission was granted from the questionnaire's author, Dr. Hyland, to use the AsthmaNet version of the survey.

The ABP is administered by participant interview and the form is completed by the study coordinator. Lead-in information for each part of the survey and questions should be read from the form directly in a clear and even tone. If the participant asks for clarification of any question, repeat the question slowly and clearly. Do not provide any additional explanation; ask the participant to answer the question as it is stated as best he/she can. Providing additional information may bias the participant's responses.

The administration of the ABP is one of the first procedures performed at an applicable visit. This timing in the visit structure is intentional so that a participant's responses are not affected by other study procedures, such as spirometry and e-diary/peak flow review. Study coordinators should observe the order of procedures as they are laid out on the visit procedure checklists to ensure that ABP results are not confounded by other study activities.

If a given visit has been partially completed and then rescheduled for a later date because of the participant's time constraints on that day, a new ABP form must be completed at the beginning of the rescheduled visit. Do not allow the participant to refer to or update his/her previously completed questionnaire. Old copies of the questionnaires should be filed in the participant's study folder and clearly marked as such; they should not be entered into the study database or forwarded to the DCC. Note that this procedure does not apply to FEV_1 re-assessment visits. For these visits, the original previously-completed questionnaires will be submitted with the visit packet.

Upon completion of the questionnaire the participant should initial, date and provide the time on the ABP form in the source documentation box on page 5 to verify that he/she

[1] Hyland ME, Ley A. Measurement of Psychological Distress in Asthma and Asthma Management Programmes. British Journal of Clinical Psychology 1995, 34:601-611.

provided the information and that it was recorded correctly. The coordinator should check the date and time provided by the participant before he/she leaves the visit to ensure that they are correct.

2.7 Asthma Control Test

Visits 1, 3-9
Administer Asthma Control Test

General Information
The Asthma Control Test (ACT) is administered at SIENA Visits 1 and 3 – 9. The ACT is designed for adolescents and adults ages 12 and above, and has been validated for use for ages 14 and above.

The administration of the ACT is one of the first procedures performed at a visit. This timing in the visit structure is intentional so that a participant's responses are not affected by other study procedures, such as spirometry and e-diary/peak flow review. Study coordinators should observe the order of procedures as they are laid out on the visit procedure checklists to ensure that ACT results are not biased by other study activities. At visits where multiple questionnaires are administered early in the visit, including the ACT, the ACT must be the first one administered.

If a given visit has been partially completed and then rescheduled for a later date because of the participant's time constraints on that day, a new ACT form must be completed at the beginning of the rescheduled visit. Do **not** allow the participant to refer to or update his/her previously completed questionnaire. Old copies of the questionnaires should be filed in the participant's study folder and clearly marked or shredded; they should not be entered into the study database or forwarded to the DCC. Note that this procedure does not apply to FEV_1 re-assessment visits. For these visits, the original previously-completed questionnaires will be submitted with the visit packet.

When administering the ACT questionnaire, request that the participant or his/her parent/guardian complete the entire form and provide answers as completely and as accurately as possible. No stated or implied time limit should be set. If the participant or guardian requests help with or clarification of any question, the study coordinator should instruct him/her to reread the instructions and to give the best answer possible to each question. The study coordinator should not provide an answer to any question. Providing guidance may bias the responses.

Following are guidelines for ACT administration to ensure the best quality data:

- Provide the participant (and his/her parent/guardian in the case of a child) a quiet place to complete the questionnaire.
- Before the participant or guardian completes the ACT, the study coordinator should do the following:
    - Complete the information in the form header.
    - Tell the participant or guardian that all questions should be answered.
    - Tell the participant or guardian that only one response may be given for each question.

- Remind the participant or guardian that he/she is scoring problems experienced due to asthma and not because of any other conditions.
- Remind the participant or guardian that the ACT is collecting data about their/their child's asthma over the past 4 weeks.

Participants or guardians should use a black or blue pen to complete the questionnaire. If the respondent wishes to change a response, the original response should be crossed out with a single line and then dated and initialed. The final response should be circled for clarification. No changes to the participant-completed or guardian-completed form may be made by study personnel; changes may only be made by the respondent.

When the participant or guardian is finished with the questionnaire, collect it and review it for completeness before proceeding with the visit. If a question has been left blank, ask the participant or guardian to do his/her best to answer it. The answers to all of the questions are necessary to score the instrument. Check that the responses are clearly marked.

Asthma Control Test (ACT)

The ACT is a trade-marked 5-item questionnaire that was developed through research by GlaxoSmithKline and is now managed by QualityMetric Incorporated. AsthmaNet has paid a licensing fee for the use of the ACT in the SIENA trial. QualityMetric supplied the version of the form that we are using, and AsthmaNet was refused permission to implement any formatting changes to make it more compatible with our database. See the data management guidelines for this form in Section 10 of the AsthmaNet General Manual of Operations for more information.

The ACT gathers information on asthma control using a 4-week recall window. The form is self-administered and participant completed. The ACT website is: www.asthmacontrol.com.

No source documentation can be provided on this questionnaire due to the constraints imposed by QualityMetric.

2.8 Asthma Monitoring Log

The Asthma Monitoring Log (P6_ASTHMA_LOG) is an administrative form that was created to give participants a centralized location to record their nighttime awakenings, scheduled peak flows, and rescue use (puffs and times) each day. The spirotel® device does not allow participants to scroll back to view data entered for previous days; the P6_ASTHMA_LOG is the only reference the participant will have to assess how his/her lung function and rescue ProAir® use may have changed over recent days, possibly signaling the onset of treatment failure or a significant asthma exacerbation. The log also includes space to record any non-study medications that are taken between visits, and any medical problems the participant experiences. This information is useful in recording concomitant medications and adverse events at the participant's next study visit. The participant should be instructed to complete this form and to return it at his/her next visit.

The P6_ASTHMA_LOG form is set up as a fillable PDF file with an auto-populating date field. When preparing a log for a participant, the coordinator should complete the current date (date of the visit) in the first date field at the top of the form. All dates will be completed automatically throughout the rest of the form. The participant should begin completing the log with his/her PM scheduled session on the day of the visit.

Visits 1-8 (as well as Visits 0A, 0B for Supervised Washout Participants)
Complete and distribute Asthma Monitoring Log (P6_ASTHMA_LOG)

At each of Visits 1 through 8 (as well as Visits 0A, 0B for Supervised Washout participants), a new P6_ASTHMA_LOG form should be completed with participant information in the key fields area and dates, starting with the date of the current visit. At Visit 1 (and Visit 0A), the participant's 65% Baseline PEF value should be calculated by multiplying his/her Baseline PEF value by 0.65. At Visits 0B and 1 for participants in the Supervised Washout, and at Visit 2 for participants starting SIENA at Visit 1, the participant's 65% Baseline PEF value will be printed on the SIENA Spirotel® Baseline Report. This value should be recorded in the blank field in the text for all visits. The form should be given to the participant to complete until the next regularly scheduled visit.

Emphasize the difference between total number of RESCUE *puffs* used and total *times* RESCUE used.

Explain that non-study medications and medical conditions should be documented on the back of asthma log. The participant should be instructed that preventive bronchodilator puffs (taken routinely prior to exercise and other strenuous activities) should not be recorded in daily rescue use counts.

Encourage the participant to record the information each and every day. It is helpful if the recording of the data can be associated with specific daily activities (e.g., brushing teeth). Emphasize that data should not be *made up* or *recalled* more than one day back if days are missed.

Visits 2-9 (as well as Visit 0B, 1 for those in Supervised Washout)
Collect Asthma Monitoring Log (P6_ASTHMA_LOG)

Near the beginning of each visit, the participant's completed P6_ASTHMA_LOG form should be collected and reviewed with him/her for any recorded comments, concomitant medications, or adverse events experienced since the last visit. Completed forms should be stored in the participant's SIENA study folder at the performance site; these forms should not be forwarded to the DCC.

Visits 90-92
Review Asthma Monitoring Log (P6_ASTHMA_LOG)

If the participant experienced a significant asthma exacerbation based on high rescue use (≥ 16 puffs per 24 hours for a period of 48 hours), the Asthma Monitoring Log will be useful in identifying when the exacerbation conditions were met.

2.9 Asthma Symptom Utility Index

Visits 3-9
Administer Asthma Symptom Utility Index (ASUI)

The Asthma Symptom Utility Index (ASUI) is an eleven-item questionnaire developed by Dennis Revicki et al[2].

When administering the ASUI, the study coordinator will ask the participant questions pertaining to specific asthma symptoms, night-time awakenings, and side effects of medication use over the 14-day period leading up to the visit. Questions should be read from the form directly in a clear and even tone.

The ASUI questionnaire is completed by participant interview and the form is completed by the study coordinator. If the participant asks for clarification of any question, repeat the question slowly and clearly. Do not provide any additional explanation; ask the participant to answer the question as it is stated as best he/she can. Providing additional information may bias the participant's responses.

The administration of the ASUI is one of the first procedures performed at a visit. This timing in the visit structure is intentional so that a participant's responses are not affected by other study procedures, such as spirometry and e-diary/peak flow review. Study coordinators should observe the order of procedures as they are laid out on the visit procedure checklists to ensure that ASUI results are not confounded by other study activities.

If a given visit has been partially completed and then rescheduled for a later date because of the participant's time constraints on that day, a new ASUI form must be completed at the beginning of the rescheduled visit. Do not allow the participant to refer to or update his/her previously completed questionnaire. Old copies of the questionnaires should be filed in the participant's study folder and clearly marked as such; they should not be entered into the study database or forwarded to the DCC. Note that this procedure does not apply to FEV_1 re-assessment visits. For these visits, the original previously-completed questionnaires will be submitted with the visit packet.

Upon completion of the questionnaire the participant should initial, date and provide the time on the ASUI form in the source documentation box on page 2 to verify that he/she provided the information and that it was recorded correctly. The coordinator should check the date and time provided by the participant before he/she leaves the visit to ensure that they are correct.

[2] Revicki DA, Leidy NK, Brennan-Diemer F, Sorensen S, Togias A. Integrating Patient Preferences Into Health Outcomes Assessment: The Multiattribute Asthma Symptom Utility Index. Chest 1998,114:998-1007.

2.10 Baseline Peak Flow and Rescue Use Values

Baseline peak flow (PEF) and rescue medication use values are determined at Visit 1 and updated at Visit 2 (or at Visit 0A, and updated at Visits 0B and 1 for Supervised Washout participants). Values are recorded on the SIENA Baseline PEF and Rescue Use Values (P6_BASELINE) form and entered into the study database. These reference values are used by the participant and clinical personnel to identify when the participant meets certain treatment failure criteria and to identify worsening on his/her asthma.

Visit 1 (or Visit 0A for Supervised Washout Participants)
Complete Baseline Peak Flow and Rescue Use Values form (P6_BASELINE)

At Visit 1 (or Visit 0A for Supervised Washout participants), the participant is just starting the SIENA run-in (or washout) period and is being given his/her spirotel® peak flow meter and e-diary device for the first time. Therefore, no peak flow or rescue use data have been recorded by the participant to this point in the study. The baseline peak flow and rescue use values are defined at Visit 1 (or Visit 0A for Supervised Washout Participants) as follows:

Baseline Peak Flow (PEF)
The baseline PEF at Visit 1 (or Visit 0A) is the spirometry peak flow value corresponding to the best effort during baseline spirometry (converted to liters/minute). This value is obtained by multiplying the value from Q1050 (FEF Max) on the Spirometry Testing (SPIRO) form by 60 and rounding to the nearest whole liter/minute. If the participant requires a Visit 1 Continuation visit to establish his or her study eligibility, the baseline PEF should be calculated from Q1050 on the SPIRO form completed at the original visit.

The baseline PEF value is recorded in Q1000 on the P6_BASELINE form. It is also recorded on the Participant Identification Card (P6_ID/P6_ID_2) given at Visit 1, and is used for calculating PEF reference values which are recorded on several of the participant handouts.

Baseline Rescue Use Value
At Visit 1 (or Visit 0A), the baseline rescue use value is the participant's self-reported average daily use (in puffs) of albuterol or levalbuterol (common RESCUE medications) during the 14 days prior to the visit. Ask the participant to recall the amount of rescue medication puffs he/she used daily over the previous 2 weeks. A ballpark average amount of daily puffs of medication is sufficient for monitoring treatment failure between Visits 1 and 2. Round to the nearest puff if calculating the value. The participant should not include preventive puffs (e.g., pre-exercise puffs or puffs taken in advance of allergen exposure) in his/her estimate. Preventive puffs also will not be included in the daily puffs of RESCUE ProAir® used, which will be input into the participant's spirotel® e-diary each day.

The baseline rescue use value is recorded in Q1010 on the P6_BASELINE form. The participant's Weekly High Rescue Use value is necessary starting at Visit 1, and is calculated by multiplying the baseline rescue use value by 14. The Weekly High Rescue Use value (equal to twice the baseline weekly rescue use) is used to determine when a participant meets certain treatment failure criteria. If the participant uses albuterol for relief of symptoms daily for seven days, and this use exceeds the Weekly High Rescue Use value, then he/she meets treatment failure conditions. The Weekly High Rescue Inhaler Use value is recorded on the Participant Identification Card (P6_ID/P6_ID_2) at Visit 1, as well as on several of the participant handouts.

If a participant reports his/her baseline daily rescue use is 0, the participant will meet treatment failure criteria if he/she uses albuterol for relief of symptoms daily for seven days. Weekly High Rescue Use will not factor into this treatment failure criteria when baseline daily rescue use is 0.

Visit 0B (for 2-Step Supervised Washout Participants)
Print and Review SIENA Spirotel® Baseline Report (P6_BASELINE)

At Visit 0B, the participant has several weeks of peak flow and rescue use data stored in his/her spirotel® device. The baseline peak flow and rescue use values are updated at Visit 0B on the basis of the spirotel® data. The baseline peak flow and rescue use values are defined at Visit 0B as follows:

Baseline Peak Flow (PEF)
At Visit 0B, the baseline PEF is defined as the average pre-bronchodilator AM PEF value recorded during the two weeks prior to the visit. This is further defined as the average of the pre-bronchodilator AM PEF values recorded the 14 days prior to Visit 0B, including the AM PEF value from the morning of Visit 0B, rounded to the nearest liter/minute. If a participant used his/her ProAir® RESCUE inhaler within 4 hours of an AM PEF measurement, the value will be excluded from the calculations. Missing AM PEF values in the 14 day interval will also be excluded from the calculation. It is possible that a participant's baseline PEF value may be based on fewer than 14 days' worth of data.

The SIENA Spirotel® Baseline Report generated at Visit 0B, after uploading data from the participant's device, summarizes the participant's Baseline PEF and 65% Baseline PEF. The 'Baseline PEF' value from the report should be recorded in Q1000 on the P6_BASELINE form at this visit. This value will also be programmed into the spirotel® device at Visit 0B, and the 65% Baseline PEF will be printed on several participant handouts.

Baseline Rescue Use Value
At Visit 0B, the baseline rescue use value is defined as the average daily use of albuterol (ProAir® RESCUE inhaler) during the last 2 weeks prior to the visit. This is further defined as the average daily RESCUE inhaler puffs used during the 14 days

prior to Visit 0B, rounded to the nearest puff. Missing daily rescue use puffs in the 14 day interval will be excluded from the calculation. It is possible that a participant's baseline rescue use value may be based on fewer than 14 days' worth of data.

The SIENA Spirotel® Baseline Report generated at Visit 0B, after uploading data from the participant's device, summarizes the participant's Baseline Rescue Use and High Weekly Rescue Use values. The 'Baseline Rescue Use' value from the report should be recorded in Q1010 on the P6_BASELINE form at this visit. This value will also be programmed into the spirotel® device at Visit 0B.

Visit 2 (or Visit 1 for Supervised Washout Participants)
Print and Review SIENA Spirotel® Baseline Report (P6_BASELINE)

At Visit 2 (or Visit 1 for Supervised Washout participants), the participant has several weeks of peak flow and rescue use data stored in his/her spirotel® device. The baseline peak flow and rescue use values are updated at Visit 2 (or Visit 1) on the basis of the spirotel® data. For 2-Step Supervised Washout participants, these values are updated for a second time at Visit 1 because the participant will have been off ICS 3 weeks prior to Visit 1. These references will be used for the remainder of the study to determine when a participant's asthma is worsening and a participant meets treatment failure criteria. The baseline peak flow and rescue use values are defined at Visit 2 (or Visit 1 for Supervised Washout Participants) as follows:

<u>Baseline Peak Flow (PEF)</u>
At Visit 2 (or Visit 1 for Supervised Washout participants), the baseline PEF is defined as the average pre-bronchodilator AM PEF value recorded during the two weeks prior to the visit. This is further defined as the average of the pre-bronchodilator AM PEF values recorded the 14 days prior to Visit 2 (or Visit 1), including the AM PEF value from the morning of Visit 2 (or Visit 1), rounded to the nearest liter/minute. If a participant used his/her ProAir® RESCUE inhaler within 4 hours of an AM PEF measurement, the value will be excluded from the calculations. Missing AM PEF values in the 14 day interval will also be excluded from the calculation. It is possible that a participant's baseline PEF value may be based on fewer than 14 days' worth of data.

The Spirotel® Baseline Report generated at Visit 2 (or Visit 1 for Supervised Washout participants), after uploading data from the participant's device, summarizes the participant's baseline PEF and 65% Baseline PEF. The 'Baseline PEF' value will also be programmed into the spirotel® device at Visit 2 (or Visit 1), updated on the Participant Identification Card (P6_ID/P6_ID_2) and several participant handouts, and the 65% Baseline PEF will be printed on several participant handouts.

Once established at Visit 2 (or Visit 1 for Supervised Washout participants), the participant's Baseline PEF value will not change for the remainder of the trial.

Baseline Rescue Use Value

At Visit 2 (or Visit 1 for Supervised Washout participants), the baseline rescue use value is defined as the average daily use of albuterol (ProAir® RESCUE inhaler) during the last 2 weeks prior to the visit. This is further defined as the average daily RESCUE inhaler puffs used during the 14 days prior to Visit 2 (or Visit 1), rounded to the nearest puff. Missing daily rescue use puffs in the 14 day interval will be excluded from the calculation. It is possible that a participant's baseline rescue use value may be based on fewer than 14 days' worth of data.

The SIENA Spirotel® Baseline Report generated at Visit 2 (or Visit 1 for Supervised Washout participants), after uploading data from the participant's device, summarizes the participant's Baseline Rescue Use and High Weekly Rescue Use values. The 'Baseline Rescue Use' value will also be programmed into the spirotel® device at Visit 2 (or Visit 1), updated on the Participant Identification Card (P6_ID/P6_ID_2) and several participant handouts, and the Weekly High Rescue Inhaler Use value will be printed on several participant handouts. The High Weekly Rescue Use value, equal to two times the baseline weekly rescue use, determines when a participant meets treatment failure conditions.

Once established at Visit 2 (or Visit 1 for Supervised Washout participants), the participant's baseline rescue use value will not change for the remainder of the trial.

For Supervised Washout Participants who require Visit 1 Continuation, the P6_BASELINE form generated at the Continuation visit (containing all of the Visit 1 spirotel® data) should be entered into the database and sent to the DCC.

2.11 Blood draw for CBC

Visit 1, 2, 2A
Obtain blood for CBC/differential (one purple-top tube)

CBC/Differential Procedures
The order of the blood draws, as specified on the Visit Procedure Checklists, must be observed.

For eligible participants only, fill one 4 mL purple-top tube with blood for CBC/differential determination. These samples will be analyzed in the performance site's local lab. Samples should be labeled according to local requirements and transported to the lab within **two hours** of the blood draw.

After the results are available, record the participant's CBC/differential values on the P6_LAB form. Note that absolute eosinophil values must be recorded in number of cells per µL (or mm3). No other units are acceptable. Any necessary conversions must be made prior to recording data on the form and entering the data into the study database.

A copy of the local lab report should be forwarded to the DCC with the P6_LAB form. All identifying information (name, medical record number, etc.) must be blackened out prior to sending the report to the DCC. Include the participant's ID number on the report.

Refer to Section 4 for more details on how to complete the P6_LAB form.

2.12 Blood draw for Periostin and ImmunoCAP/Total IgE

Visit 1
Obtain blood for ImmunoCAP/IgE determination, periostin, backup serum (one 8.5 mL tiger top (SST) tube)
Log ImmunoCAP/IgE serum (P6_IGE_SAMP_LOG)
Log Periostin serum (P6_PERI_SAMP_LOG)
Log Backup serum (P6_SERUM_SAMP_LOG)
Enter ImmunoCAP/IgE serum sample data into Biological Sample Tracking module
Enter Periostin serum sample data into Biological Sample Tracking module
Enter backup serum sample data into Biological Sample Tracking module

Visit 2, 2A
Obtain blood for periostin, backup serum (one 8.5 mL tiger top (SST) tube)
Log Periostin serum sample (P6_PERI_SAMP_LOG)
Log Backup serum (P6_SERUM_SAMP_LOG)
Enter Periostin serum sample data into Biological Sample Tracking module
Enter backup serum sample data into Biological Sample Tracking module

Supplies
The following supplies are required to collect the serum samples for periostin, ImmunoCAP/Total IgE and backups at Visits 1, 2 and 2A:

Item	Vendor	Catalog #	# Per Collection
8.5 ml tiger top serum separator tube (SST) (BD #367988)	Fisher Sci.	0268396	1
SST label (Avery #5160)	Staples	209882	1
Sterile pipette			1
For Periostin and Back-up Serum			
2.5 mL false-bottom Sarstedt tube (provided by DCC)	Sarsdtedt	60.614.010	2
Sarstedt screw cap (provided by DCC)	Sarsdtedt	65.163	2
Fiberboard storage box for cryovials (Fisherbrand Cryo/Freezer boxes, 5x5x3“ with 49 cells; no substitutes)	Fisher Sci.	03-395-456 03-395-460	2 boxes 2 49 cell dividers

For ImmunoCAP/Total IgE (Visit 1 Only) and Back-up Serum			
2.0 ml self-standing Saf-T-Seal screw cap tube, natural (USA Scientific, no substitutions)	Fisher Sci.	1420-9700	2
Fiberboard storage box for cryovials (Fisherbrand Cryo/Freezer boxes, 5x5x2“ with 81 cells; no substitutes)	Fisher Sci.	03-395-464	2 boxes with 81 cell dividers
White Laser Cryo-Tags barcode label (Cryo-Tags 1.5”x0.75”)	Diversified Biotech	LCRY-1200	2

Processing

1. Fill one 8.5 mL tiger top (red/grey stopper) vacutainer with the participant’s blood. The vacutainer must be labeled with participant ID, initials and visit number. A template for labels for the red-top tubes (Avery #5160) can be found on the AsthmaNet secure website in the Protocols: SIENA: Labels folder.

2. Complete an entry for the blood draw on the:

   a. SIENA Periostin Serum Sample Log (P6_PERI_SAMP_LOG);
   b. SIENA ImmunoCAP/IgE Serum Sample Log (P6_IGE_SAMP_LOG) – Visit 1 Only;
   c. SIENA Serum Sample Log (P6_SERUM_SAMP_LOG).

   Complete the participant’s SIENA ID number and collection date/time.

3. Invert the SST 5 times. Allow the blood sample to clot at room temperature for 20 minutes to 1 hour.

4. While the blood is clotting, prepare the 2.5 mL false-bottom tubes (provided by the DCC) and 2.0 ml cryovials (specified in the above table; no substitutions) for the participant’s serum samples.

   Periostin: Label one 2.5 mL false-bottom tube with a SIENA Periostin barcode label (also provided by the DCC). The barcode label includes a pre-printed 11-digit barcode number, starting with “S1486”. Labels should be placed vertically on tube so that the barcode can be scanned. The length of the label is 2”. The sample type associated with this tube in the BST module is “SIENA Periostin”. The SIENA Periostin label appears as follows:

ImmunoCAP/Total IgE (Visit 1 Only): Label one 2 mL cryovial with a SIENA ImmunoCAP/IgE barcode label (Cryo-Tag) generated through the Biological Sample Tracking (BST) module of the AsthmaNet database management system. The barcode label includes a pre-printed 10-digit barcode number, starting with "6IMCAP". Labels should be placed vertically on tube so that the barcode can be scanned. The length of the label is 1.5" so the label should be placed as high as possible (just under the screw top). The sample type associated with this tube in the BST module is "SIENA ImmunoCAP". The SIENA ImmunoCAP/IgE label appears as follows:

Serum: At Visit 1, label one 2.5 mL false-bottom tube and one 2 mL cryovial with a SIENA Serum label. At Visits 2 and 2A, label one 2.5 mL false-bottom tube and two 2 mL cryovials with a SIENA Serum label. The barcode label includes a pre-printed 9-digit barcode number, starting with "6SER". Labels should be placed vertically on tube so that the barcode can be scanned. The length of the label is 1.5" so the label should be placed as high as possible on the 2 mL cryovial (just under the screw top). The sample type associated with this tube in the BST module is "SIENA Serum". The SIENA Serum label appears as follows:

5. At the end of the clotting period, complete the time spinning is initiated on P6_PERI_SAMP_LOG, P6_IGE_SAMP_LOG (Visit 1 Only) and P6_SERUM_SAMP_LOG. Centrifuge the clotted blood at 1000-1300 RCF (*g*) for 10 minutes to separate the serum from the red blood cells.

6. Using a sterile pipette, carefully remove the serum from above the clot and aliquot as follows at these visits:

   Visit 1:

Periostin:	*Aliquot* 0.5 mL into the 2.5 mL false-bottom tube with Periostin label (barcode starting with "S1486")
ImmunoCAP:	*Aliquot* 1.25 mL into 2 mL cryovial with ImmumoCAP label (barcode starting with "6IMCAP")
Serum:	*Aliquot* 0.5 mL into the 2.5 mL false-bottom tube AND

Aliquot up to 1.25 mL into one 2 mL cryovial, both with Serum label (barcode starting with "6SERUM")

Visits 2, 2A:

Periostin: *Aliquot* 0.5 mL into the 2.5 mL false-bottom tube with Periostin label (barcode starting with "S1486")

Serum: *Aliquot* 0.5 mL into the 2.5 mL false-bottom tube AND

Aliquot 1 mL into two 2 mL cryovials, both with Serum label (barcode starting with "6SER")

7. Screw each tube shut. Be sure the cap is secure.

8. Access the BST module and scan the barcodes to insert record for all the samples. Input the participant ID information to link the barcodes to the correct SIENA participant. It is imperative that all samples be scanned the day of collection so that they are associated with the correct participant ID and are available for inclusion in the next shipment. For details on accessing and interacting with the BST Module in the AsthmaNet Database Application, see the AsthmaNet Computing and Networking Environment details in Section 7 of the AsthmaNet General Manual of Operations.

9. Record sample barcode number and sample volume on P6_PERI_SAMP_LOG, P6_IGE_SAMP_LOG (Visit 1 Only) and P6_SERUM_SAMP_LOG.

10. Store the samples as follows:

    Periostin: Store in one 5x5x3 chipboard storage box. These samples will be shipped to UCSF at the end of the study. See the shipping instructions and schedule in the Shipping: Periostin discussion in this section.

    ImmunoCAP/IgE (Visit 1 Only): Store in one 5x5x2 chipboard storage box. These samples will be shipped to ADx labs in Denver every 6 months. See the shipping instructions and schedule in the Shipping: ImmunoCAP/Total IgE discussion in this section.

    Serum: Store 2 mL cryovials in one 5x5x2 chipboard storage box and 2.5 mL false-bottom tubes in one 5x5x3 chipboard storage box. These samples should be in separate boxes from the Periostin and ImmunoCAP samples. These samples will be stored at the site as backups.

11. Store the serum samples at -80° C until the shipment day. Record the date/time the sample is placed in the freezer and the current freezer temperature on P6_PERI_SAMP_LOG, P6_IGE_SAMP_LOG (Visit 1 Only) and P6_SERUM_SAMP_LOG.

See Shipping – ImmunoCAP/Total IgE and Shipping – Periostin discussions in this section for details on shipping these samples.

2.13 Certification

Study Coordinators and Technicians
Coordinators who carry out SIENA study visits must be certified to do so. That is, personnel who complete pregnancy tests (PREG_TEST form) or any of the protocol-specific SIENA forms (designated by a P6 prefix in the form name) must possess SIENA protocol certification, as well as certification in Human Subjects Protection Training, HIPAA and Good Clinical Practice. Note that protocol-specific forms include completion of the SIENA Pulmonary Procedure Checklist (P6_PULMONARYCHK).

To obtain SIENA coordinator certification, clinic personnel must complete the following steps:

- Thoroughly read the SIENA protocol and this Manual of Operations.
- Pass the SIENA coordinator certification exam. This exam can be found on the AsthmaNet secure website in the Certification: SIENA folder. Exams should be completed, scanned into a pdf file, and e-mailed to the AsthmaNet-Certification alias. Include 'SIENA Exam' and your performance site number on the subject line of the e-mail message to ensure efficient processing and routing at the DCC.

Any individual who performs spirotel® procedures, spirometry, sputum induction, methacholine challenge, eNO testing or inhaler technique assessment as part of a SIENA visit must be AsthmaNet certified in these procedures or be supervised by a certified technician, as applicable. Certification for these procedures is tracked independently of SIENA study certification. It is acceptable for these procedures to be performed during the SIENA study by technicians who possess only individual procedure certification and not SIENA protocol certification, but it is preferred that technicians review the protocol and take the certification exam, as well. If a technician is only certified in spirometry and not in the SIENA protocol, a SIENA-certified coordinator must complete the SIENA Pulmonary Procedure Checklist (P6_PULMONARYCHK) to qualify participants for spirometry and methacholine challenge testing.

Protocol deviations will be assigned when an uncertified individual performs protocol-related tasks or carries out procedures for which he/she is uncertified. Protocol violations will be assigned if this persists at a given site over a period of time. The AsthmaNet Quality Control Committee (QCC) will be informed of continued neglect of appropriate certification procedures.

The quality of AsthmaNet data is tracked and reported on a regular basis to the individual performance sites, clinical center partnerships, the AsthmaNet Quality Control Committee (QCC), and to the Data and Safety Monitoring Board (DSMB). It is possible to become decertified in some of the procedures (e.g., spirometry, sputum induction) if lack of quality becomes an issue and the study data begins to be affected adversely. The DCC will contact individuals who are in danger of becoming decertified to discuss

the situation before they are decertified formally in the certification tracking system. It is also possible to become decertified if a coordinator or technician leaves the Network and returns later, not having performed spirometry or other procedures for an extended period of time. See the individual procedure MOPs in the AsthmaNet General MOP for details.

Licensed Medical Practitioners (LMPs)
Physicians who are listed on the local IRB application as 'key personnel' must take and pass the SIENA physician certification exam before interacting with study participants. The physician exam is located on the secure website in folder Certification: SIENA.

Non-physician LMPs, such as nurse practitioners and physician's assistants, may perform physical exams for the SIENA study (see the Physical Exams discussion in this section for details). If these individuals will be performing exams for SIENA participants on a regular basis, then they should take either the coordinator or the physician exam and become certified. If they fill in for study physicians only occasionally, then certification is not required. Note that certification requirements for non-physician LMPs will vary from study to study.

Data Entry Personnel
Individuals who are only providing data entry support for the SIENA study and are not collecting data or performing study procedures do not have to meet any specific AsthmaNet certification requirements. However, it should be ensured that local institutional requirements for these individuals (e.g., HIPAA, GCP, and Human Subjects' Protection) have been met and are clearly documented on-site. This documentation may be subject to audit during an AsthmaNet site visit.

2.14 Concomitant Medications

Participants in AsthmaNet protocols are likely to be taking medications for asthma and allergy-related symptoms, both over-the-counter and prescription. It is important to document the medications a participant is taking, or begins to take, throughout the study to ensure that he/she is not taking medications that are excluded during the trial because they may confound the study results. Further, it is important to document any non-study asthma medications the participant begins using during the trial, as such use may indicate that the participant has experienced, or is experiencing, a significant asthma exacerbation.

The SIENA trial will employ the two standard concomitant medications forms: Concomitant Medications for Asthma/Allergy and Adverse Events (CMED) and Concomitant Medications for Non-Asthma Drugs (CMED_NON).

Medications taken for treatment of adverse events, both asthma-related and those unrelated to asthma, should be recorded on the CMED form. Medications taken for treatment of asthma/allergy symptoms, other than dispensed study medications, should also be recorded on this form.

Medications not taken for asthma, allergies or adverse events should be recorded on the CMED_NON form. Examples include multivitamins and herbs the participant is taking for health maintenance and maintenance drugs taken for a pre-existing condition (e.g., Paxil for depression). Other non-asthma, non-allergy drugs the participant takes chronically, such as oral contraceptives, should also be recorded on this form.

Study medications, including ProAir® rescue medication (i.e., albuterol) and blinded Respimat® and Twisthaler®/MDI inhalers, should not be regarded as concomitant medications and should not be recorded on CMED or CMED_NON. Open-label Asmanex® (YELLOW) inhaler taken for treatment failure and prednisone taken to treat an asthma exacerbation or other adverse event *should* be recorded on the CMED form as a concomitant medication and linked to the appropriate adverse event on the Clinical Adverse Events (AECLIN) form.

Non-study asthma medications (e.g, Advair, Flovent, etc.) are considered concomitant medications and should be recorded on the CMED form if they are prescribed during the study (note that these drugs are excluded during the study and their use should be avoided if at all possible).

The following classes of drugs/solutions/products do not need to be recorded on a participant's CMED or CMED_NON form:

- Anesthesia medications administered during surgery and outpatient procedures
- Sedatives used prior to and during procedures
- Novacaine and other dental anesthetics

- Solutions/drugs taken prior to specialized procedures [e.g., Golytely (Colye, Nulytely), phospho-soda, and sodium phosphate tablets (Osmo-Prep, Visicol) taken prior to colonoscopy, Glucola taken during an oral glucose tolerance test]
- Iodine dye and other contrast materials used for MRIs and other procedures
- Allergy shots (i.e., immunotherapy injections)
- Vaccinations (e.g., flu vaccine)

Visit 1 (or Visit 0A for Supervised Washout Participants)

Record concomitant medications the participant has taken since the informed consent was signed on the appropriate concomitant medications (CMED, CMED_NON) form

Thorough questioning about medication use during the initial study visit will prevent the presentation of unexpected information when it is time to randomize a participant. It also will help to prevent misinterpretation of medications reported at subsequent contacts, particularly if the participant interacts with a different coordinator.

During the first visit, prompt participants with the following questions:

- What over-the-counter medications do you typically take during a given month, including continuous use and as-needed medications, such as laxatives, antacids, stool softeners, ibuprofen, etc.? Inquire about the participant's use of vitamins and herbal remedies. Use of certain herbs, such as St. John's wort or valerian, during study participation should be discouraged.
- What prescription medications do you typically take during a given month, including continuous use and as-needed medications?
- What over-the-counter medications do you typically pack when you go on vacation or away for business? What prescription medications?
- What over-the-counter medications do you keep in your desk drawer or purse? What prescription medications?

If the participant has taken any medications for asthma or allergies or adverse events that have occurred since he/she (or his/her parent or guardian) signed the informed consent (original signature date), record them on the Concomitant Medications for Asthma/Allergy and Adverse Events (CMED) form. Medications taken on the day of Visit 1 (or Visit 0A for Supervised Washout participants) should be recorded even if the participant has agreed to stop taking them after completing the visit. List the consent date as the start date for the medication (i.e., when the use of the medication became concomitant with study participation) if the participant started taking the drug prior to his/her original consent signature date.

Note: SIENA requires that participants who will need an intranasal steroid during the study begin using one as of Visit 1. These drugs also must be listed on CMED.

Any medications that were used to treat conditions other than asthma, allergies or adverse events since the participant (or his/her parent or guardian) signed the informed consent should be recorded on the Concomitant Medications for Non-Asthma Drugs (CMED_NON) form. This includes substances like multivitamins, vitamin D and calcium supplements, and herbs the participant is taking for health maintenance. It also includes maintenance drugs for a pre-existing condition (e.g., Paxil for depression or insulin for diabetes) and other drugs the participant takes chronically, such as oral contraceptives.

Probing for medication use during Visit 1 (and Visit 0A for Supervised Washout Participants) affords an opportunity to recognize clinically significant medical problems early in the study. For example, a participant may take several medications to treat hypertension. The participant's condition may be deemed unstable and poorly controlled, therefore, ineligible on the basis of the information collected for the concomitant medications form. If a participant is taking medications for a condition that may exclude him/her from study participation, first check the SIENA Exclusionary Medical Conditions (P6_EXCLMED) reference card. If the applicable condition is not listed specifically, contact the DCC for guidance.

When scheduling Visit 1 (or Visit 0A for Supervised Washout participants), the potential participant should be asked to bring all over-the-counter and prescribed medications and supplements he/she is currently taking to the visit. Alternatively, the participant may write down the names of the medications and supplements and the date he/she started taking each medication and bring this list to the visit.

Note that participants must wash out of inhaled and oral corticosteroids, leukotriene modifiers, antibiotics, etc. for a period of time prior to Visit 1. See the Eligibility Criteria discussion in this section for more details. Some institutions require that participants read and sign the study informed consent document prior to washing out of medications for purposes of study enrollment.

Visits 2-9 (as well as Visits 0B, 1 for Supervised Washout participants)
Follow up medication use from the previous visit and record any new concomitant medications (CMED, CMED_NON)

Each time the clinic has contact with a participant, whether for a scheduled visit or phone contact, impromptu visit, or unexpected phone call, information on concomitant medications should be collected. During these contacts, the concomitant medication information obtained during previous contacts should be updated. If the participant discontinued a medication that he/she was taking, update the stop date on the CMED or CMED_NON form, as appropriate. Probe the participant for any new medications that may have been taken and record these on the appropriate form for the next visit. If the participant began taking a new medication for a condition or disease that existed prior to study enrollment and no adverse event (i.e., worsening of the condition) is associated with the change in medication, record this information on the CMED_NON form. If the

participant has not taken any new medications for asthma, allergy or an adverse event, mark the 'None' box on the CMED form for the applicable visit.

Visit 9 and other early termination visits

Medications that are still in use at the time of the final study visit or contact should be left open for stop dates. On the CMED form, these are coded as 'ongoing at final visit' (Q1090 = 1). On the CMED_NON form these are coded as 'ongoing at end of study.' During the participant's final visit or contact with the clinical site, finalize his/her CMED and CMED_NON forms. All CMED forms for a given individual should be forwarded to the DCC following his/her study termination. CMED_NON forms are not sent to the DCC.

2.15 Contact Information

Visit 1 (or Visit 0A for Supervised Washout Participants)
Administer Adult or Pediatric Participant Contact Information form (CONTACT_ADULT or CONTACT_PED)

Administer the following Contact Information form depending on the participant's age track:

- Ages 12-17: CONTACT_PED
- Ages 18+: CONTACT_ADULT

Adult Participant Contact Information form (CONTACT_ADULT)
The Adult Participant Contact Information (CONTACT_ADULT) form is completed by the participant. The purpose is to collect pertinent participant identification information such as full name, address, and telephone number, as well as alternative ways to contact the participant through work, family, or friends. It also includes contact information for the participant's health care provider.

Pediatric Participant Contact Information form (CONTACT_PED)
The Pediatric Participant Contact Information (CONTACT_PED) form is completed by the participant's parent or guardian. Its purpose is to collect pertinent participant identification information such as full name, address, and telephone number. The parent/guardian's information is also collected, along with contact information for the participant's pediatrician and asthma care doctor. Contact information for alternative contacts (family, friends, neighbors) is also collected.

General Information

- This form serves as source documentation proving the existence of the participant. It **must** be completed.
- A space for the participant's social security number (and parent/guardian social security numbers for pediatric participants) has been included on the form for the convenience of the performance site in paying participant stipends. This field may be left blank if institutional policies prohibit recording and storing this information with the clinical records, or if social security number is not needed.
- It is important to obtain complete and accurate phone number information for the participant during Visit 1 (or Visit 0A for Supervised Washout participants). The participant or his/her parent/guardian will need to be contacted via phone if they miss a visit and for phone contacts as part of the SIENA trial.
- Store the CONTACT_ADULT or CONTACT_PED form in the participant's study folder; do not forward it to the DCC. This form contains the participant's name, address, and other identifying information. A protocol violation may be assigned if this form is misdirected to the DCC or another off-site group affiliated with AsthmaNet (e.g., sputum lab, ADx Lab, etc.).

2.16 Continuation Visit 1

If participant does not reverse ≥ 12% at Visit 1 and does not have source documentation within the past 6 months for an overread AsthmaNet methacholine challenge with PC20 ≤ 16 mg/ml, Visit 1 will be stopped following post-albuterol spirometry testing and a continuation visit will be scheduled. Continuation visit should try to be scheduled to take place within 24-48 hours, and within 7 days maximum. No Visit 1 data should be entered into the database unless/until the participant's eligibility is confirmed at the continuation visit. Exclusion criteria assessed at the initial Visit 1 apply to the continuation Visit 1 as well (i.e. respiratory infection in past 4 weeks, medication exclusions, etc.). Review Eligibility Checklist 1 and 2 to be sure nothing has changed, and participant still meets eligibility criteria at Continuation Visit 1. Visit will start with completing Urine Pregnancy Test (PREG_TEST) form for all female participants, administering urine pregnancy test if necessary, followed by the completion of the Pulmonary Procedure Checklist (P6_PULMONARYCHK), FeNO testing (ENO) and spirometry testing (SPIRO).

Participants must pass all of the checks on the SIENA Pulmonary Procedure Checklist (P6_PULMONARYCHK) and the appropriate Methacholine Challenge Testing Checklist (METHACHK_ADULT or METHACHK_PED) before proceeding with the challenge. Results of the challenge are recorded on the Methacholine Challenge Testing (METHA) form and are referenced on SIENA Eligibility Checklist 3 (P6_ELIG3). The methacholine challenge report generated through the MedGraphics system must be printed and submitted with the data forms.

If an individual does not meet all the criteria on the Adult Methacholine Challenge Testing Checklist (METHACHK_ADULT) at Visit 1 continuation visit, the participant is ineligible to continue participation in SIENA. Likewise, participants who qualify for the methacholine challenge but do not meet the PC20 criterion for eligibility (PC20 ≤ 16 mg/ml) are also ineligible for the SIENA study. In these cases, data collected at Visit 1 for Supervised Washout participants should be data entered and submitted to the DCC, a SIENA Termination of Study Participant form (P6_TERM) should be completed, and study termination procedures followed. Data collected at Visit 1 for non-Supervised Washout participants should not be entered, and the Visit 1 packet should be filed in the participant's study folder. See the discussion of Withdrawals in this section for further details.

If the participant meets the methacholine challenge criteria (PC_{20} ≤ 16 mg/ml), he or she will continue with Visit 1 procedures. All Visit 1 data collected at the initial Visit 1 and the continuation visit should be entered into the study database. See Section 4 of this manual for information concerning entry of the forms completed at these visits.

Supervised Washout Participants
For Supervised Washout participants who require a Continuation Visit 1, cleaned turbine will need to be replaced in spirotel® device and spirotel® QC performed before participant leaves clinic. spirotel® device should be returned to participant with return

visit number (1) and baseline reference values unchanged. Asthma Monitoring Log (P6_ASTHMA_LOG) should also be returned to participant.

For Supervised Washout participants who require a Continuation Visit 1, two Visit 1 SPIROTELQCs will be performed – one at the original Visit 1 and one at the Continuation visit. Both should be entered into the database. The original Visit 1 SPIROTELQC should be entered as a single form and the SPIROTELQC performed at the Continuation visit should be entered with the visit packet. At the original Visit 1 visit, return the spirotel® device to the participant with the same visit ID (1) and baseline values programmed. All Visit 1 spirotel® data (from the original Visit 1 and the Continuation visit) should be uploaded to the Central Database. For the P6_ELIG_RPT, the spirotel report generated at the original Visit 1 visit (containing just the spirotel® data since Visit 0B) should be entered into the database (and used for the P6_ELIG1 form) and sent to the DCC. For the P6_COMPLY_RPT and P6_BASELINE form, only the spirotel reports generated at the Continuation visit (containing all of the Visit 1 spirotel® data) should be entered into the database and sent to the DCC.

2.17 Daily Activities Handout

Visit 0A
Complete and distribute Daily Activities Handout (P6_DAILYACT0A_1STEP or P6_DAILYACT0A_2STEP)

Near the end of Visit 0A, review SIENA Washout Flowchart (P6_WASH_FLOW) to determine 1-Step or 2-Step Washout, then review the appropriate summary handout "SIENA Daily Activities (Visit 0A – 1-Step)" (P6_DAILYACT0A_1STEP) or "SIENA Daily Activities (Visit 0A – 2-Step)" (P6_DAILYACT0A_2STEP). For participants in the 2-Step Supervised Washout, this handout summarizes what the study participant must carry out each day until Visit 0B. For participants in the 1-Step Supervised Washout, this handout summarizes what the study participant must carry out each day until Visit 1. The following should be completed:

- *2-Step Washout Only:* The number of puffs the participant should take from the inhaler, as well as the name of the medication, in the blank spaces provided on page 1 of P6_DAILYACT0A_2STEP. Participant's current ICS dose will be halved at Visit 0A adhering to the standard recommended BID or QD dosing schedule (i.e., BID for all ICS except mometasone which may be BID or QD).
    - If a participant is taking 2 puffs BID of his/her current inhaler at the time of Visit 0A, the participant's new daily dose should be 1 puff BID from his/her current inhaler.
    - If a participant is taking 1 puff Flovent 100 mcg BID at the time of Visit 0A, the participant's new daily dose should be 1 puff 50 mcg BID.
    - If a participant is taking 1 puff Asmanex 110 mcg BID at the time of Visit 0A, the participant's new daily dose should be 1 puff Asmanex 110 mcg QD from his/her current inhaler.
- 65% of the participant's Baseline PEF value, calculated from Q1000 on the Baseline PEF and Rescue Use Values form (P6_BASELINE), in the blank space provided on page 2 of P6_DAILYACT0A_1STEP or P6_DAILYACT0A_2STEP. Multiply Q1000 by 0.65 to get this value.

Review the handout and confirm that the participant understands how to monitor his/her asthma.

Visit 0B (for 2-Step Supervised Washout participants)
Complete and distribute Daily Activities Handout (P6_DAILYACT0B)

Near the end of Visit 0B, remove the "SIENA Daily Activities (Visit 0A – 2-Step)" handout (P6_DAILYACT0A_2STEP) from the participant's folder and discard it. Obtain a copy of the "SIENA Daily Activities (Visit 0B)" (P6_DAILYACT0B) handout and review with participant. This handout summarizes what the study participants must carry out each day until Visit 1. The following should be completed:

- 65% Baseline PEF value, as printed on the SIENA spirotel® Baseline Report, in the blank space provided on page 2.

Review page 2 of the handout and confirm that the participant understands how to monitor his/her asthma.

Visit 1 (for Supervised Washout Participants)
Complete and distribute Daily Activities Handout (P6_DAILYACT1)

Near the end of Visit 1, remove the "SIENA Daily Activities (Visit 0B)" handout (P6_DAILYACT0B) from the participant's folder and discard it. Obtain a copy of the "SIENA Daily Activities (Visits 1-3)" (P6_DAILYACT1) handout and review with participant. This handout summarizes what the study participants must carry out each day of the run-in phase until Visit 3. The following should be completed:

- 65% Baseline PEF value, as printed on the SIENA spirotel® Baseline Report, in the blank space provided on page 2.
- Weekly High Rescue Use value, as printed on the SIENA spirotel® Baseline Report, in the blank space provided on page 2. Note: If a participant's Weekly High Rescue Use value is 0, the underlined portion of this statement should be blacked out: "Use albuterol for relief of symptoms daily for 7 days and this use exceeds____puffs".

Review page 2 of the handout and confirm that the participant understands how to monitor his/her asthma.

Visit 1 (for participants not in Supervised Washout)
Complete and distribute Daily Activities Handout (P6_DAILYACT1)

Near the end of Visit 1, review the summary handout "SIENA Daily Activities (Visit 1)" (P6_DAILYACT1). This handout summarizes what the study participants must carry out each day of the run-in phase until Visit 3. The following should be completed:

- 65% of the participant's Baseline PEF value, calculated from Q1000 on the Baseline PEF and Rescue Use Values form (P6_BASELINE), in the blank space provided on page 2. Multiply Q1000 by 0.65 to get this value.
- Weekly High Rescue Use value, calculated from Q1010 on the Baseline PEF and Rescue Use Values form (P6_BASELINE), in the first blank space provided on page 2. Multiply Q1010 by 14 to get this value. Note: If Q1010 is 0, the underlined portion of this statement should be blacked out: "Use albuterol for relief of symptoms daily for 7 days and this use exceeds puffs".

Review page 2 of the handout and confirm that the participant understands how to monitor his/her asthma.

Visits 2 (for participants not in Supervised Washout)

Update and review Daily Activities Handout (P6_DAILYACT1)

For participants who started SIENA at Visit 1, the following should be updated at Visit 2:

- 65% Baseline PEF value, as printed on the SIENA spirotel® Baseline Report, in the blank space provided on page 2.
- Weekly High Rescue Use value, as printed on the SIENA spirotel® Baseline Report, in the blank space provided on page 2. Note: If a participant's Weekly High Rescue Use value is 0, the underlined portion of this statement should be blacked out: "Use albuterol for relief of symptoms daily for 7 days and this use exceeds____puffs".

Visits 2A
Review Daily Activities Handout (P6_DAILYACT1)

Visit 3
Complete, distribute and review Daily Activities Handout (P6_DAILYACT3_2)

Near the end of Visit 3, remove the "SIENA Daily Activities (Visits 1-3)" handout (P6_DAILYACT1) from the participant's folder and discard it. Obtain a copy of the "SIENA Daily Activities (Visit 3-9)" (P6_DAILYACT3_2) handout. This reference lists what the participant must carry out each day until Visit 9. The 65% Baseline PEF and Weekly High Rescue Use values from the last SIENA spirotel® Baseline Report (Visit 1 for Supervised Washout participants, and Visit 2 otherwise) should be completed on the blank spaces provided on page 2. Note: If a participant's Weekly High Rescue Use value is 0, the underlined portion of this statement should be blacked out: "Use albuterol for relief of symptoms daily for 7 days and this use exceeds____puffs". Review page 2 of the handout and confirm that the participant understands how to monitor his/her asthma and switch inhalers when empty.

Visits 4-8
Review Daily Activities Handout (P6_DAILYACT3/P6_DAILYACT_2)

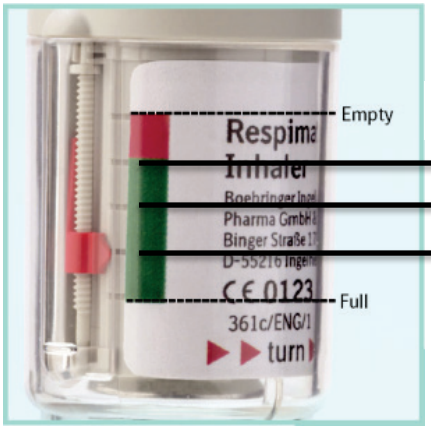
P6_DAILYACT3 is for participants randomized to Twisthaler; P6_DAILYACT3_2 is for participants randomized to MDI.

2.18 Dosing Compliance

Visits 2, 2A, 3
Check compliance with run-in Respimat® (P6_COMPLY)

The Respimat® has an indicator that shows the number of puffs remaining (out of a total of 60 puffs in a new Respimat®). This indicator will be used to assess the participant's compliance with dosing from the Respimat® during the run-in and randomized treatment phase. For both the run-in and randomized treatment phase, participants are instructed to take 2 puffs once daily in the morning from the Respimat®.

The indicator on the Respimat® appears as follows:



D (0 puffs remaining)
C (15 puffs remaining)
B (30 puffs remaining)
A (45 puffs remaining)
60 puffs

After the Respimat® has been prepared for first-time use, as explained on page 1 of the "How to Use Your Respimat® (First Use)" (HTRESP) handout, the device will have 60 puffs (30 doses). The red indicator will be at the bottom of the indicator mark (labeled "Full" in the picture), with 60 puffs remaining.

Since there is no dose counter on the device, the markings will need to be used to calculate compliance, noting that the indicator line marked "A" represents 45 puffs remaining, the indicator line marked "B" represents 30 puffs remaining, the indicator line marked "C" represents 15 puffs remaining, and the indicator line marked "D" or "Empty" represents 0 puffs remaining. To best estimate the number of puffs remaining on the device, puffs will need to be "dumped" until one of these markings is reached. Number of puffs remaining in the device is then equal to the number of "dumped" puffs + the number of puffs remaining based on indicator. If puffs are "dumped" to get to Line:

- A: # of remaining puffs = # of "dumped" puffs + 45
- B: # of remaining puffs = # of "dumped" puffs + 30
- C: # of remaining puffs = # of "dumped" puffs + 15
- D: # of remaining puffs = # of "dumped" puffs + 0

The number of scheduled puffs should include all doses the participant should have taken since leaving the last clinic visit.

Compliance with dosing from the Respimat® is documented on the SIENA Compliance Checklist (P6_COMPLY) and entered into the study database.

Visits 4-9
Check compliance with Respimat® and Twisthaler®/MDI study inhalers (P6_COMPLY)

(For participants randomized to mometasone Twisthaler® device at Visit 3) The Twisthaler® contains a counter that shows the number of puffs remaining (out of a total of 60 puffs in a new Twisthaler®). The counter will be used to assess the participant's compliance with dosing from the Twisthaler® during the randomized treatment phase. Participants are instructed to take 2 puffs BID from the Twisthaler® during the randomized treatment phase.

(For participants randomized to mometasone MDI device at Visit 3) The MDI contains a counter that shows the number of puffs remaining (out of a total of 120 puffs in a new MDI). The counter will be used to assess the participant's compliance with dosing from the MDI during the randomized treatment phase. Participants are instructed to take 1 puff BID from the MDI during the randomized treatment phase.

Example Compliance Calculations
The following chart shows the number of Scheduled Respimat® and Twisthaler® puffs a participant should have taken between Visit 3 and Visit 4 (ideal 6-week interval). Visit 3 took place on 6/06/2014 and Visit 4 takes place on 7/19/2014. Two Respimat® devices were returned – one at Line D and the other between Lines A and B (dumping 13 puffs to reach Line B). Three Twisthaler® devices were returned – two with 0 puffs remaining and one with a counter value of 15.

Date	7/19 Visit day	7/18	7/17	7/16	7/15	7/14	7/13	7/12	7/11	7/10	7/09
Scheduled Twisthaler Puffs	2 – regular AM dose	4	4	4	4	4	4	4	4	4	4
Scheduled Respimat Puffs	2 – regular AM dose	2	2	2	2	2	2	2	2	2	2

Date	7/08 Visit day	7/07	7/06	7/05	7/04	7/03	7/02	7/01	6/30	6/29	6/28
Scheduled Twisthaler Puffs	4	4	4	4	4	4	4	4	4	4	4
Scheduled Respimat Puffs	2	2	2	2	2	2	2	2	2	2	2

Date	6/27	6/26	6/25	6/24	6/23	6/22	6/21	6/20	6/19	6/18	6/17
Scheduled Twisthaler Puffs	4	4	4	4	4	4	4	4	4	4	4
Scheduled Respimat Puffs	2	2	2	2	2	2	2	2	2	2	2

Date	6/16	6/15	6/14	6/13	6/12	6/11	6/10	6/09	6/08	6/07	6/06 Visit Day
Scheduled Twisthaler Puffs	4	4	4	4	4	4	4	4	4	4	2 – regular PM dose
Scheduled Respimat Puffs	2	2	2	2	2	2	2	2	2	2	0

Respimat® Compliance assessment (follow P6_COMPLY, Questions #2a-2d):

2a. Number of scheduled puffs (from above table): 86

2b. Number of remaining puffs (from Respimat® counters): 0 + 43 = 43

Remaining puffs on both returned Respimat devices should be added together to get total number of remaining puffs. On the second Respimat, 13 puffs were dumped to get to Line B, which means 43 (30 + 13) puffs remained on the device.

2c. Number of puffs taken:

The number of puffs taken is equivalent to the number of puffs packaged in the Respimat ® (or 60 puffs) x number of returned inhalers – the number of puffs remaining in the Respimat ®.

The number of puffs taken is equivalent to 60 x 2 inhalers – 43 = 77

2d. Percent compliance = # puffs taken / # puffs scheduled x 100

= 77 / 86 x 100
= 89.5%.

∴ Because the participant's compliance percentage exceeds the 75% goal laid out for the study, the participant is doing a good job of dosing with his or her Respimat®. He or she should be praised and encouraged to continue being diligent with taking study medications according to protocol.

Twisthaler®/MDI Compliance assessment (follow P6_COMPLY, Questions #3a-3d):

3a. Number of scheduled puffs (from above table): 172

3b. Number of remaining puffs (from Twisthaler®/MDI counters): 0 + 0 + 15 = 15

Remaining puffs on all returned Twisthaler®/MDI devices should be added together to get total number of remaining puffs.

3c. Number of puffs taken:

➔ Twisthaler®: The number of puffs taken is equivalent to the number of puffs packaged in the Twisthaler ® (or 60 puffs) x number of returned inhalers – the number of puffs remaining in the Twisthaler®.

➔ MDI: The number of puffs taken is equivalent to the number of puffs packaged in the MDI (or 120 puffs) x number of returned inhalers – the number of puffs remaining in the MDI.

In this Twisthaler® example, the number of puffs taken is equivalent to (60 x 3 inhalers) – 15 = 165

3d. Percent compliance = # puffs taken / # puffs scheduled x 100

= 165 / 172 x 100
= 95.9%.

∴ Because the participant's compliance percentage exceeds the 75% goal laid out for the study, the participant is doing a good job of dosing with his or her Twisthaler®. He or she should be praised and encouraged to continue being diligent with taking study medications according to protocol.

Visit 3 Compliance Calculation

Visit 2 Respimat® compliance will determine how to calculate Visit 3 compliance for eligibility:

- If a participant's Respimat® compliance is **≥75% at Visit 2**, Visit 3 Respimat® compliance will be assessed using data from the entire run-in.
- If a participant's Respimat® compliance is **<75% at Visit 2**, a minimum of 3 weeks will be required between Visits 2 and 3, and Respimat® compliance will be assessed using data from those 3+ weeks.

Example 1. Participant's compliance is ≥75% at Visit 2, so compliance data from Visits 2 and 3 will be combined for Visit 3 eligibility assessment. The participant did not complete a Visit 2A, so there is no data for that column.

	Visit 2	Visit 2A	Visit 3	Total
2a. Number of scheduled puffs since last visit (Q1030)	42		22	66
2c. Number of puffs taken (Q1050)	38		20	58

The Total column represents the sum of values for 2a and 2c across the completed visits.

% compliance during run-in = (Total # puffs taken / Total # puffs scheduled) x 100
= (58 / 66) x 100
= 87.9%

The resulting % compliance (87.9%) should be used to complete Q1110 on Eligibility Checklist 5 (P6_ELIG5). Because the participant's overall run-in compliance exceeds the minimum 75%, Q1110 would be answered yes to indicate he/she meets this eligibility requirement.

Example 2. Participant's compliance is <75% at Visit 2, so compliance data at Visit 2 will not be included in compliance calculation. Participant required a Visit 2A.

	Visit 2	Visit 2A	Visit 3	Total
2a. Number of scheduled puffs since last visit (Q1030)	~~42~~	42	22	66
2c. Number of puffs taken (Q1050)	~~31~~	35	20	55

The total column represents the sum of values for 2a and 2c across Visits 2A and 3.

% compliance after Visit 2 = (Total # puffs taken / Total # puffs scheduled) x 100
= (55 / 66) x 100
= 83.3%

The resulting % compliance (83.3%) should be used to complete Q1110 on Eligibility Checklist 5 (P6_ELIG5). Because the participant's compliance between Visits 2 and 3 exceeds the minimum 75%, Q1110 would be answered yes to indicate he/she meets this eligibility requirement.

2.19 Eligibility Criteria for Supervised Washout

Visit 0A
Complete Eligibility Checklist 0A (P6_ELIG0A)

Participants who are well-controlled and who are taking low-dose ICS (equivalent of BDP 80-240 mcg/day), intermittent ICS (<5 days/week), intermittent ICS/LABA (<5 days/week) or LTRA may be withdrawn from their asthma controller medication prior to enrollment into the Run-in. Visit 0A assesses the participant's eligibility for the Supervised Washout and also screens for Visit 1 eligibility. If the participant meets all of the eligibility criteria on SIENA Eligibility Checklist 0A (P6_ELIG0A), the participant will either undergo a 1-Step or 2-Step Washout. Participants on low-dose ICS whose dose can be halved, adhering to the standard recommended BID or QD dosing schedule (i.e., BID for all except mometasone which may be BID or QD), will enter the 2-Step Washout. In the 2-Step Washout, the participant's current ICS dose will be cut in half, the participant will be given a spirotel®, and will return to the clinic in two weeks for Visit 0B. Participants on low-dose ICS that cannot be halved, intermittent ICS, intermittent ICS/LABA or LTRA will enter the 1-Step Washout. In the 1-Step Washout, the participant's medication will be discontinued, the participant will be given a spirotel®, and will return to the clinic in three weeks for Visit 1.

Participants who pass all the eligibility checks on P6_ELIG0A and successfully complete Visit 0A are formally enrolled in the SIENA study. Data for these participants should be entered into the SIENA database and forwarded to the DCC.

Participants who do not meet all of the eligibility checks on P6_ELIG0A are not eligible for study enrollment. Forms that were completed at Visit 0A should not be entered into the study database or forwarded to the DCC; they should be filed in the participant's study folder at the performance site.

Participants should review the data recorded on P6_ELIG0A and initial/date the source documentation box on the form.

Visit 0A Inclusion Criteria

- For participants ages 18 and over: Ability to provide informed consent, as evidenced by the signing of a copy of the SIENA study consent form approved by the study institution's Committee on Human Subjects' Research (i.e., Institutional Review Board).

  For participants ages 12-17: Ability of parent or guardian to provide informed consent, as evidenced by signing a copy of the consent form approved by the study institution's Committee on Human Subjects' Research (i.e., Institutional

Review Board). Verbal or written assent by the minor participant should be documented according to local institutional guidelines.

The informed consent (and assent, as applicable) documents must be signed on or before the Visit 0A date.

See the discussion of Informed Consent in this section for further details.

This criterion is documented in Q1000, Q1010, and Q1020 on P6_ELIG0A.

- Male or female, age 12 and older as of Visit 1.

  This criterion is documented in Q1040 on P6_ELIG0A.

- Inhaled corticosteroid or combination inhaled corticosteroid/LABA use in past 3 weeks

  This criterion is documented in Q1043 on P6_ELIG0A.

- Leukotriene antagonist use in past 3 weeks

  This criterion is documented in Q1045 on P6_ELIG0A.

- A history over past 3 months of ICS ≤ BDP 80-240 mcg/day (or equivalent), OR ICS < 5 days/week

  This criterion is documented in Q1050 – Q1070 on P6_ELIG0A.

- A history over past 3 months of combination ICS/LABA < 5 days/week

  This criterion is documented in Q1073 and Q1075 on P6_ELIG0A.

- A history over past 3 months of daytime asthma symptoms ≤ 2 days/week

  This criterion is documented in Q1080 and Q1090 on P6_ELIG0A.

- A history over past 3 months of nighttime awakenings due to asthma ≤ 2 times/month

  This criterion is documented in Q1100 and Q1110 on P6_ELIG0A.

- A history over past 3 months of short-acting beta-agonist (i.e. albuterol, levalbuterol) use < 2days/week for relief of symptoms

  This criterion is documented in Q1120 and Q1130 on P6_ELIG0A.

- FEV_1 % predicted > 70%

  This criterion is documented in Q1145 on P6_ELIG0A.

- Ability of the participant to use the spirotel® e-diary/peak flow meter correctly.

This criterion will be evaluated objectively for all participants using the Spirotel® Performance Checklist (SPIROTEL_PERF) (use Version 2.0 to coordinate with the Spirotel II device) along with the BARD/SIENA/STICS demo device. Train the participant on the use of the spirotel® device (configured for SIENA), including the e-diary questions and peak flows for scheduled AM and PM sessions, as well as unscheduled peak flows. Observe the participant using the device to do an AM scheduled session and a PM scheduled session (no peak flows are required for the PM session for this evaluation). Complete a SPIROTEL_PERF checklist as you observe the participant go through each step. If the participant does not demonstrate satisfactory performance, retrain him/her and complete a new checklist until his/her understanding of the device and subsequent performance improve. Participants must achieve a score of 13 out of 13 to be considered proficient at using the spirotel®.

Checklists should be filed in the participant's study folder at the performance site; do not forward them to the DCC.

This criterion is documented in Q1180 on P6_ELIG0A.

Visit 0A Exclusion Criteria

- Chronic diseases (other than asthma) that in the opinion of the local investigator would prevent participation in the trial or put the participant at risk by participating, based on physical exam and medical history at Visit 0A.

  In particular, individuals with an established diagnosis of vocal cord dysfunction or chronic diseases of the lung (other than asthma; e.g., emphysema, chronic bronchitis, pulmonary embolism, malignancy, cystic fibrosis, etc.), kidney, heart, liver, endocrine or nervous system, or immunodeficiency will be excluded.

  Note that the majority of the conditions are exclusionary only if deemed clinically unstable or contraindicated for the protocol in the judgment of the local investigator and the principal investigator for the protocol. If a potential participant's eligibility is in question, contact the SIENA scientific coordinator at the DCC for assistance.

  Medical history forms completed at Visit 0A will be reviewed at Visit 1 for Supervised Washout participants who make it to Visit 1; these forms will be entered with the Visit 1 packet.

  See page 68 for exclusionary medical conditions.

  This criterion is documented in Q1150 on P6_ELIG0A.

- Need for the use of any of the drugs listed in Table 1 on page 64; inability to go off these drugs for the required washout periods prior to Visit 1 and for the

duration of the SIENA study. The SIENA Exclusionary Drugs (P6_EXCLDRUG) reference card contains a summary of the table on page 64.

This criterion is documented in Q1160 and Q1170 on P6_ELIG0A.

Visit 0B
Complete Eligibility Checklist 0B (P6_ELIG0B)

At Visit 0B, diary and peak flow data will be reviewed for asthma control and spirometry will be performed; those participants who continue to meet the criteria for well controlled (see below) will discontinue ICS. Participants will continue to monitor symptoms and PEF, and will return to the study site for Visit 1.

Visit 0B Inclusion Criteria

- A history over past month of symptoms ≤ 2 days/week

  This criterion is documented in Q1000 and Q1010 on P6_ELIG0B.

- A history over past month of nighttime awakenings due to asthma ≤ 2 times/month

  This criterion is documented in Q1020 and Q1030 on P6_ELIG0B.

- A history over past month of short-acting beta-agonist (i.e. albuterol, levalbuterol) use < 2 days/week for relief of symptoms

  This criterion is documented in Q1040 and Q1050 on P6_ELIG0B.

- FEV_1 % predicted > 70%

  This criterion is documented in Q1065 on P6_ELIG0B.

2.20 Eligibility Criteria for Run-in

Visit 1
Complete Eligibility Checklist 1 (P6_ELIG1)
Complete Eligibility Checklist 2 (P6_ELIG2)
Complete Eligibility Checklist 3 (P6_ELIG3)

At Visit 1, participants who did not undergo Supervised Washout will have a thorough medical history taken and will undergo a comprehensive physical examination. Findings from these procedures can affect the participant's continued study eligibility. Basic eligibility criteria and eligibility criteria related to the participant's medical condition and medical history are recorded on Eligibility Checklists 1 and 2 (P6_ELIG1 and P6_ELIG2). Medical history forms for Supervised Washout participants, which were completed at Visit 0A, will be reviewed and updated at Visit 1.

If the participant remains eligible at Visit 1 following his/her exam and medical history assessment, he/she will perform spirometry and reversibility testing. If the participant's FEV_1 does not improve at least 12% in response to 4 puffs albuterol, the participant must demonstrate $PC_{20} \leq 16$ mg/ml. If the participant does not have source documentation of $PC_{20} \leq 16$ mg/ml with the past 6 months for an overread AsthmaNet methacholine challenge, he/she will need to be scheduled for a continuation visit to perform methacholine challenge. Continuation visit should try to be scheduled to take place within 24-48 hours, and within 7 days maximum. If the participant has a $PC_{20} \leq 16$ mg/ml, the participant is eligible to continue with Visit 1 procedures.

Eligibility criteria related to baseline FEV_1 and PC_{20} are documented on Eligibility Checklist 3 (P6_ELIG3). Participants who remain eligible following completion of P6_ELIG3 will perform sputum induction and provide blood samples for lab testing.

Participants should review the data recorded on P6_ELIG1, P6_ELIG2, and P6_ELIG3 and initial/date the source documentation box on the forms.

Visit 2, 2A
Complete Eligibility Checklist 4 (P6_ELIG4)

Eligibility criteria assessed at Visit 2 and 2A are recorded on Eligibility Checklist 4 (P6_ELIG4). Participants who have had two or more treatment failures, one or more asthma exacerbations, or have used exclusionary medications are not eligible to continue and will be terminated. If a participant remains eligible following completion of P6_ELIG4, he/she will proceed with the visit which includes the participant's second (or third at Visit 2A) sputum induction.

Note: Nightshift workers and others with altered schedules

SIENA has no specific exclusion for nightshift workers and individuals with other altered day/night schedules. Individuals working the 11 PM to 7 AM shift or the 12 AM to 8 AM shift may be screened and enrolled at the local investigator's discretion. These participants should follow normal AM and PM daily procedures

Visit 1 Inclusion Criteria

- For participants ages 18 and over: Ability to provide informed consent, as evidenced by the signing of a copy of the SIENA study consent form approved by the study institution's Committee on Human Subjects' Research (i.e., Institutional Review Board).

  For participants ages 12-17: Ability of parent or guardian to provide informed consent, as evidenced by signing a copy of the consent form approved by the study institution's Committee on Human Subjects' Research (i.e., Institutional Review Board). Verbal or written assent by the minor participant should be documented according to local institutional guidelines.

  The informed consent (and assent, as applicable) documents must be signed on or before the Visit 1 date.

  See the discussion of Informed Consent in this section for further details.

  This criterion is documented in Q1000, Q1010, and Q1020 on P6_ELIG1. If participant participated in Supervised Washout, this is documented on P6_ELIG0A.

- Male or female, age 12 and older.

  This criterion is documented in Q1030 on P6_ELIG1.

- Physician-diagnosed asthma at least 12 months ago or history consistent with asthma for the previous 12 months.

  Participant report is sufficient. Medical records and prescriptions for asthma medications are not required, but are helpful if the performance site has routine access to them.

  This criterion is documented in Q1145 on P6_ELIG2.

- $FEV_1 \geq 70\%$ predicted

  This criterion is documented in Q1000 on P6_ELIG3.

- At least 1 of the following indications for chronic controller therapy:
  1. Daytime asthma Symptoms > 2 days/week OR
  2. Nighttime awakenings > 2 nights/month OR

3. Short-acting beta-agonist use for symptom control > 2 days/week

This criterion is documented in Q1070 – Q1130 on P6_ELIG1.

- FEV_1 improvement ≥ 12% and ≥ 200 ml in response to four puffs of albuterol OR PC_{20} ≤ 16 mg/ml.

  At Visit 1, asthmatic participants who do not demonstrate FEV_1 improvement ≥ 12% in response to four puffs of albuterol (reversibility testing) will be required to undergo methacholine challenge. Source documentation of a PC20 ≤ 16 mg/ml within the past 6 months for an overread AsthmaNet methacholine challenge is acceptable.

  During reversibility testing, participants perform baseline spirometry followed by the administration of 4 puffs of albuterol and another spirometry session 10-15 minutes later. See the Spirometry discussion in this section and the Spirometry Manual of Operations in Appendix 1 of the AsthmaNet General Manual of Operations for further details on the reversibility testing procedures.

  For purposes of eligibility assessment, reversibility is calculated on the basis of the baseline spirometry results (recorded on the Spirometry Testing (SPIRO) form) and the post 4 puffs spirometry session (recorded on the Post-Albuterol (4 puffs) Spirometry Testing (PALB4_SPIRO) form). Reversal is the relative change in FEV_1 expressed as a percentage.

  Sample reversal calculations:

  > To calculate the participant's % reversal with 4 puffs of albuterol, take the difference in raw FEV_1 values (in liters) (post FEV_1 value – pre FEV_1 value) and divide by the pre FEV_1 value. Multiply the result by 100.
  >
  > Pre-test FEV_1 (from Q1030 SPIRO form): 3.24 liters
  > Post-test FEV_1 (from Q1030 PALB4_SPIRO form): 3.80 liters
  >
  > Reversal % = (3.80 – 3.24) / 3.24 * 100 = 17.28%

  If the participant's reversal % is ≥ 12% (rounding to the nearest whole number), he/she meets the criterion. The participant in the example meets the criterion.

  This criterion is documented in Q1010 – Q1070 on P6_ELIG3.

- Ability of the participant to use the spirotel® e-diary/peak flow meter correctly.

  This criterion will be evaluated objectively for all participants using the Spirotel® Performance Checklist (SPIROTEL_PERF) (use Version 2.0 to coordinate with the Spirotel II device) along with the BARD/SIENA/STICS demo device. Train the participant on the use of the spirotel® device (configured for SIENA),

including the e-diary questions and peak flows for scheduled AM and PM sessions, as well as unscheduled peak flows. Observe the participant using the device to do an AM scheduled session and a PM scheduled session (no peak flows are required for the PM session for this evaluation). Complete a SPIROTEL_PERF checklist as you observe the participant go through each step. If the participant does not demonstrate satisfactory performance, retrain him/her and complete a new checklist until his/her understanding of the device and subsequent performance improve. Participants must achieve a score of 13 out of 13 to be considered proficient at using the spirotel®.

Checklists should be filed in the participant's study folder at the performance site; do not forward them to the DCC.

This criterion is documented in Q1080 on P6_ELIG3.

- Ability of the participant to use the Respimat® properly.

  This criterion will be evaluated objectively for all participants using the Respimat® Technique Checklist. Participants must achieve a perfect score of thirteen to pass the performance check on the Respimat® Technique Checklist (P6_TECH_RESP). Participants will dose from Respimat® training devices for purposes of this assessment. See the Inhalation Technique Assessment discussion in this section for further details.

  P6_TECH_RESP checklist(s) will be entered into the database.

  This criterion is documented in Q1090 and Q1100 on P6_ELIG3.

- Ability of the participant to use a metered dose inhaler (MDI) properly.

  This criterion will be evaluated objectively for all participants using the the MDI Inhalation Technique Checklist (Without Spacer). Participants must achieve a perfect score of eleven (which evaluates two separate inhalations) to pass the performance check on the MDI Inhalation Technique Checklist (Without Spacer) (P6_TECH_MDI_NOSP). Participants will dose from an albuterol rescue inhaler from the clinic's bulk supply as part of the pre/post-bronchodilator spirometry session at Visit 1 for purposes of this assessment. See the Inhalation Technique Assessment discussion in this section for further details.

  P6_TECH_MDI_NOSP checklist(s) will be entered into the database.

  This criterion is documented in Q1110 on P6_ELIG3.

Visit 1 Exclusion Criteria

- Plans to move away from the clinical site in the upcoming 11 months such that a participant's ability to complete the study will be jeopardized.

  If a participant is planning to move in the near future to a location that would preclude his/her completion of the study at the original performance site or at another AsthmaNet SIENA performance site, then he/she should not be enrolled. This concern should be discussed with students who tend to relocate during the summer months to determine if they will be able to complete all study visits at the local site or make alternate arrangements. Only participants who have a high likelihood of completing the entire study (through Visit 9) should be enrolled.

  This criterion is documented in Q1040 on P6_ELIG1.

- Use of investigative drugs or enrollment in an intervention trial in the past 30 days, or plans to enroll in such a trial during the SIENA study.

  Good clinical practice dictates that an individual should not participate in multiple intervention trials at the same time, due to possible interactions of study interventions which pose a safety concern and confounding of the resulting data. When screening potential SIENA participants, ensure that they are not currently participating in another intervention trial and, if they participated in one recently, that at least 30 days have elapsed since they terminated from the other study. Do not screen or enroll individuals who indicate that they are interested in participating in other intervention studies while they are still in the SIENA trial.

  While in the SIENA trial, individuals may participate in non-intervention studies that do not interfere with the medications and procedures required for the SIENA trial. Contact the SIENA scientific coordinator at the DCC to discuss individual circumstances as they arise.

  This criterion is documented in Q1050 on P6_ELIG1.

- History of a respiratory infection in past 4 weeks.

  A respiratory tract infection is defined as a cough, runny nose plus or minus fever, or sore throat that is not related to allergen exposure. This criterion is evaluated by participant self-report; no specific medications need to have been taken to meet this criterion. At all subsequent visits, the occurrence of a recent infection should be documented on the Clinical Adverse Events (AECLIN) form.

  If the participant experiences a respiratory infection between Visits 1 and 3, Visit 3 will be delayed so that 4 weeks pass from resolution of respiratory infection.

  This criterion is documented in Q1065 on P6_ELIG1.

- Chronic diseases (other than asthma) that in the opinion of the local investigator would prevent participation in the trial or put the participant at risk by participating, based on physical exam and medical history at Visit 1.

  In particular, individuals with an established diagnosis of vocal cord dysfunction or chronic diseases of the lung (other than asthma; e.g., emphysema, chronic bronchitis, pulmonary embolism, malignancy, cystic fibrosis, etc.), kidney, heart, liver, endocrine or nervous system, or immunodeficiency will be excluded.

  Note that the majority of the following conditions are exclusionary only if deemed clinically unstable or contraindicated for the protocol in the judgment of the local investigator and the principal investigator for the protocol. If a potential participant's eligibility is in question, contact the SIENA scientific coordinator at the DCC for assistance.

  At Visit 1, medical history forms will be reviewed and updated for participants who participated in Supervised Washout and underwent physical exam and medical history at Visit 0A.

  Exclusionary conditions include, but are not limited to:

  - Addison's disease
  - AIDS
  - Benign Prostatic Hyperplasia (BPH)
  - Bladder-neck obstruction
  - Cardiac arrhythmias or disorders (clinically significant)
  - Congenital anomaly, including growth abnormalities (clinically significant)
  - Congestive heart failure
  - Coronary artery disease (unstable or severe)
  - Cushing's disease
  - Diabetes mellitus (poorly controlled)
  - Dyspnea due to cause other than asthma, in judgment of investigator
  - Eating disorder (e.g., active anorexia or bulimia)
  - Glaucoma (narrow angle)
  - Hematologic disease (unstable, e.g., severe anemia)
  - Hepatic disease[3]
  - Hypertension (poorly controlled)
  - Hyperthyroidism[4]
  - Immunologic compromise[5]
  - Chronic kidney disease (e.g., glomerulonephritis, polycystic kidney disease, etc.)
  - Lactation

[3] Nonactive hepatitis B/C is allowable; active hepatitis (including antigen positivity or disease requiring treatment) is exclusionary.
[4] Controlled hypothyroidism is allowable.
[5] Resulting in prior infections and/or susceptibility to new infections.

- Lung disease other than asthma (e.g., COPD, emphysema, chronic bronchitis, pulmonary embolism, malignancy, cystic fibrosis, among others)
- Lupus (active disease, requiring immunosuppressant)
- Any malignancy other than basal cell skin cancers
- Mental illness (uncontrolled)[6]
- Mental retardation
- Neurologic disease (including epilepsy requiring treatment)
- Peptic ulcer disease (active)
- Pregnancy
- Schizophrenia
- Skeletal disorders, including osteoporosis and rheumatoid arthritis[7]
- Sleep apnea (untreated)[8]
- Substance abuse (including active drug or alcohol abuse)
- Tuberculosis (active disease excluded; history of positive skin test with negative chest X-ray allowed)
- Urinary retention (active symptoms within last 6 months)
- Vocal cord dysfunction (diagnosis of)

These illnesses are listed on the SIENA Exclusionary Medical Conditions (P6_EXCLMED) reference card.

This criterion is documented in Q1000 and Q1000D on P6_ELIG2.

- History of bladder-neck obstruction, urinary retention, benign prostatic hyperplasia (BPH), or a clinically relevant urologic disorder that precludes study participation.

  This criterion is documented in Q1010 on P6_ELIG2.

- History of narrow angle glaucoma

  This criterion is documented in Q1020 on P6_ELIG2.

- History of significant cardiovascular disorders or arrhythmias

  This criterion is documented in Q1030 on P6_ELIG2.

- Need for the use of any of the drugs listed in Table 1 (that follows); inability to go off these drugs for the required washout periods prior to Visit 1 and for the duration of the SIENA study. The SIENA Exclusionary Drugs (P6_EXCLDRUG) reference card contains a summary of this table.

[6] Anxiety, depression, or bipolar disease well-controlled on allowed medications are allowable conditions for the SIENA trial.
[7] Participants who have rheumatoid arthritis and are on excluded medications should not be screened; osteoarthritis is an allowable condition for the SIENA trial. Scoliosis, degenerative disc disease, and spinal stenosis are not exclusionary.
[8] Individuals with an OSA diagnosis who are receiving treatment with CPAP, BiPAP, or APAP are eligible.

Excluded drugs/substances on P6_EXCLDRUG must be washed out prior to Visit 1, and the participant must refrain from using them for the duration of the trial. If a participant is taking one or more of these medications at the time of Visit 1, the indication for the drug should be discussed with the local investigator to determine if it is safe for him/her to go off the drug to participate in the trial starting with Visit 1.

It is important to note that any and all changes in a participant's medications must be approved by a study physician and documented in the participant's clinic notes.

This criterion is documented in Q1040 on P6_ELIG2.

Table 1. Drugs to be withheld throughout the study.

Excluded Drug	Generic Names (may not be inclusive)	Trade Names (may not be inclusive)	Washout Prior to Visit 1
Steroid Medications			
Oral or intravenous steroids for any reason except as provided in study	dexamethasone, prednisone, prednisolone	Decadron, Medrol, Orapred, Prednisone, Prelone	6 weeks
Inhaled steroids, except as provided in study	beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, triamcinolone acetonide	Advair, Aerobid, Alvesco, Asmanex, Azmacort, Dulera, Flovent, Pulmicort, QVAR, Symbicort	3 weeks
Intranasal steroids, except at stable drug and dose throughout study	beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, triamcinolone acetonide	Beconase AQ, Flonase, Nasacort AQ, Nasarel, Nasonex, Omnaris, Rhinocort	None
Nonsteroidal Antiinflammatory Medications			
Leukotriene modifiers	montelukast, zafirlukast, zileuton	Accolate, Singulair, Zyflo	3 weeks
Cromolyn/Nedocromil for asthma	cromolyn, nedocromil	Intal, Tilade	1 week
Bronchodilators			
Oral β-agonists	albuterol, metaproterenol, terbutaline	Alupent, Brethine, Bricanyl, Metaprel, Proventil, Repetabs, Ventolin, Volmax	1 week
Short-acting inhaled β-agonists	epinephrine	Bronkaid Mist, Duo-Medihaler, Medihaler-Epi, Primatene Mist	6 hours

Excluded Drug	Generic Names (may not be inclusive)	Trade Names (may not be inclusive)	Washout Prior to Visit 1
Intermediate-acting inhaled β-agonists, except study RESCUE drug	albuterol, bitolterol, levalbuterol, metaproterenol, pirbuterol, terbutaline	Alupent, Brethaire, Brethine, Bronkometer, Maxair, Metaprel, Proventil, Tornalate, Ventolin, Xopenex	6 hours
Long-acting inhaled β-agonists	formoterol, salmeterol	Advair, Dulera, Foradil, Serevent, Symbicort	24 hours
Short-acting inhaled anticholinergics	atropine, ipratropium bromide, pirenzepine, scopolamine	Atrohist, Atrovent, Bellatal, Combivent, Donnatal, Scopoderm, Transderm-Scop	6 hours
Long-acting inhaled anticholinergics, except study drug	tiotropium	Spiriva	24 hours

Drugs to be withheld throughout the study.

Excluded Drug	Generic Names (may not be inclusive)	Trade Names (may not be inclusive)	Washout Prior to Visit 1
Xanthine Derivatives			
Short-acting theophylline	theophylline	Aminophylline, Slo-Phyllin	12 hours
Long-acting theophylline	theophylline	Slo-bid, Theo-Dur	24 hours
Ultra long-acting theophylline	theophylline	Theo-24, Uniphyl	48 hours
Anti-IgE Therapy			
	omalizumab	Xolair	3 months
Cardiac Drugs			
Alpha-beta blockers	labetalol	Normodyne	2 weeks
Beta blockers	acebutolol, atenolol, betaxolol, bisoprolol, carteolol, metoprolol, nadolol, penbutolol, pindolol, propranolol, timolol	Blocadren, Cartrol, Corgard, Inderal, Kerlone, Levatol, Lopressor, Sectral, Tenormin, Visken, Zebeta	2 weeks
Psych or CNS-Related Drugs			
Monoamine oxidase (MAO) inhibitors	harmaline, iproclozide, iproniazid, isocarboxazid, nialamide, phenelzine, selegiline, toloxatone, tranylcypromine	Nardil, Parnate	4 weeks

Excluded Drug	Generic Names (may not be inclusive)	Trade Names (may not be inclusive)	Washout Prior to Visit 1
Antibiotics			
Macrolide antibiotics, chronic use excluded	azithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, troleandomycin	Biaxin, Dynabac, Rulid, Surlid, TAO, Zithromax, Zitromax	2 weeks
Miscellaneous Exclusionary Drugs			
Drugs contraindicated when taking tiotropium	dicyclomine, glycopyrrolate, hyoscyamine, orphenadrine, tolterodine tartrate	Anaspaz, Antiflex, Banflex, Bentyl, Cystospaz, Detrol, Disipal, Donnamar, Flexoject, Levsin, Mio-Rel, Myolin, Myotrol, Orfro, Orphenate, Robinul	None
Drugs for urinary hesitancy	oxybutynin, tolterodine tartrate	Detrol, Ditropan	None
Drugs for narrow angle glaucoma	betaxolol, pilocarpine, timolol maleate	Betoptic S, Ocusert Pilo, Timoptic	None

Drugs/substances to be withheld prior to Visits 0A, 0B, 1-9*.

Drug/Substance	Trade Names (may not be inclusive)	Washout Prior to Visits
albuterol (study RESCUE inhaler)	ProAir	6 hours
Methylxanthine-containing food or beverages (caffeinated colas, coffee, tea)	Coke, Barq's Rootbeer, Mello-Yellow, Mountain Dew, Pepsi, Red Bull	4 hours
Methylxanthine-containing medications	Anacin, Darvon, Esgic, Excedrin, No-Doz, Norgesic, Vivarin	4 hours
Weight loss medications	Belviq, bitter orange, Xenadrine, EFX, Thermorexin, Qsymia	4 hours
Alcohol-containing foods or beverages		4 hours

*These drugs/substances are allowed between visits, but not prior to pulmonary function testing.

- Use of any prescription or over-the-counter medication other than those listed on the SIENA Allowed Medications (P6_MEDALLOW) reference card.

  Chronic use of any medications other than RESCUE beta-agonist except:

  - analgesics for acute/chronic pain management (with MD discretion)
  - antianxiety agents/anxiolytics (e.g., diazepam, chlordiazepoxide, alprazolam, clonazepam, lorazepam, gabapentin, buspirone) at a stable dose
  - antibiotics (e.g. penicillins, cephalosporins, quinolones, monobactams, sulfonamides, doxycycline, minocycline, nitroimidazoles (Flagyl), macrolides) for intermittent use

- antibiotics for acne (topical/oral) (macrolides allowed for intermittent use only)
- anti-cholesterol medications (e.g., gemfibrozil, statins, fenofibrate, niacin), except cholestipol and cholestyramine
- specific antidepressants at a stable dose
  - Selective Serotonin Reuptake Inhibitors (SSRI) (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)
  - Selective Serotonin Norepinephrine Reuptake Inhibitors (SSNRI) (e.g. desvenlafaxine, duloxetine, venlafaxine)
  - Non-SSRI/SSNRI antidepressants (except MAOI class drugs) (e.g. amitriptyline, amoxapine, bupropion, mirtazapine, nefazodone, trazodone and others)
- antihistamines (e.g. chlorpheniramine (Chlor-Trimeton), desloratadine (Clarinex), diphenhydramine (Benadryl), fexofenadine (Allegra, Allegra-D), loratadine (Claritin), cetirizine (Zyrtec), and others)
- specific antihypertensive medications
  - alpha blockers (e.g. doxazosin, prazosin, terazosin)
  - angiotensin converting enzyme (ACE) inhibitors (e.g. benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril, ramipril)
  - angiotensin receptor blockers (Sartans) (e.g. candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan)
  - calcium channel blockers (e.g. amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, verapamil)
  - diuretics (e.g. amiloride, bumetanide, chlorothiazide, chlorthalidone, furosemide, hydrochlorothiazide, indapamide, methyclothiazide, metolazone, spironolactone, triameterene)
  - mineralocorticoid receptor antagonists (e.g. eplerenone)
  - sympathetic nerve inhibitors (e.g. clonidine, guanabenz, guanfacine, methyldopa)
- antitussives (OTC only) (e.g. dextromethorphan)
- bisphosphonates (e.g. alendronate (Fosamax), ibandronate (Boniva), risedronate (Actonel), zoledronic acid (Zometa))
- calcium-based antacids used PRN (e.g. TUMS®)
- calcium supplements at a stable dose throughout study (up to 2500 mg/day)
- CNS stimulants/appetite suppressants (e.g. lisdexamfetamine, methylphenidate (Ritalin), amphetamine preps)
- Cox-2 drugs (e.g. celecoxib (Celebrex))
- decongestants (e.g. pseudoephedrine (Sudafed), oxymetazoline (Afrin), and others)
- Depo-Provera®
- oral diabetes medications (for treatment of stable, controlled diabetes)
- erectile dysfunction medications (e.g. sildenafil, tadalafil, vardenafil)
- estrogen/progesterone replacement therapy for postmenopausal women
- expectorants (OTC only) (e.g. guaifenesin)
- eye preparations for allergic eye symptoms (topical) (e.g. antihistamines, NSAIDS, antiallergic compounds)
- H2 blockers (e.g. ranitidine, cimetidine, famotidine, nizatidine) for GERD

- hair growth preparations (e.g. finasteride (Propecia®))
- hemorrhoid treatments
- herpes medications (e.g. acyclovir (Zovirax), valacyclovir (Valtrex))
- insulin and injectable antidiabetic medications (for treatment of stable, controlled diabetes)
- intranasal steroids (any drug) at a stable dose throughout study
- laxatives
- Librax
- lithium
- migraine analgesics/preventatives (e.g. butalbital, triptans, topiramate)
- nasal antiallergic spray (Cromolyn/Atrovent)
- nasal saline spray
- non-steroidal anti-inflammatory medications (e.g. aspirin, ibuprofen, naproxen, meloxicam, ketoprofen)
- Norplant®
- oral contraceptives
- proton pump inhibitors (e.g. omeprazole (Prilosec), pantoprazole, lansoprazole (Prevacid), esomeprazole (Nexium)) for GERD
- psyllium
- sleep aids used PRN
- stool softeners
- study medications
- thyroid replacement medication (e.g. Levothroid, Levoxyl, Synthroid)
- tretinoin (Retin-A) for acne
- vitamins, minerals
- Low potency topical corticosteroids (BID) (e.g., alclometasone dipropionate, desonide, dexamethasone, dexamethasone sodium phosphate, fluocinolone acetonide, hydrocortisone, hydrocortisone acetate)
- Medium potency topical corticosteroids (BID) (e.g., betamethasone benzoate, flurandrenolide, betamethasone dipropionate, fluticasone propionate, betamethasone valerate, hydrocortisone butyrate, clocortolone pivalate, hydrocortisone valerate, desoximetasone, mometasone furoate, fluocinolone acetonide, triamcinolone acetonide)

If a participant's use of a specific allowed medication is chronic, a complete clinical assessment should be performed to ensure the participant's safety and his/her ability to complete the entire study. Care should be taken to evaluate any underlying conditions the participant may be treating with these medications, in the event that he/she may have an exclusionary medical condition.

If a participant is taking a medication that does not appear in the above list, but also does not appear on the SIENA Exclusionary Drugs (P6_EXCLDRUG) reference card, first consult the local investigator. If the local investigator feels the participant should be considered eligible, then contact the SIENA scientific coordinator at the DCC with the details. She will contact the lead study

investigators and will document the final decision on the participant's suitability for the study.

This criterion is documented in Q1050 on P6_ELIG2.

- If intranasal steroids will be needed at any time during the study, willingness of the participant to use a single intranasal steroid at a stable dose continuously for the duration of the study, starting at or before Visit 1.

  Any intranasal steroid may be used, as long as it is used at a constant dose continuously throughout the participant's study participation. The study physician should be consulted if the participant is not using an intranasal steroid at the time of screening (Visit 1) and the need for one is unclear. Examples include: Nasonex, Flonase, Nasacort, Rhinocort, etc. Intranasal steroids are not provided by the SIENA study.

  Use of intranasal steroids must be recorded on the Concomitant Medications for Asthma/Allergy and Adverse Events form (CMED). It is important to the goals of the study to be able to account for all steroid dosing, including intranasal steroids.

  This criterion is documented in Q1060 and Q1070 on P6_ELIG2.

- Allergen immunotherapy other than an established maintenance regimen implemented continuously for a minimum of 3 months.

  Allergen immunotherapy (also referred to as hyposensitization therapy or allergy shots) is allowed during the SIENA trial. Participants must be on consistent immunization therapy for at least 3 consecutive months prior to Visit 1 for the program to be considered an established maintenance regimen. Participants must be willing to continue on the same program, and new programs should not be initiated, for the duration of the individual's participation in the SIENA trial.

  Before screening a participant who is receiving allergen immunotherapy *other than allergy shots*, contact the SIENA Scientific Coordinator at the DCC for an assessment of the participant's eligibility.

  This criterion is documented in Q1080 on P6_ ELIG2.

- Omalizumab use within past 3 months.

  This criterion is documented in Q1090 on P6_ELIG2.

- Smokeless tobacco product (e.g., chew, snuff) in past year.

  This criterion is documented in Q1100 on P6_ELIG2.

- Smoking of any substance (cigarettes, a pipe, cigar, marijuana, electronic cigarettes, other substance, etc.) in the past year (12 months).

  This criterion is documented in Q1110 on P6_ELIG2.

  Note: Participants should not use smokeless tobacco products (e.g., chew, snuff etc.) for the duration of the SIENA study.

- Ages 18 and over: Lifetime smoking history greater than 10 pack-years.

  Ages 12-17: Lifetime smoking history greater than 5 pack-years.

  The pack-year limit applies regardless of when an individual stopped smoking.

  Definition of pack-year: A participant smoked for one pack-year if he/she smoked one pack of cigarettes (i.e., 20 cigarettes) a day for a period of one year. In general, the number of pack-years someone smoked is computed as:

  pack-years = #packs/day * #years smoked that quantity

  A participant with a 10-pack-year history could have smoked one pack of cigarettes per day over 10 years or two packs a day for 5 years, or many other combinations of packs/day and durations.

  If a participant smoked an odd number of cigarettes per day, or had a history of smoking variable amounts of cigarettes per day over time, the resulting number of pack-years should be estimated to one decimal place for each part of the calculation.

  For example, suppose a participant smoked an average of 8 cigarettes per day for 6 years, and 3 cigarettes per day for 3 years, eventually quitting. His/her pack-year history would be computed as:

  (8/20) * 6 + (3/20) * 3 = 2.4 + 0.5 = 2.9 pack-years

  This criterion is documented in Q1120 and Q1130 on P6_ELIG2.

  Note: Pack-year history is quantified on the Adult Asthma and Allergy History (ASTHMA_HX_ADULT) form completed at Visit 1.

- A life-threatening asthma exacerbation requiring treatment with intubation or mechanical ventilation in the past 5 years

  This criterion is documented in Q1150 on P6_ELIG2.

- Asthma exacerbation requiring systemic corticosteroid treatment in past 6 weeks.

Participants who have experienced a significant asthma exacerbation requiring systemic corticosteroid treatment within 6 weeks of Visit 1 should not complete the visit at this time. These individuals should defer Visit 1 until the full 6 weeks have passed and their asthma is stable.

Systemic corticosteroids include oral (e.g., prednisone), injectable (IM), and intravenous (IV) steroids.

This criterion is documented in Q1160 on P6_ELIG2.

- Use of an oral corticosteroid within past 6 weeks.

  This criterion is documented in Q1173 on P6_ELIG2.

- Use of an inhaled corticosteroid or leukotriene modifier within past 3 weeks.

  This criterion is documented in Q1175 on P6_ELIG2.

- Pregnancy or lactation or plans to become pregnant in the next 11 months.

  If the participant is a woman of child-bearing potential, she will undergo a urine pregnancy test at Visit 1 and 9. For additional details, see the Pregnancy Test discussion in this section.

  This criterion is documented in Q1190 on P6_ELIG2.

- If potentially able to bear children, not using an acceptable form of birth control.

  Acceptable forms of birth control include:

  - Birth control patches (Ortho Evra™)
  - NuvaRing®
  - Oral contraceptives
  - Norplant®
  - Depo-Provera®
  - IUD
  - IUS
  - Single and double barrier methods (e.g., condom, spermicidal foam)
  - Surgical sterilization (i.e., hysterectomy, tubal ligation, or vasectomy in monogamous partner)
  - Post-menopausal (at least 1 year since last menses)
  - Abstinence

  This list is summarized on the Birth Control Methods (BIRTH_CTRL) reference card.

  A history of infertility may <u>not</u> be used as a substitute for appropriate birth control.

This criterion is documented in Q1200 on P6_ELIG2.

- Any condition or compliance issue which, in the opinion of the investigator, might interfere with study participation.

  After the physician interacts with the participant at Visit 1, and the results of the physical exam and medical history are known, it may become apparent that the participant is not an ideal candidate for the SIENA study for a variety of reasons. If this is the case, the participant should be terminated from the study.

  This criterion is documented in Q1120 on P6_ELIG3.

Visit 2, 2A Exclusion Criteria:

- Two or more treatment failures since Visit 1.

  This criterion is documented in Q1010 on P6_ELIG4.

- One or more asthma exacerbations since Visit 1.

  This criterion is documented in Q1020 on P6_ELIG4.

- Treatment with any excluded medication (P6_EXCLDRUG) since Visit 1.

  This criterion is documented in Q1030 on P6_ELIG4.

- Any condition or compliance issue which, in the opinion of the investigator, might interfere with study participation.

  After the participant is in the study for a couple weeks, it may become apparent that the participant is not an ideal candidate for the SIENA study for a variety of reasons. If this is the case, the participant should be terminated from the study.

  This criterion is documented in Q1060 on P6_ELIG4.

2.21 Eligibility for Randomization

Visit 3
Complete Eligibility Checklist 5 (P6_ELIG5)

Visit 3 Inclusion Criteria

- Two acceptable sputum induction samples during the run-in

  The Participant Status report displays whether the Visit 1, 2 and 2A sputum samples are acceptable. The intention is for results to be posted within one week of shipment.

  This criterion is documented in Q1000 on P6_ELIG5.

- At least 75% compliance with AM and PM peak flow measurements and symptoms on spirotel® during run-in

  This can be found on the SIENA Spirotel® Eligibility Report (P6_ELIG_RPT) under V3 Spirotel Compliance.

  This criterion is documented in Q1100 on P6_ELIG5.

- At least 75% compliance with required puffs from Respimat® during the run-in

  See Dosing Compliance discussion in this section for details on how to calculate Respimat® compliance for eligibility.

  This criterion is documented in Q1110 on P6_ELIG5.

- Pre-bronchodilator $FEV_1 \geq 70\%$

  This criterion is documented in Q1120 on P6_ELIG5.

- Ability of the participant to use the Twisthaler® properly *(**ONLY** for those randomized to Twisthaler at Visit 3)*

  This criterion will be evaluated objectively for all participants randomized to Twisthaler at Visit 3 using the Twisthaler® Technique Checklist. Participants must achieve a perfect score of twelve to pass the performance check on the Twisthaler® Technique Checklist (P6_TECH_TWIST). Participants will dose from Twisthaler® training devices for purposes of this assessment. See the Inhalation Technique Assessment discussion in this section for further details.

  P6_TECH_TWIST checklist(s) will be entered into the database.

  This criterion is documented in Q1140 on P6_ELIG5.

Visit 3 Exclusion Criteria

- Receiving treatment for treatment failure within the past 3 weeks

  If a participant experienced only one treatment failure in the run-in, the run-in should be extended so that 3 weeks pass from completion of open-label Asmanex® (YELLOW) treatment to randomization at Visit 3.

  This criterion is documented in Q1035 on P6_ELIG5.

- Two or more treatment failures since Visit 1.

  This criterion is documented in Q1020 on P6_ELIG5.

- One or more asthma exacerbations since Visit 1.

  This criterion is documented in Q1040 on P6_ELIG5.

- Treatment with any excluded medication (P6_EXCLDRUG).

  This criterion is documented in Q1050 on P6_ELIG5.

- Respiratory infection in last 4 weeks.

  If the participant experienced a respiratory infection within 4 weeks of Visit 3, the run-in should be extended so that 4 weeks pass from resolution of the respiratory infection to randomization at Visit 3.

  This criterion is documented in Q1065 on P6_ELIG5.

- Night-time awakenings more than twice per week during run-in

  This can be found on the SIENA Spirotel® Eligibility Report (P6_ELIG_RPT) under V3 Eligibility Symptoms.

  Data from the entire run-in is used to calculate nighttime awakenings per week. If the participant experienced a treatment failure as a result of nighttime awakenings in the run-in, the participant may average night-time awakenings more than once per week during the run-in. In this situation, scan and send the Spirotel Participant Visit Reports (P6_SPIROTEL_RPT) for the entire run-in to the SIENA Scientific Coordinator at the DCC. Run-in data will be reviewed excluding the period of time when nighttime awakenings caused the treatment failure. If awakenings during that time (excluding the period of nighttime awakenings causing the treatment failure) do not average > 2 per week, then the participant will be eligible to proceed.

  This criterion is documented in Q1085 on P6_ELIG5.

- Daily albuterol use for asthma symptom control during run-in

This can be found on the SIENA Spirotel® Eligibility Report (P6_ELIG_RPT) under V3 Eligibility Symptoms.

This criterion is documented in Q1090 on P6_ELIG5.

- Participant wishes to withdraw consent.

  This criterion is documented in Q1150 on P6_ELIG5.

- New information that makes the participant ineligible according to the eligibility criteria.

  This criterion is documented in Q1160 on P6_ ELIG5.

- Any condition or compliance issue which, in the opinion of the investigator, might interfere with study participation.

  After the participant is in the study for a couple weeks, it may become apparent that the participant is not an ideal candidate for the SIENA study for a variety of reasons. If this is the case, the participant should be terminated from the study.

  This criterion is documented in Q1170 on P6_ELIG5.

2.22 Exhaled Nitric Oxide Procedures

Visits 1, 2, 2A
Perform FeNO testing (ENO)

Levels of forced exhaled nitric oxide (FeNO) are known to be elevated in people with asthma. In addition, FeNO may be involved in airway inflammation. FeNO is an important secondary outcome variable in the SIENA study.

FeNO will be collected at Visits 1, 2 and 2A, at visits where sputum induction is also performed. Results are documented on the Exhaled Nitric Oxide (ENO) form. The FeNO collection procedures should precede any pulmonary function testing procedures at a given visit. Clinical personnel should follow the order of procedures outlined on the visit procedure checklists. Any deviation from this order of procedures will result in the assignment of a protocol violation.

The NIOX MINO will be used to measure FeNO. Any individual who participates in eNO collection must possess AsthmaNet eNO certification or be directly supervised by a certified coordinator. A biological control test must be performed on the NIOX MINO every day before it is used with participants. This must be performed by a QC tester who has qualified for this procedure. See Appendix 8 of the AsthmaNet General Manual of Operations for details regarding eNO certification and QC procedures.

Prior to proceeding with exhaled nitric oxide testing, participants must pass the eligibility checks on the SIENA Pulmonary Procedure Checklist (P6_PULMONARYCHK). If any of the required washouts are not met, the participant should not proceed with collection of FeNO or pulmonary function testing at the visit. The FeNO levels may be affected by eating, drinking and strenuous activity/exercise, so participants should be encouraged to refrain from these activities for 1 hour prior to their visit. Testing will still be performed at the visit if a participant has eaten, drank, or taken part in strenuous activity/exercise in the past hour, but this will be documented on the ENO form. Mobile phones and cordless phones may interfere with the MINO, so they should be kept away from the MINO device.

The FeNO collection process may be attempted up to eight times in an effort to achieve an acceptable measurement. These eight attempts include all blows, even those when the NIOX MINO did not calculate and display a measurement because it did not find the maneuver technically acceptable.

The technician doing the collection should record the FeNO reading on the ENO form. If after eight attempts, no acceptable measurement was attained, the technician should record the time when the maneuver started and write “No acceptable maneuver” in Q6000.

Detailed instructions on using the NIOX MINO to collect exhaled nitric oxide measurements are documented in the Exhaled Nitric Oxide Manual of Operations located in Appendix 8 of the AsthmaNet General Manual of Operations.

See Section 10 of the AsthmaNet General Manual of Operations for specific information on completing the ENO form.

2.23 Extra Visit due to Washout

Participants receiving treatment for treatment failure (or experiencing a respiratory infection in the run-in) may need additional medication to last the 3-week washout required prior to Visits 3, 5, 7 and 9. Whether a participant returns to the clinic for study medication will depend on the amount of time between the participant's last visit and 3-week washout date. During the run-in, it is preferred the participant not go more than 3-4 weeks without being seen at the clinic. During the randomized treatment phase, it is preferred the participant not go more than 6-7 weeks without being seen at the clinic. For participants who return to the clinic for medication, the following visit procedures should be performed:

- Download spirotel and convert data
- Review Asthma Monitoring Log and dispense new log, if necessary
- Print and review spirotel reports
- Follow up on medication use and adverse events since last visit
- Assess participant for treatment failure
- Collect medication and check compliance
- Dispense new run-in Respimat®, open-label Asmanex®(YELLOW) inhaler, and albuterol (if necessary)

Completed forms will be entered as single forms with the visit number of the last completed regular visit. See Extra Visit due to Washout Visit Checklist (P6_VISIT_WASHOUT) for and Section 4 for more details.

Run-in
If the extended run-in requires 5 or more weeks between the participant's last run-in visit and Visit 3, it is recommended that the participant be contacted by phone at 10 days, and return to the clinic 3 weeks following last visit to receive a new Respimat® and open-label Asmanex® (YELLOW) inhaler. If the extended run-in requires 3 to 4 weeks between the participant's last run-in visit and Visit 3, a phone contact at the mid-way point between the last run-in visit and Visit 3 is sufficient.

Randomized Treatment Phase
In general, if the extended treatment period requires 8 or more weeks between the participant's last visit and Visits 5, 7 or 9, it is recommended that the participant return to the clinic to receive new blinded Twisthaler®/MDI and Respimat® devices necessary to meet washout, and open-label Asmanex® (YELLOW) inhaler. If the extended treatment period requires 6 to 7 weeks between the participant's last visit and Visits 5, 7 or 9, medication necessary to meet washout can be mailed to the participant.

See Study Medications discussion in this section for further details on dispensing additional inhaler(s) due to washout.

2.24 FEV_1 Re-assessment Visit

Visit 2, 2A, 3

Complete Pulmonary Procedure Checklist (P6_PULMONARYCHK)
Perform FeNo Testing (ENO) – Visit 2 and 2A only
Complete Spirometry Testing (SPIRO)
Assess participant for Asthma Exacerbation (P6_SIGEX). If participant meets asthma exacerbation criteria, the participant is ineligible. Please update the Treatment Failure Checklist (P6_TXFAIL_CHK) and complete the SIENA Termination of Study Participant (P6_TERM) form. Otherwise, complete steps below, and continue with remainder of the visit checklist.
Upload spirotel®
Collect Asthma Monitoring Log (P6_ASTHMA_LOG)
Print and review Spirotel® Participant Visit Report (replace previously generated report)
Print and review Spirotel® Participant Compliance Report (replace previously generated report) and update the SIENA Compliance Checklist (P6_COMPLY)
Update Treatment Failure Checklist (P6_TXFAIL_CHK), and complete Treatment Failure Information (P6_TXFAIL) if necessary (for participants who met treatment failure but not significant asthma exacerbation criteria)

- ➔ If treatment failure has occurred, re-schedule current visit so that open-label Asmanex® washout requirements are met. *(Visit 3 only)*
- ➔ Otherwise, continue with remainder of visit packet.

Visit 4, 6, 8

Complete Pulmonary Procedure Checklist (P6_PULMONARYCHK)
Complete Spirometry Testing (SPIRO)
Complete assessment of Asthma Exacerbation (P6_SIGEX). If participant does not meet asthma exacerbation criteria, continue with "Upload spirotel®" below. If participant meets asthma exacerbation criteria, complete 1-6:

1. Update Treatment Failure Checklist (P6_TXFAIL_CHK)
2. Administer Asthma-Specific Work Productivity and Activities Impairment Questionnaire (WPAI_ASTHMA) for Visit 9X
3. Instruct participant to begin completing WURSS-21 forms
4. Administer Acute Asthma Assessment Questionnaire (AAAQ) for Visit 9X
5. Run AE Visit Scheduler
6. Instruct participant in use of prednisone and schedule combined Asthma Exacerbation (9XA) and crossover (or last) visit. STOP HERE; do not proceed with current visit.

Upload spirotel®
Collect Asthma Monitoring Log (P6_ASTHMA_LOG)
Print and review Spirotel® Participant Visit Report (replace previously generated report)
Print and review Spirotel® Participant Compliance Report (replace previously generated report) and update the SIENA Compliance Checklist (P6_COMPLY)

Update Treatment Failure Checklist (P6_TXFAIL_CHK), and complete Treatment Failure Information (P6_TXFAIL) if necessary (for participants who met treatment failure but not significant asthma exacerbation criteria)

➔ If treatment failure has occurred, re-schedule crossover (or last) visit so that open-label Asmanex® washout requirements are met (i.e. 3 weeks for first event, 14 days for second event in treatment period).

➔ Continue with remainder of visit packet.

Visit 5, 7, 9

Complete Pulmonary Procedure Checklist (P6_PULMONARYCHK)

Complete Spirometry Testing (SPIRO)

Complete assessment of Asthma Exacerbation (P6_SIGEX). If participant does not meet asthma exacerbation criteria, continue with "Upload spirotel®" below. If participant meets asthma exacerbation criteria, complete 1-6:

1. Update Treatment Failure Checklist (P6_TXFAIL_CHK)
2. Administer Asthma-Specific Work Productivity and Activities Impairment Questionnaire (WPAI_ASTHMA) for Visit 9X
3. Instruct participant to begin completing WURSS-21 forms
4. Administer Acute Asthma Assessment Questionnaire (AAAQ) for Visit 9X
5. Run AE Visit Scheduler
6. Instruct participant in use of prednisone and schedule combined Asthma Exacerbation (9XA) and crossover (or last) visit. STOP HERE; do not proceed with current visit.

Upload spirotel®

Collect Asthma Monitoring Log (P6_ASTHMA_LOG)

Print and review Spirotel® Participant Visit Report (replace previously generated report)

Print and review Spirotel® Participant Compliance Report (replace previously generated report) and update the SIENA Compliance Checklist (P6_COMPLY)

Update Treatment Failure Checklist (P6_TXFAIL_CHK), and complete Treatment Failure Information (P6_TXFAIL) if necessary (for participants who met treatment failure but not significant asthma exacerbation criteria)

➔ If treatment failure has occurred, re-schedule current visit so that open-label Asmanex® washout requirements are met (i.e. 3 weeks for first event, 14 days for second event in treatment period).

➔ Otherwise, continue with remainder of visit packet.

General Information

If a participant's prebronchodilator FEV_1 is < 50% of baseline (Visit 1) OR < 40% of predicted for the first time and the participant does not meet any other significant asthma exacerbation criteria, he/she must return to the performance site within 24-96 hours to have FEV_1 re-assessed.

Before dismissing the participant for 1-4 days, he/she should be given albuterol (≤6 puffs in one hour) to assess the degree of reversibility in his/her airflow obstruction. These values must be reported to the physician responsible for the care of the participant on that day. If the physician determines that the participant's response to the

bronchodilator is satisfactory, and the participant's clinical condition is stable, then the participant may continue in the study, as usual, provided he/she returns to the performance site in 1-4 days for repeat spirometry. The site coordinator should telephone the participant every 24 hours to assess his/her condition in the event that asthma exacerbation conditions have progressed. No additional procedures (e.g., sputum induction) scheduled for the day of the original visit should be performed. Be sure to return the participant's spirotel® device and SIENA Asthma Monitoring Log (P6_ASTHMA_LOG) to him/her before he/she leaves the performance site. Do not update the visit ID in the spirotel® device until the FEV_1 re-assessment visit date. If this occurs during the randomized treatment period and additional drugs are needed, backup dispensation for the previous visit should be performed.

At the FEV_1 re-assessment visit scheduled in the next four days, the participant will begin the visit by performing spirometry to determine if the FEV_1 criterion for significant asthma exacerbation is met. At Visits 2 and 2A, Exhaled Nitric Oxide testing will be performed prior to spirometry. Note that although participants should be encouraged to meet all the necessary drug and substance holds for spirometry testing, they may proceed with testing at re-assessment visits even if all the holds on the SIENA Pulmonary Procedure Checklist (P6_PULMONARYCHK) are not met. The P6_PULMONARYCHK form, ENO form during the run-in, and the Spirometry Testing (SPIRO) form from the re-assessment visit should be entered into the SIENA database as single forms (in addition to the regular packet forms), even if the participant does not meet the FEV_1 criterion.

Does not meet Significant Asthma Exacerbation criteria at Re-assessment Visit
If participant does not meet significant asthma exacerbation criteria at the FEV_1 re-assessment visit, after spirometry testing is complete, the participant's spirotel® device should be uploaded and his/her P6_ASTHMA_LOG should be collected. The Spirotel® reports (Participant Visit Report and Compliance Report) should be regenerated so that they include the balance of the visit data collected over the past 1-4 days since the original visit took place. The Participant Visit Report and P6_ASTHMA_LOG should be reviewed to determine if the participant has met the rescue use criteria for significant asthma exacerbation (or treatment failure, or symptom criteria for treatment failure) since the original visit. In the event that a criterion has changed, the applicable question on the Significant Asthma Exacerbation form (P6_SIGEX) should be updated. The Treatment Failure Checklist (P6_TXFAIL_CHK) should also be updated, and Treatment Failure Information (P6_TXFAIL) form completed if a participant met treatment failure but not significant asthma exacerbation criteria.

If the participant meets significant asthma exacerbation criteria based on rescue use, please see "Meets Significant Asthma Exacerbation criteria at Re-assessment Visit" below.

If the participant does not meet significant asthma exacerbation criteria, but does meet treatment failure criteria, see Treatment Failure discussion in this section for further information.

If the participant does not meet either signification asthma exacerbation or treatment failure criteria, the SIENA Compliance Checklist (P6_COMPLY) should be updated to reflect the additional spirotel® data in Question 1, and additional medication taken between original visit and FEV_1 re-assessment visit in Questions 2 and 3. Dates on these forms should be updated to the re-assessment visit date to confirm that they have been reviewed and updated accordingly. Original visit should proceed as outlined following FEV1 re-assessment section.

Meets Significant Asthma Exacerbation criteria at Re-assessment Visit
If a participant meets significant asthma exacerbation criteria during the Supervised Washout or run-in, he/she is ineligible and should be terminated.

If a participant meets significant asthma exacerbation during an FEV_1 re-assessment visit in the randomized treatment period, no additional visit procedures will be performed. Instead, forms completed at the Asthma Exacerbation phone visit, or Visit 9X (AAAQ, WPAI_ASTHMA, WURSS-21), will be completed and the Asthma Exacerbation visit scheduler will be run. At the time of the Asthma Exacerbation visit (Visit 9XA), which will occur after 3-7 days of prednisone treatment, the participant will cross over to the next treatment period (or have his/her final visit). In other words, the Asthma Exacerbation visit will coincide with the participant's crossover/last visit.

For FEV_1 re-assessments at Visits 4, 6 and 8, with exception to P6_COMPLY, forms completed at the original visit and those updated at the re-assessment visit (P6_TXFAIL_CHK) will be entered with the initial visit packet. This includes the ACT, ASUI, CMED, AECLIN, P6_TXFAIL_CHK, SEXAM_PED, P6_PULMONARYCHK, and SPIRO. The P6_PULMONARYCHK and SPIRO forms completed during the re-assessment visit will be entered as single forms with the visit number of the initial visit. P6_SIGEX will be entered with the Asthma Exacerbation visit packet, and P6_COMPLY will be entered with the crossover visit (or Visit 9) packet. See Compliance Monitoring below for details on handling spirotel® data.

For Visits 5, 7 and 9, only the P6_PULMONARYCHK, SPIRO, P6_TXFAILCHK and SEXAM_PED (for 12-17 only) forms for the initial visit and re-assessment visit will be entered. These forms will all be single forms, with the visit number prior to the cross-over visit. No other forms from the initial visit should be entered. See Compliance Monitoring below for details on handling spirotel® data. See the Significant Asthma Exacerbation discussion in this section for further details, including scheduling of crossover visit.

Note: When the participant returns for the FEV_1 re-assessment visit, the first procedure performed is eNO at Visits 2 and 2A and spirometry at Visits 3-9. Do not have the participant redo previously completed questionnaires at these visits; the questionnaires completed on the original visit date will be submitted with the visit packet.

Compliance Monitoring (P6_COMPLY)

Participants who experience a significant asthma exacerbation, causing him/her to not complete the middle visit of the treatment period (Visits 4, 6 or 8), should have the visit number of the cross-over/last visit (5, 7 or 9) for the entire period's spirotel® data. Following download and conversion of the spirotel® data, the visit ID should be updated in Breeze before the crossover/last visit occurs and reports are run at the crossover/last visit.

2.25 Genetics Blood Draw

Visit 2
Obtain blood sample for DNA extraction and genetic analysis (three 10 ml purple-top tubes) (optional)
Complete Genetic Analysis Blood Draw (GABLOOD) form
Enter genetics sample information into Genetics Tracking module, if applicable
Record genetic sample information on log (GEN_SAMP_LOG), if applicable

Genetics Consent
Before drawing blood for genetic analysis, verify that the participant or his/her guardian has given consent to participate in the genetic analysis component of the SIENA study. The genetic analysis blood draw is optional; as stated in the consent, participants can refuse this blood draw and still participate in every other aspect of the SIENA study. The genetic analysis participation rate for each clinical center partnership and performance site will be summarized on the SIENA Accrual Report.

Blood Draw
The genetic analysis blood draw is scheduled for Visit 2 in the SIENA protocol; however, blood may also be drawn at another future visit. See below for details on managing data in this case.

AsthmaNet genetics procedures are described in Appendix 4 of the AsthmaNet General Manual of Operations. The standard blood sample for genetic analysis purposes for participants ≥ 12 years old consists of three purple-top 10 mL vacutainers. Make certain that all tubes are as full as possible to ensure sufficient DNA for future genetic analyses. If a participant cannot provide three full purple-top vacutainers of blood, collect as much blood as possible and submit it to the Arizona Genetics Lab in Tucson for DNA extraction and storage.

Genetics Sample Tracking
Blood tubes collected for genetic analysis should be scanned into the AsthmaNet Genetics Tracking module immediately after they are drawn. The scan date is saved in the database and must be interpretable as the blood draw date. This information is forwarded to the Arizona Genetics Lab electronically and is needed for their tracking database and possible future sample submissions to the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC). Discrepancies between the scan date in the database and the blood draw date written on the blood tubes will be noted by the lab and reported to the DCC.

Information regarding the genetics blood drawn for a given participant must be entered onto the AsthmaNet Genetics Sample Log (GEN_SAMP_LOG) just prior to refrigerating the samples. This log tracks the collection date and time, refrigeration date and time and the volume of blood collected in each tube. The log collects information needed for BioLINCC purposes.

GABLOOD Form

Complete the Genetic Analysis Blood Draw (GABLOOD) form for all participants, regardless of whether or not they consent to provide a genetics blood sample. For those who elect to provide a blood sample, this form records information about their level of consent for future genetic analyses, as well as the total volume of blood drawn.

See Section 10 and Appendix 4 of the AsthmaNet General Manual of Operations and Section 4 of the SIENA MOP for specific information on completing the GABLOOD form. Note that the participant/guardian must review the form and complete the source documentation information (initials and date), even if he/she did not provide a blood sample.

Note: If a participant consents to provide a genetic blood sample, but the sample is not obtained at Visit 2 (due to a hard stick, dehydration or another problem), the blood draw may be delayed to any subsequent protocol visit. If the genetics blood draw is deferred to a future visit, the Visit 2 packet GABLOOD form should be marked missing. The GABLOOD form should be completed and data entered as a single form for the visit at which the blood draw takes place (e.g., Visit 3). If the blood draw is attempted at Visit 2 but is unsuccessful, and the participant is unwilling to have another draw attempted at a future visit, then the GABLOOD form should be completed and data entered as part of the Visit 2 packet. In that case, Q1000 and Q1010 should be completed, indicating that a blood sample was not obtained, and the participant should provide source documentation. All individuals who make it past Visit 2 in the study must have a GABLOOD form present in the database.

2.26 Geographic Information Systems (GIS) Add-on Study

Dr. Fernando Holguin, an investigator from the University of Pittsburgh AsthmaNet site, is the Principal Investigator on an R01 grant that is studying the application of geographic information systems (GIS) methodology in clinical trials. He plans to analyze the effect that local neighborhood and environmental factors have on asthma and the response to asthma drugs used in clinical trials. He has received approval from the Protocol Review Committee and the Data and Safety Monitoring Board to add the GIS study to the BARD, SIENA and STICS protocols.

It is well known that environmental factors, like traffic emissions, outdoor air pollution and neighborhood characteristics are related to asthma. The add-on study will help determine whether participants living in more polluted environments are less responsive to treatment or, alternatively, whether a particular treatment protects from the effects of traffic or air pollution. The GIS analysis will link the location of each SIENA participant's home to information about the local environment.

To carry out this project, Dr. Holguin must have access to a given participant's home address in order to map its geographic coordinates and link to databases that contain environmental, crime, and other statistics. A separate GIS consent has been developed to explain the project to each randomized participant (and his/her guardian, if applicable) and to ask for his/her consent for performance site personnel to download his/her address information to a secure site at the University of Pittsburgh where geographic coordinates will be determined and saved. Participation in the add-on study is optional. No participant stipend will be paid.

The full GIS Add-On study protocol and Manual of Procedures are posted on the secure AsthmaNet website in the Protocols: GIS Add-On Study folder.

Visit 3 (for randomized participants only)
Administer GIS consent; document assent as appropriate
Complete GIS Consent Tracking Form (GIS)

After the participant is randomized at Visit 3, introduce the GIS Add-On Study to him/her (and his/her guardian, if under 18). Explain that participation is optional and what it entails. Document the participant's decision regarding participation on the GIS Consent Tracking Form (GIS). One form should be completed for each randomized participant to allow the DCC to monitor participation and to provide input to the GIS researchers on which addresses they should have received. A form should be completed for randomized participants who do not consent to participate so that their status can be tracked.

Visit 3 (for randomized participants who consent to participate in the GIS Add-On Study only)
Complete the GIS Address Tracking Form (GIS_ADDRESS) with all addresses where

the participant has resided since enrolling in SIENA at Visit 1 (or Visit 0A)
Add the participant's address(es) to the GIS SIENA spreadsheet
Upload the updated spreadsheet to Pitt (see GIS MOP)

If the participant agrees to participate in the GIS Add-On Study, then further documentation is required. Complete an administrative GIS Address Tracking Form (GIS_ADDRESS) including all addresses where the participant has lived since enrolling in the SIENA trial at Visit 1 (or Visit 0A for Supervised Washout participants). Provide approximate dates of residence.

All addresses recorded on GIS_ADDRESS should be added to the bottom of the GIS SIENA address spreadsheet for the performance site. Ensure that addresses are being added to the correct spreadsheet. Each site should maintain a separate spreadsheet for BARD, SIENA, and STICS; IDs for participants from the various studies should not be combined into one spreadsheet.

The updated spreadsheet should be uploaded to the University of Pittsburgh each time an addition or update is made.

Visits 5, 7, 9 (for randomized participants who consent to participate in the GIS Add-On Study only)

Ask the participant for updated home address information (GIS_ADDRESS)
Add the participant's new address to the GIS SIENA spreadsheet, if applicable
Upload the updated spreadsheet to Pitt (see GIS MOP), if applicable

At each cross-over visit and at the final SIENA visit, participants who consented for the GIS Add-On Study should be asked to verify their current home address. If they have changed addresses, the updated address should be recorded on the GIS_ADDRESS form.

If a new address has been added to the GIS_ADDRESS form, the address should also be added to the bottom of the GIS SIENA address spreadsheet for the performance site. Ensure that addresses are being added to the correct spreadsheet. Each site should maintain a separate spreadsheet for BARD, SIENA, and STICS; IDs for participants from the various studies should not be combined into one spreadsheet.

The SIENA spreadsheet should be uploaded to the University of Pittsburgh each time an addition or update is made.

See the GIS Add-On Study MOP for additional information and general procedures related to this study.

2.27 Home Environment Questionnaire

Visit 2
Administer Home Environment Questionnaire (HEQ)

The Home Environment Questionnaire (HEQ) was developed by AsthmaNet. This questionnaire collects information about characteristics of the participant's home in general, his/her bedroom, his/her pets, and exposure to others' pets. Information regarding exposure to potential allergens that might affect the participant's asthma is collected in detail.

The questionnaire is completed by participant or guardian interview. The coordinator should provide assistance for any questions when requested. If the participant would rather not answer certain questions, they may be left blank. The participant/guardian should initial and date the source documentation box on the last page of the form when he/she is finished.

2.28 Household Socio-Economic Information Form

Visit 2
Administer Household Socio-Economic Information form (HOUSEHOLD_SEI)

Socio-economic status (SES) and health outcomes tend to be positively correlated (i.e., the higher the SES, the better the health outcome in terms of morbidity and mortality). Dr. Sheldon Cohen, affiliated with the Pittsburgh clinical center partnership, is an expert in this field and provided assistance for AsthmaNet to develop a very brief Household Socio-Economic Information (HOUSEHOLD_SEI) form. This form collects the highest level of education attained by members in a participant's household, the combined gross annual income of all members of the household, and the number of individuals supported by the income.

This form is completed by the participant or his/her parent/guardian. The respondent can decline to answer any question he/she wishes.

2.29 Informed Consent

Visit 1 (or Visit 0A for Supervised Washout Participants)
Acquire signed SIENA informed consent (acquire parent/legal guardian signature for ages 12 – 17)
Acquire signed (if applicable) or verbal SIENA assent

Informed consent **must** be obtained before any study information is collected or any study procedures are performed.

The SIENA consent template explains the procedures and time commitment necessary to participate in the SIENA trial, should the potential participant be deemed eligible. The AsthmaNet Data and Safety Monitoring Board reviewed and approved the template language which was prepared and submitted to each performance site's Institutional Review Board (IRB) for consideration. Some IRBs require or request changes to the template language which are reviewed by the DCC for consistency with the intent of the original document and completeness in terms of included information. A copy of the IRB approval memo and an IRB-stamped version of the consent document must be forwarded to the DCC prior to the start of recruitment at a given performance site. Each performance site must use its most recent IRB-approved version of the consent document in obtaining consent. The potential study participant must be given the opportunity to read, understand, and sign the consent document before any study-related activities take place. If the participant is a minor, his/her parent or guardian must read and sign the consent, and the participant must provide either written or verbal assent (according to local guidelines) before any study-related activities take place.

Guidelines for obtaining consent:

- At the beginning of Visit 1 (or Visit 0A for Supervised Washout Participants), or prior to scheduling the visit, provide the potential participant a copy of the informed consent document and ask him/her to read it thoroughly. The participant should not sign the form until after you have discussed its contents with him/her. A copy of the study assent form should accompany the consent if the potential participant is a minor. Follow local IRB guidelines on assenting participants.
- Allow ample time for the potential participant and/or the parent/guardian to read the informed consent form thoroughly. This will take some time, as the documents are often lengthy and include very detailed information for full disclosure.
- If the potential participant and/or the parent/guardian is unable to read the informed consent form or seems to be struggling, offer to read it to him/her or to help him/her with the more difficult sections.
- Be prepared to answer any questions the potential participant and/or the parent/guardian may have. If the person does not appear to understand the

study or what participation entails, or if he/she has any other doubts about enrolling or enrolling his/her child, do not ask him/her to sign the informed consent form. This person is not eligible to participate in the study.

- Maintain the signed informed consent form in the participant's study folder. To ensure confidentiality, **do not send this form to the DCC**. This document will be reviewed during data quality site visits.

If the participant fails to qualify during the Supervised Washout or run-in for a reason that can be remedied (e.g., respiratory tract infection, borderline compliance, etc.), he/she may be re-enrolled starting at Visit 1 (or Visit 0A) at a later date. During the new Visit 1 (or Visit 0A), the participant should be given a clean copy of the performance site's most current, IRB-approved SIENA consent document to review and sign. See the Re-Enrollment discussion in this section for further details.

If modifications are made to the SIENA consent document and approved by the local IRB while a participant is in the study, he/she must be re-consented following local IRB rules. All versions of the SIENA consent document the participant signed must be retained in his/her SIENA study folder and are subject to audit.

Local IRB rules and regulations regarding the consenting and assenting process should be followed at all times.

Note: The SIENA consent template contained language for the SIENA main study and optional genetic analysis participation. Some IRBs required the language for optional sections to be placed into its own consent document. At the participant's first visit, consent should be sought for the SIENA main study and genetics component, regardless of how they are packaged at a given performance site. All signed documents must be retained in the participant's study folder.

The date the participant signed the SIENA study consent is recorded and tracked on SIENA Eligibility Checklist 1 (or P6_ELIG0A for Supervised Washout participants). Genetic analysis participation is tracked on the Genetic Analysis Blood Draw (GABLOOD) form which is completed at the blood draw visit (Visit 2). See the Genetics Blood Draw discussion in this section for further details.

Visit 1
Administer BioLINCC consent; document assent, as appropriate
Complete BioLINCC Consent Tracking Form (BIOLINCC)

As a network funded by the National Institutes of Health, National Heart, Lung, and Blood Institute (NIH/NHLBI), AsthmaNet is expected to participate in the NHLBI's biobank which is coordinated by the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC). A biobank is a centralized collection of biological samples and health information that can be used by researchers outside of AsthmaNet for future studies in the areas of asthma and other diseases. At some time

in the future, with the acceptance of BioLINCC, leftover samples from the SIENA study (potentially including sputum supernatant, plasma, serum, DNA) will be transferred to BioLINCC and made available to other researchers. A participant or his/her parent or guardian must be asked to give his/her consent to transfer samples to BioLINCC. Samples for participants who refuse to provide consent will be retained by AsthmaNet. Participation is voluntary. See the AsthmaNet Genetics Procedures and BioLINCC manual in Appendix 4 of the AsthmaNet General Manual of Operations for further details regarding BioLINCC.

At Visit 1, after providing consent to be in the SIENA trial, the participant or his/her parent or guardian must be given the IRB-approved SIENA BioLINCC consent document to review. If he/she agrees to allow his/her leftover SIENA samples to be transferred to BioLINCC, he/she should sign the document and indicate the level of consent he/she is providing. Two levels of consent are possible: 1) allowing consent for all types of analyses, including genetic analyses, on the transferred samples and 2) allowing analyses with the exception of genetic analyses by researchers outside of AsthmaNet. The participant should indicate his/her preference in the consent document, prior to signing it. If the participant or his/her parent or guardian consents to participate in BioLINCC for his/her SIENA samples, then his/her consent document must be retained with the SIENA study consent document in his/her SIENA study folder at the performance site. This consent document is also subject to audit during an AsthmaNet data quality site visit.

Minor participants should be given an opportunity to provide assent for BioLINCC participation (either written or verbal, per local guidelines). The concept of the biobank should be explained to them in simple terms and they should be asked if they agree to participate, or not. Assent should be documented accordingly.

Every SIENA participant must have a BioLINCC Consent Tracking Form (BIOLINCC) completed at Visit 1. This form tracks whether or not the participant agreed to donate his/her leftover SIENA samples to BioLINCC and, if so, what level of consent he/she provided. Information submitted to the DCC on the BIOLINCC form must match the participant's consent document. The BIOLINCC form data will be used to determine which samples are transferred to BioLINCC in the future.

Visit 3
Administer GIS consent; document assent, as appropriate

After the participant is randomized at Visit 3, introduce the Geographic Information Systems add-on study to him/her (and his/her guardian, if under 18). Explain that participation is optional and requires the transmission of the participant's street address to the University of Pittsburgh so that its geographic coordinates can be mapped and stored for analysis. See the discussion of the Geographic Information Systems (GIS) Add-On Study in this section for further details. Document the participant's decision regarding participation on the GIS Consent Tracking Form (GIS). One form should be completed for each randomized participant to allow the DCC to monitor participation

and to provide input to the GIS researchers on which addresses they should have received. A form should be completed for randomized participants who do not consent to participate so that their status can be tracked.

Refer to the GIS Add-On Study MOP for information on storage of consent documentation and general procedures related to this study. There is no compensation to the participant or his/her parent/guardian for participation in this add-on study.

Note: Only individuals who become randomized at Visit 3 are eligible to participate in this add-on study.

2.30 Inhalation Technique Assessment

General Information
In the SIENA study, technique assessment will be done at Visit 1 for the RESCUE MDI, and at Visits 1, 3, 5, 7 and 9 for the tiotropium Respimat®. Technique assessment will be done at Visits 1, 3, 5, 7 and 9 for the mometasone Twisthaler® or MDI, depending on which mometasone device the participant is randomized to at Visit 3. Assessments are done to assure the participant is able to use these devices, as well as to document his/her ability to use them during the course of the study. Technique assessment forms will be data entered in SIENA.

MDI
For SIENA, the MDI Inhalation Technique Checklist (Without Spacer) (TECH_MDI_NOSP) has been adapted for data entry (P6_TECH_MDI_NOSP). During the MDI technique assessment, eleven separate criteria are assessed. Due to our inability to secure a supply of placebo MDIs to be used for technique assessment, technique assessment will be performed as part of the post-albuterol spirometry test, assessing after each two puffs of albuterol (up to 4 puffs) is given. The participant is given one point for each of the following steps that are completed correctly:

1. Removes cap of inhaler.
2. Shakes inhaler up and down.
3. Breathes OUT fully.
4. When breathing out fully, does so away from MDI.
5. Puts mouthpiece in mouth, closes lips around mouthpiece.
6. Activates inhaler by pressing down on canister one time.
7. Breathes IN SLOWLY, filling lungs with medicine.
8. Holds breath for at least 5 seconds (with or without mouthpiece in mouth).
9. Removes mouthpiece from mouth before breathing normally.
10. Breathes normally for at least 30-60 seconds.
11. Repeats steps #1 - #10

It is important to remind participants that exactly one actuation from the inhaler is allowed for each inspiration (i.e., no double, triple, etc. actuations for a single inspiration).

Results of the technique assessment are recorded on the P6_TECH_MDI_NOSP form. The P6_TECH_MDI_NOSP form should be completed until the participant achieves a score of 11.

Respimat®
For SIENA, the Respimat® Inhalation Technique Checklist (P6_TECH_RESP) has been developed. During the Respimat® technique assessment, thirteen separate criteria are assessed by observing the participant inhale from a training Respimat®. Training

Respimat® devices have been provided by Boehringer Ingelheim, along with mouthpieces. Participants will be assigned a mouthpiece at Visit 1 so that each training Respimat® can be used for multiple participants. The participant is given one point for each of the following steps that are completed correctly:

1. Holds the Respimat® upright with the grey cap closed.
2. Turns the clear base in the direction of the red arrows on the label until it clicks (half a turn).
3. Opens the grey cap until it snaps fully open.
4. Breathes OUT slowly and fully.
5. When breathing out fully (step #4), does so away from Respimat®.
6. Puts mouthpiece in mouth keeping it horizontal.
7. Closes lips around the end of the mouthpiece without covering air vents.
8. While taking SLOW, DEEP breath through mouth, PRESSES the dose release button.
9. Continues to breathe in slowly for as long as he/she can.
10. Holds breath for 10 seconds (or for as long as comfortable).
11. Removes Respimat® from mouth before breathing normally.
12. Closes the grey cap on the Respimat®.
13. Repeats steps #1 - #12.

Results of the technique assessment are recorded on the P6_TECH_RESP form. The P6_TECH_RESP form should be completed until the participant achieves a score of 13.

Twisthaler®

For SIENA, the Twisthaler® Inhalation Technique Checklist (P6_TECH_TWIST) has been developed. During the Twisthaler® technique assessment, thirteen separate criteria are assessed by observing the participant inhale from a placebo Twisthaler® provided by the DCC. The placebo Twisthaler® will be assigned to the participant for use throughout the study. The participant is given one point for each of the following steps that are completed correctly:

1. Holds inhaler upright with dose counter at bottom.
2. Twists the cap counterclockwise until it clicks.
3. Lifts off cap.
4. Breathes OUT fully.
5. When breathing out fully (step #4), does so away from inhaler.
6. Puts mouthpiece into mouth, closes lips around mouthpiece.
7. Holds inhaler horizontally.
8. Breathes IN QUICKLY, filling lungs with medicine.
9. Holds breath for at least five seconds (with or without mouthpiece in mouth).
10. Removes mouthpiece from mouth before breathing normally.
11. Replaces cap on inhaler.
12. Twists the cap clockwise until it clicks.
13. Repeats steps #1 - #12.

Results of the technique assessment are recorded on the P6_TECH_TWIST form. The P6_TECH_TWIST form should be completed until the participant achieves a score of 13.

Visit 0A

Instruct participant on use of albuterol (RESCUE) inhaler (HTMDI*, P6_ASWORSE*)

At Visit 0A, participant will be instructed on use of albuterol inhaler; however, no technique assessment will be done due to lack of placebo MDI.

Visit 1

Assess pre-education inhalation technique using the MDI Inhalation Technique Checklist (P6_TECH_MDI_NOSP) while participant takes his/her first two puffs of albuterol for the post-albuterol spirometry session

Instruct participant on use of albuterol (RESCUE) inhaler (HTMDI*) and coach/correct as needed

Administer an additional 2 puffs of albuterol (4 acceptable puffs total) and wait 10-15 minutes

- ➔ If pre-education score perfect, no post-education technique assessment is needed.
- ➔ If pre-education score is not perfect, assess post-education inhalation technique using the MDI Inhalation Technique Checklist (P6_TECH_MDI_NOSP) while participant takes 2 puffs of albuterol.

Assign participant an 'Inhalation Technique' Respimat® mouthpiece. Write participant's ID number on mouthpiece.

If participant has used Respimat® before, assess pre-education inhalation technique using the Respimat® Inhalation Technique Checklist (P6_TECH_RESP), placebo Respimat®, and assigned mouthpiece.

Instruct the participant on how to take the run-in inhaler (HTRESP*, P6_DAILYACT1*)

If using Respimat® for first time, or used Respimat® before and pre-education score not perfect, assess post-education inhalation technique using the Respimat® Inhalation Technique Checklist (P6_TECH_RESP) and placebo. Complete as many P6_TECH_RESP forms as necessary.

Store participant's Respimat® mouthpiece for use at future visits

Instruct participant on how to take RED albuterol and YELLOW Asmanex® 200 mcg MDI (HTMDI*, P6_ASWORSE*, P6_INHALE_KEY_DIF_2*)

MDI inhalation technique will be assessed at Visit 1 while participants receive albuterol as part of the post-albuterol spirometry session. A spacer should not be used. Participant's pre-education inhalation technique will be assessed while taking first two puff of albuterol. If pre-education score is perfect, no post-education technique assessment will be done. If pre-education score is not perfect, coach/correct as needed and assess post-education inhalation technique while participant takes their additional two puffs of albuterol. Complete up to two P6_TECH_MDI_NOSP forms.

A participant handout titled "How to Use Your Metered Dose Inhaler (MDI)" has been developed as a quick reference for the participant to ensure that he/she is using correct MDI technique at home. The coordinator should review this handout with the participant at the visit and answer any questions that arise.

At Visit 1, the participant will be assigned a Respimat® mouthpiece to be used throughout the study. Participant ID should be written on mouthpiece, and stored for use during the study. If participant has used Respimat® before, a pre-education inhalation technique assessment should be performed. All participants should then be instructed in how to use the Respimat® device. For those participants using Respimat® for first time and those who used Respimat® before but did not attain a score of 13 on the pre-education assessment, a post-education assessment should be performed.

A participant handout titled "How to Use Your Respimat®" has been developed as a quick reference for the participant to ensure that he/she is using correct Respimat® technique at home. The coordinator should review this handout with the participant at the visit and answer any questions that arise.

Because proper medication dosing is crucial for the success of the SIENA study, each participant must demonstrate that he/she can accurately use the MDI and Respimat® at Visit 1. Participants are considered eligible at Visit 1 only after they are able to carry out each of the eleven steps (corresponding to eleven points) listed on the P6_TECH_MDI_NOSP form and each of the thirteen steps (corresponding to thirteen points) listed on the P6_TECH_RESP form. This requirement is documented at Visit 1 on SIENA Eligibility Checklist 3 (P6_ELIG3). There is no upper limit on the number of test Respimat® puffs a participant may take to satisfy these requirements.

A participant handout titled "SIENA Inhalers: Key Differences" has been developed as a quick reference for the participant to ensure that he/she knows some of the slight differences on how to use an MDI and Respimat® at home. The coordinator should review this handout with the participant at the visit and answer any questions that arise.

Visit 3

Assign participant an 'Inhalation Technique' MDI. Write participant's ID number on MDI.
Assess pre-education inhalation technique using the MDI Inhalation Technique Checklist (No Spacer) (P6_TECH_MDI_NOSP) and placebo .
Re-educate participant on how to take the MDI inhaler (HTMDI*)
If pre-education score not perfect, assess post-education inhalation technique using the MDI Inhalation Technique Checklist (P6_TECH_MDI_NOSP) and placebo. Complete as many P6_TECH_MDI_NOSP forms as necessary.
Assess pre-education inhalation technique using the Respimat® Inhalation Technique Checklist (P6_TECH_RESP), placebo Respimat® and mouthpiece assigned at Visit 1. Re-educate participant on how to take the Respimat® inhaler (HTRESP*).

If pre-education score not perfect, assess post-education inhalation technique using the Respimat® Inhalation Technique Checklist (P6_TECH_RESP). Complete as many P6_TECH_RESP forms as necessary.

MDI Inhalation Technique will be assessed at Visit 3. Prior to reviewing how to take the MDI inhaler, a pre-education inhalation technique assessment will be performed. All participants will be re-educated on how to take the MDI inhaler, and post-education assessment will be performed for those participants not achieving a score of 10 on their pre-education assessment. There is no upper limit on the number of test puffs a participant may take to achieve a score of 10. Since the participant will dose one puff of the blinded MDI twice daily, the final step (repeating prior steps to take another puff) is not performed at Visit 3, 5, 7 and 9.

Because proper medication dosing is crucial for the success of the SIENA study, each participant must demonstrate that he/she can accurately use the MDI at Visit 3. There is no upper limit on the number of test puffs a participant may take to satisfy this requirement.

Respimat® Inhalation Technique will also be assessed at Visit 3. Prior to reviewing how to take the Respimat® inhaler, a pre-education inhalation technique assessment will be performed. All participants will be re-educated on how to take the Respimat® inhaler, and post-education assessment will be performed for those participants not achieving a score of 13 on their pre-education assessment. There is no upper limit on the number of test puffs a participant may take to achieve a score of 13.

Visit 5, 7

Assess pre-education inhalation technique using the Respimat® Inhalation Technique Checklist (P6_TECH_RESP), placebo Respimat® and mouthpiece assigned at Visit 1. Re-educate participant on how to take the Respimat® inhaler (HTRESP).

If pre-education score not perfect, assess post-education inhalation technique using the Respimat® Inhalation Technique Checklist (P6_TECH_RESP). Complete as many P6_TECH_RESP forms as necessary.

(For participants randomized to mometasone Twisthaler® at Visit 3) Assess pre-education inhalation technique using the Twisthaler® Inhalation Technique Checklist (P6_TECH_TWIST) and placebo Twisthaler® assigned at Visit 1. Re-educate participant on how to take the Twisthaler® inhaler (HTTWIST*).

(For participants randomized to mometasone Twisthaler® at Visit 3) If pre-education score not perfect, assess post-education inhalation technique using the Twisthaler® Inhalation Technique Checklist (P6_TECH_TWIST). Complete as many P6_TECH_TWIST forms as necessary.

(For participants randomized to mometasone MDI at Visit 3) Assess pre-education inhalation technique using the *MDI* Inhalation Technique

Checklist (P6_TECH_MDI_NOSP) and placebo MDI assigned at Visit 3. Re-educate participant on how to take the MDI inhaler (HTMDI*).

(For participants randomized to mometasone MDI at Visit 3) If pre-education score not perfect, assess post-education inhalation technique using the MDI Inhalation Technique Checklist (P6_TECH_ MDI_NOSP). Complete as many P6_TECH_ MDI_NOSP forms as necessary.

Respimat® Inhalation Technique will be assessed again at Visits 5 and 7. Prior to reviewing how to take the Respimat® inhaler, a pre-education inhalation technique assessment will be performed. All participants will be re-educated on how to take the Respimat® inhaler, and post-education assessment will be performed for those participants not achieving a score of 13 on their pre-education assessment. There is no upper limit on the number of test puffs a participant may take to achieve a score of 13.

For participants randomized to mometasone Twisthaler® at Visit 3, Twisthaler® Inhalation Technique will be assessed again at Visits 5 and 7. Prior to reviewing how to take the Twisthaler® inhaler, a pre-education inhalation technique assessment will be performed. All participants will be re-educated on how to take the Twisthaler® inhaler, and post-education assessment will be performed for those participants not achieving a score of 13 on their pre-education assessment. There is no upper limit on the number of test puffs a participant may take to achieve a score of 13.

For participants randomized to mometasone MDI at Visit 3, MDI Inhalation Technique will be assessed again at Visits 5 and 7. Prior to reviewing how to take the MDI inhaler, a pre-education inhalation technique assessment will be performed. All participants will be re-educated on how to take the MDI inhaler, and post-education assessment will be performed for those participants not achieving a score of 10 on their pre-education assessment. There is no upper limit on the number of test puffs a participant may take to achieve a score of 10.

Visit 9

Assess pre-education inhalation technique using the Respimat® Inhalation Technique Checklist (P6_TECH_RESP), placebo Respimat® and mouthpiece assigned at Visit 1.

(For participants randomized to mometasone Twisthaler® at Visit 3) Assess pre-education inhalation technique using the Twisthaler® Inhalation Technique Checklist (P6_TECH_TWIST) and placebo Twisthaler® assigned at Visit 1.

(For participants randomized to mometasone MDI at Visit 3) Assess pre-education inhalation technique using the MDI Inhalation Technique Checklist (P6_TECH_MDI_NOSP) and placebo MDI assigned at Visit 3.

Respimat® Inhalation Technique will be assessed again at Visit 9, but only a pre-education inhalation technique assessment will be performed.

For participants randomized to mometasone Twisthaler® at Visit 3, Twisthaler® Inhalation Technique will be assessed again at Visit 9, but only a pre-education inhalation technique assessment will be performed.

For participants randomized to mometasone MDI at Visit 3, MDI Inhalation Technique will be assessed again at Visit 9, but only a pre-education inhalation technique assessment will be performed.

Requirements for Technique Assessment Certification
Individuals must be certified on inhaler technique assessment for MDI (without spacer), Respimat®, and Twisthaler® devices before they can assess inhaler technique on SIENA participants. To obtain inhaler technique assessment certification for all three devices, the following must be completed:

1. Watch the MDI (without spacer), Respimat®, and Twisthaler® tutorial video links listed here and posted on the AsthmaNet secure website in the Certification: SIENA folder.
    - MDI without Spacer Tutorial Video
      http://youtu.be/X0beiU_abuw
    - Respimat Tutorial Video
      http://youtu.be/bdpmhbifcCM
    - Twisthaler Tutorial Video
      http://youtu.be/TubSIvOWj70
2. For *each* device, watch each of the certification exam videos one at a time, and assess technique by completing the appropriate device technique certification checklist for each of the videos (and noting the Video #):
    - P6_TECH_MDI_NOSP_CERT
        - MDI without Spacer Certification Exam Video 1
          http://youtu.be/1m5cfkTP2TE
        - MDI without Spacer Certification Exam Video 2http://youtu.be/9JQpo4ASoc0
        - MDI without Spacer Certification Exam Video 3
          http://youtu.be/6wbk3FDMmN4
    - P6_TECH_RESP_CERT
        - Respimat Certification Exam Video 1
          http://youtu.be/CVLVGIAld1k
        - Respimat Certification Exam Video 2
          http://youtu.be/iKf2uFqXBAg
        - Respimat Certification Exam Video 3
          http://youtu.be/dGLs9sCOXng

- P6_TECH_TWIST_CERT
    - Twisthaler Certification Exam Video 1 http://youtu.be/jPbMICuhLMU
    - Twisthaler Certification Exam Video 2 http://youtu.be/5C6MOSgc-oc
    - Twisthaler Certification Exam Video 3 http://youtu.be/EX2D2RNwx7c

Certification checklists, as well as links to videos, are posted on the AsthmaNet secure website in the Certification: SIENA folder.

3. For *each* device, assess inhaler technique using a placebo device on one naïve volunteer and complete the appropriate device technique certification checklist. The volunteer does not have to be an asthmatic; inhaler technique can be assessed for a healthy individual. Complete as many certification checklists for each device and provide feedback to the naïve volunteer until he/she has shown mastery of inhaler technique (teach-to-goal).
4. Once the assessor has successfully completed the above steps, the certification checklists should be scanned and emailed to the DCC at AsthmaNet-Certification@phs.psu.edu. In the subject of the email, type "Inhaler Technique Assessment Certification, Site #__, Coordinator ID#__". There should be 12 certification checklists, four for each device (three completed when watching the certification videos, and one completed on a naïve volunteer for each device).

2.31 Medical History

Visit 1 (or Visit 0A for Supervised Washout Participants)
Complete Adult Asthma and Allergy History form (ASTHMA_HX_ADULT)
Complete Prior Conditions for All Participants form (PRIOR_COND_ALL)
Complete Prior Conditions for Adult Participants form (PRIOR_COND_ADULT)
Complete Prior Asthma/Allergy Treatment form (PRIOR_TRT)

A comprehensive medical history is taken at Visit 1 (or Visit 0A for Supervised Washout participants). The medical history is broken into three parts recorded on four data collection forms:

1. The Adult Asthma and Allergy History (ASTHMA_HX_ADULT) form collects information regarding the onset of asthma and family history, recent asthma symptoms and acute episodes of asthma, asthma triggers, allergies, and basic smoking history.

   Note that smoking history is quantified in pack-years. One pack-year is defined as a one-year period when the participant smoked one pack (20 cigarettes per pack) per day. Participants whose smoking history changed over time will have their pack-year history calculated in pieces and summed over the entire history. For example:

   Sam smoked ½ a pack of cigarettes per day (10 cigs per day) while in his last year of college. Following college, he smoked a pack per day (20 cigs per day) for four years, until his employer no longer allowed smoking in the building. At that point he cut back to 5 cigarettes per day (0.25 packs per day) for 6 months while trying to quit. He has been a non-smoker ever since.

   Sam's pack-year history is calculated as follows:

   (1 x .5) + (4 x 1.0) + (.50 x .25) = 4.625 pack-years

   Sam may be eligible for SIENA, given his current non-smoker status and less than 10 pack-year history. Note that pack-year history is assessed for eligibility on Eligibility Checklist 2 (P6_ELIG2). Actual pack-years are recorded on ASTHMA_HX_ADULT.

2. The Prior Conditions for All Participants (PRIOR_COND_ALL) and Prior Conditions for Adult Participants (PRIOR_COND_ADULT) forms collect detailed information on prior diseases, illnesses, conditions and surgeries the participant has had.

   Ages 12-17: Complete only PRIOR_COND_ALL
   Ages 18 and over: Complete PRIOR_COND_ALL and PRIOR_COND_ADULT

3. The Prior Asthma/Allergy Treatment (PRIOR_TRT) form collects detailed information about the medications the participant used to treat asthma and allergies in the past 12 months. This form also collects non-asthma/allergy use of oral and injectable steroids. Information on this form will be used to determine if the participant meets necessary washouts for spirometry and for entry into the study according to the eligibility criteria.

For Supervised Washout participants, these forms will be reviewed at Visit 1, any necessary updates made, and entered with the Visit 1 packet.

The medical history is administered early in the visit so that eligibility criteria that are relatively easy to confirm can be checked quickly. All portions of the medical history are obtained by participant interview. Read each question to the participant in a consistent, even tone, exactly as written on the forms. Provide clarification when asked.

When available, information contained in medical records should be considered more accurate than participant reporting. If the coordinator chooses to report interview information rather than information from the participant's medical record (when it is available), the affected item(s) should be dated and initialed to document this override. A notation indicating the override should also appear in the clinic notes. This documentation will be necessary when the data are audited during a site visit.

See Section 10 of the AsthmaNet General Manual of Operations for further details regarding the completion of the medical history forms.

2.32 Methacholine Challenge

General Instructions
Methacholine challenges are used in the SIENA trial to establish a participant's study eligibility (through the PC_{20} criterion evaluated at Visit 1 continuation visit). Methacholine challenge will only be performed if the participant fails to qualify by reversibility at Visit 1.

Individuals performing methacholine challenges must be AsthmaNet-certified in this procedure or, at minimum, supervised by AsthmaNet-certified personnel.

To maximize supplies, old (unexpired) stock of methacholine should be used before newer lots.

Participants must pass all of the checks on the SIENA Pulmonary Procedure Checklist (P6_PULMONARYCHK) to proceed with spirometry and methacholine challenge at the visit. They must also pass all of the checks on the version of the Methacholine Challenge Testing Checklist that is applicable for their age group as follows:

- Age 12-17: Pediatric Methacholine Challenge Testing Checklist (METHACHK_PED)
- Age 18 and over: Adult Methacholine Challenge Testing Checklist (METHACHK_ADULT)

Note that METHACHK_ADULT and METHACHK_PED Q1050 exclude a participant from performing the challenge only if he/she used systemic corticosteroids for 4 or more days for treatment of an asthma exacerbation; if systemic steroid was used for a different indication, the question should be answered 'No.'

General procedures for carrying out a methacholine challenge can be found in the Methacholine Manual of Operations in Appendix 2 of the AsthmaNet General Manual of Operations.

Post-Methacholine Challenge Procedures
After a methacholine challenge has been completed, the participant should be reversed back to at least 90% of baseline (pre-challenge) lung function with albuterol. Baseline lung function (FEV_1) is obtained from Q1030 on the participant's Spirometry Testing (SPIRO) form completed at the visit.

Standard reversal is two puffs of albuterol if no sputum induction will follow at the visit. Eligible participants who will be proceeding with sputum induction should be reversed with four puffs of albuterol. Results of standard reversal are recorded on the Methacholine Challenge Testing (METHA) form.

Puffs of albuterol given to reverse the participant from a methacholine challenge should not be counted in the RESCUE ProAir® puffs the participant records on the Asthma Monitoring Log (P6_ASTHMA_LOG) the evening of the visit.

If a participant requires additional treatment to achieve reversal, this information should be recorded on the Additional Treatment Post Methacholine Challenge Testing (METHA_ADD_TRT) form. This form is entered as a single form.

See Section 10 of the AsthmaNet General Manual of Operations for details on the completion of these forms.

Visit 1

Complete Pediatric Methacholine Testing Checklist (METHACHK_PED) or Adult Methacholine Challenge Testing Checklist (METHACHK_ADULT)
Perform Methacholine Challenge Testing (METHA)
Complete Additional Treatment Post Methacholine Challenge (METHA_ADD_TRT) form, if needed

If participant does not reverse ≥ 12% at Visit 1 and does not have source documentation within the past 6 months for an overread AsthmaNet methacholine challenge with PC20 ≤ 16 mg/ml, Visit 1 will be stopped following post-albuterol spirometry testing and a continuation visit will be scheduled. Continuation visit should try to be scheduled to take place within 24-48 hours, and within 7 days maximum. Visit will start with completing Urine Pregnancy Test (PREG_TEST) form for all female participants, administering urine pregnancy test if necessary, followed by the completion of the Pulmonary Procedure Checklist (P6_PULMONARYCHK), FeNO testing (ENO) and spirometry testing (SPIRO).

Participants must pass all of the checks on the SIENA Pulmonary Procedure Checklist (P6_PULMONARYCHK) and the appropriate Methacholine Challenge Testing Checklist (METHACHK_ADULT or METHACHK_PED) before proceeding with the challenge. Results of the challenge are recorded on the Methacholine Challenge Testing (METHA) form and are referenced on SIENA Eligibility Checklist 3 (P6_ELIG3). The methacholine challenge report generated through the MedGraphics system must be printed and submitted with the data forms.

If an individual does not meet all the criteria on the Adult Methacholine Challenge Testing Checklist (METHACHK_ADULT) at Visit 1 continuation visit, the participant is ineligible to continue participation in SIENA. Likewise, participants who qualify for the methacholine challenge but do not meet the PC_{20} criterion for eligibility (PC_{20} ≤ 16 mg/ml) are also ineligible for the SIENA study. In these cases, data collected at Visit 1 for Supervised Washout participants should be data entered and submitted to the DCC, a SIENA Termination of Study Participant form (P6_TERM) should be completed, and study termination procedures followed. Data collected at Visit 1 for non-Supervised Washout participants should not be entered, and the Visit 1 packet should be filed in the

participant's study folder. See the discussion of Withdrawals in this section for further details.

2.33 Missed Visits

A missed visit is defined as one for which the participant is unavailable to undergo any clinic procedures for purposes of obtaining important outcome data for analysis. If spirometry is attempted during a visit, the visit is not considered missed, even if not all procedures are completed. If the Pulmonary Procedure Checklist (P6_PULMONARYCHK) is completed, the visit is not considered missed, even if the participant does not qualify to perform spirometry at the visit.

Spirometry is important to the SIENA study because it represents the third tier comparison between treatments for the primary composite outcome variable. Visits for which only administrative procedures, such as drug collection/dispensation, spirotel® download and quality control, and compliance assessments are carried out are considered missed visits as reflected on the SIENA Accrual Report.

Ideally, all visits for a participant should occur at the same time of day, as measured by the time that baseline spirometry takes place during a visit (+/- 3 hours of Visit 1 spirometry for run-in visits, +/- 3 hours of Visit 1 spirometry for post-randomization visits if randomized on or before September 8, 2015 OR +/- 3 hours of Visit 3 spirometry for post-randomization visits if randomized after September 8, 2015). When this is not possible, it is desirable for all visits to fall within a 4-hour window. Do not skip a visit if it is not possible to maintain these goals. Consistency in spacing of visits is more important for the collection of outcome data. If a participant cannot be seen within the 3-hour time window, contact the SIENA Scientific Coordinator at the DCC to discuss the allowance of an exception. Visits that take place outside the 3-hour window from the time of baseline spirometry at Visit 1 without a pre-approved exception will be assigned protocol deviations.

If it is not possible to schedule a visit within the regular visit window, schedule it in the extended window, if possible. If a participant cannot be seen within the extended windows, contact the SIENA Scientific Coordinator at the DCC to discuss alternate arrangements. See the Visit Windows discussion in this section for further details.

If a participant cannot come to the clinic at all within the regular or extended windows and no suitable alternate arrangements can be made, the visit will be considered missed. Arrangements should be made to send new study medications to the participant and an Asthma Monitoring Log (P6_ASTHMA_LOG). If at all possible the participant's spirotel® device should be returned to the performance site for downloading and quality control. Note that in the SIENA trial, due to its design, most visits cannot be missed. See below for visit-specific information.

Visits 1, 2, 3
These visits are mandatory. Eligibility assessments take place at Visits 1, 2 and 3, and randomization takes place at Visit 3. Contact the SIENA Scientific Coordinator at the

DCC if scheduling issues arise for these visits. If the participant cannot accommodate the screening visit schedule, then he/she may need to be terminated from the study and re-enrolled at a later date as his/her schedule permits.

Visit 2A

This visit is not required. Visit 2A is only needed for participants who require a third sputum induction to qualify for the study.

Visits 5, 7

These visits are mandatory. Visits 5 and 7 are the last visit of Periods 1 and 2, respectively, and serve as the end-of-treatment visits for these two periods. At these visits, participants will also be randomized to their next treatment assignment.

Visits 4, 6, 8

These visits occur in the middle of each of the three treatment periods. While it is not ideal for these visits to be missed, these visits may be missed if the participant experienced a significant asthma exacerbation and must crossover to the next treatment period or if absolutely necessary. Contact the SIENA Scientific Coordinator at the DCC to discuss possible options to prevent missed data for these visits.

If one of these visits must be missed for a reason other than crossing over into the next treatment period, the participant should be asked to return his/her spirotel® device to the performance site for download and quality control around the time of the ideal visits date for the missed visit, if at all possible. Arrangements should be made to get a new supply of study drugs to the participant before he/she runs out of his/her blinded Respimat® and Twisthaler®/MDI inhalers. New Respimat® and Twisthaler®/MDI inhaler numbers should be generated through the SIENA Randomization Module using the number of the missed visit, and a SIENA Scheduled Medications (P6_MED) form should be completed and data entered as a single form using visit ID of missed visit. When the inhalers are collected, a SIENA Compliance Checklist (P6_COMPLY) form should be completed for all returned inhalers. In this case, for participants randomized to the mometasone Twisthaler® device at Visit 3, the number of Twisthaler® puffs taken is equivalent to [(60 x # of returned Twisthalers®) – (# remaining puffs on all returned Twisthalers®)], as reflected on the Twisthaler® counters. For participants randomized to the mometasone MDI device at Visit 3, the number of MDI puffs taken is equivalent to [(120 x # of returned MDIs) – (# remaining puffs on all returned MDIs)], as reflected on the MDI counter(s). The same method applies for the Respimat® inhalers.

Visit 9

Visit 9 is the termination visit, and end-of-treatment visit for Period 3. For this reason, it cannot be missed.

2.34 Participant Assignment Log and Protocol Enrollment

A Participant Assignment Log (P6_LOG) has been developed for SIENA for each performance site. This log includes columns for unique participant ID numbers, participant initials, participant's name, and randomization status.

Participant ID numbers are preprinted on P6_LOG and are comprised of 7 digits:

- The first digit is the number of the AsthmaNet protocol. For the SIENA protocol the first digit is 6.
- The next 3 digits are the AsthmaNet performance site identifier
- The last 3 digits constitute the participant identification (ID) number that is unique within the performance site. Participant IDs start with 001 and increase sequentially for the number of participants who are screened for the SIENA protocol at Visit 0A and Visit 1 at a given site.

To assign an individual a participant ID number, select the next available blank entry on the SIENA Participant Assignment Log. This number will be the primary participant identifier used during the SIENA study; it should be used in all communications with the DCC. The participant ID number also should be used to label the participant's SIENA study folder at the performance site.

Once issued, a participant ID number cannot be re-assigned to any other person.

If a participant re-enrolls, a new participant ID number should be assigned. See the Re-Enrollment discussion in this section for further details.

In order to maintain participants' confidentiality, do NOT use participants' names in any communications with the DCC, either written or oral. Provide only participant ID numbers and initials.

The Participant Assignment Log (P6_LOG) is a confidential document because it ties a participant ID number to a name. This document is required when it is necessary to verify a participant's actual treatment assignment, either during or after the study. For this reason, this log should be stored in a secure location and retained indefinitely at the performance site following the close of the study.

Visit 1 (or Visit 0A for Supervised Washout Participants)
Assign participant ID number (P6_LOG)

Immediately following assignment of the participant's ID number on the SIENA Participant Assignment Log (P6_LOG), the protocol enrollment module should be accessed to formally enroll the participant in the SIENA database. Close attention should be paid when entering the participant's information to ensure that the correct ID

is entered. If a participant is enrolled mistakenly under an incorrect participant ID, the DCC should be contacted immediately for assistance in correcting the error.

Visit 3
Randomize participant, if eligible (Check box on P6_LOG)

After accessing the randomization module at Visit 3 to randomize the participant, check the box in the 'Randomized' column on the SIENA Participant Assignment Log (P6_LOG).

2.35 Participant Identification Card

The SIENA Participant Identification Card (P6_ID/P6_ID_2) provides a quick reference for the participant or his/her parent/guardian to use to monitor his/her asthma. It includes information for determining when an individual may be experiencing a treatment failure (prompting use of YELLOW open-label Asmanex® inhaler) or asthma exacerbation. The ID card also contains instructions for treatment of asthma attacks by physicians and emergency department personnel who may not be familiar with the SIENA study. The ID card should be carried by the participant at all times in a wallet or purse that is readily accessible.

P6_ ID is for participants randomized to Twisthaler; P6_ ID_2 is for participants randomized to MDI.

Visit 1
Complete and distribute Participant ID Card (P6_ID_2)

Print a SIENA Participant Identification (ID) Card (P6_ID_2). Write the participant's name, SIENA participant ID number, and the names and phone numbers of study personnel on the card. The participant may enter the name and number of his/her primary physician, if applicable. All information should be written in dark ink.

Fill in the participant's Baseline PEF and Rescue Use value in the spaces provided on the front of the ID card:

- The Baseline PEF can be found on the SIENA Baseline PEF and Rescue Use form (P6_BASELINE) in Q1000. (For Supervised Washout Participants, value can be found on SIENA Spirotel® Baseline Report.)
- The Baseline Rescue Use can be found on the SIENA Baseline PEF and Rescue Use form (P6_BASELINE) in Q1010. (For Supervised Washout Participants, value can be found on SIENA Spirotel® Baseline Report.)

On the back of the ID card, fill in the participant's Weekly High Rescue Use and 65% Baseline PEF values in the spaces provided:

- Weekly High Rescue Use value is calculated by multiplying Baseline Rescue Use value (Q1010 on P6_BASELINE) by 14. This result should complete the space here: "You used albuterol for relief of symptoms daily for 7 days and use exceeds____ puffs". (For Supervised Washout Participants, value can be found on SIENA Spirotel® Baseline Report.)

  Note: If a participant reports his/her baseline daily rescue use is 0, Weekly High Rescue Use will not factor into this criteria for treatment failure. The underlined portion of this statement should be blacked out: "You used albuterol for relief of symptoms daily for 7 days and use exceeds____ puffs".

- 65% Baseline PEF is calculated by multiplying Baseline PEF (Q1000 on P6_BASELINE) by 0.65. (For Supervised Washout Participants, value can be found on SIENA Spirotel® Baseline Report.)

Review the contents of the ID card with the participant or his/her guardian and explain the use of the card. Stress to the participant that the ProAir® (RESCUE) inhaler is the first-line treatment for asthma symptoms. Further information can be found on "If Your Asthma Gets Worse" handout (P6_ASWORSE). Rescue use should be monitored for treatment failure and need for YELLOW open-label Asmanex® inhaler. If no relief is achieved, the participant should contact performance site personnel to determine whether he/she should come to the clinical site or go to the emergency department for care. Review when and where emergency care should be sought. Remind the participant that he/she should seek care from study personnel, if possible. However, participants should never delay seeking care if study personnel cannot be reached.

Treatment procedures have been developed with the utmost regard for participant safety. Instruct the participant to contact study personnel if he/she receives emergency treatment outside the study. Document medications, procedures, and other treatments the participant received.

As indicated on the ID card, and the "If Your Asthma Gets Worse" handout, the participant should start the YELLOW open-label Asmanex® inhaler at 2 puffs, twice a day for 10 days, and contact study coordinator if he/she has:

- awakened due to asthma 3 or more times in a 2 week period, or on two consecutive nights, or
- used albuterol for relief of symptoms 4 or more times per day for 2 or more consecutive days, or
- used albuterol but it has relieved symptoms less than 4 hours after treatment, or
- used albuterol for relief of symptoms daily for 7 days and use exceeds X puffs (where X = two times the weekly use of albuterol in the baseline period), or
- Regular exercise has caused severe shortness of breath 2 or more days over a 7 day period.

Note: If a participant reports his/her baseline daily rescue use is 0, Weekly High Rescue Use will not factor into the criteria for treatment failure listed in the 4th bullet. The underlined portion of bullet #4 should be blacked out on ID card.

spirotel® alerts have been developed to inform the participant if his/her electronic diary entries meet any of the above criteria. Alert will read 'E-diary data indicates you need YELLOW inhaler. Call clinic ASAP.'

As indicated on the ID card, and the "If Your Asthma Gets Worse" handout, the participant should contact study coordinator if he/she has:

- taken 16 or more puffs of RESCUE albuterol inhaler on each of past 2 days, or
- started YELLOW inhaler for treatment failure and symptoms have not improved in 48 hours, or

- experienced a PEF that does not increase to greater than 65% of baseline after 60-90 minutes of RESCUE albuterol use, or
- experienced symptoms that are not satisfactorily relieved after 60-90 minutes of RESCUE albuterol use.

spirotel® alerts have been developed to inform the participant if his/her electronic diary entries meet the first or third criteria. Alerts will read 'Rescue use high; Call Clinic ASAP' or 'Peak flow is low. Call Clinic ASAP', respectively.

The first and second bullets (≥ 16 puffs albuterol on each of past 2 days, or taken YELLOW inhaler for treatment failure and symptoms have not improved in 48 hours) are SIENA significant asthma exacerbation criteria. If a participant meets either criterion, he/she will receive treatment with prednisone. The third and fourth bullets (PEF does not increase > 65% of baseline or symptoms are not satisfactorily relieved after 60-90 minutes of RESCUE use) may necessitate use of prednisone.

Visit 2 (for those not in Supervised Washout)
Update Participant ID Card (P6_ID_2)

Collect the participant's SIENA Participant ID Card (P6_ID_2). Print a new SIENA Participant Identification (ID) Card (P6_ID_2), and do the following:

- Complete the participant's name, SIENA participant ID number, site personnel contact information and primary physician contact information.
- The participant may enter the name and number of his/her primary physician, if applicable. All information should be written in dark ink.
- Fill in the participant's new Baseline PEF and Rescue Use values in the spaces provided on the front of the ID card. These values can be found on SIENA Spirotel® Baseline Report. Note: If a participant's Weekly High Rescue Use value is 0, the underlined portion of bullet #4 under "Start YELLOW inhaler" on Side 2 should be blacked out as is done at Visit 1: "You used albuterol for relief of symptoms daily for 7 days and use exceeds ____ puffs".
- On the back of the ID card, fill in the participant's Weekly High Rescue Use and 65% Baseline PEF values in the spaces provided. These values can be found on SIENA Spirotel® Baseline Report.

2.36 Participant Status Report

A SIENA Participant Status Report has been developed to communicate important information from the SIENA database to the performance sites on a participant-specific basis. The report shows, in numeric order of participant ID number, all participants enrolled in the SIENA trial at a specific performance site for whom Visit 1 (or Visit 0A) data have been entered, along with the columns of information defined below.

The Participant Status Report is accessed through the AsthmaNet secure website by clicking on the 'Participant Status Reports' link on the homepage and then choosing SIENA from the protocol list. If a coordinator has access to data from more than one performance site, he/she will need to choose the site for which the report is requested from a dropdown list. If a coordinator has access to data from only one performance site, the report request will be submitted automatically.

The Participant Status Report runs in real-time, accessing the current data in the database each time a request is submitted. Because the report is running a program in the background, it may take several seconds (or minutes as the database grows) for the results to appear.

Sputum Status: This displays results for the participant's V1, V2 and V2A (if performed) sputum slide reads. Displays 'Yes' if sputum was "Acceptable" at the visit or 'No' if sputum was not "Acceptable" based on data recorded on the sputum forms.

Eosinophil Group: Indicates if the participant is in the "High" or "Low" eosinophil group. This is necessary for back-up randomization.

Pre-Rand Term: Indicates if the participant was terminated from SIENA prior to randomization at Visit 3. Sets to 'Yes' if P6_TERM indicates that the participant terminated prior to randomization.

Randomized: Participant's randomization status. Updates to 'Yes' when the participant is randomized at Visit 3.

Visit 3-8 Inhalers: Displays Respimat® and Twisthaler®/MDI code numbers assigned to a participant at each of the referenced visits (through randomization module). If backup inhaler(s) are assigned for a particular visit, its number will show under the original inhaler number(s) assigned for that visit.

Post-Rand Term: Indicates if the participant terminated from SIENA after randomization and before completion of Visit 9. Sets to 'Yes' if

participant terminates early (when P6_TERM is entered); sets to 'No' when a randomized participant completes the trial.

Completed Study: Indicates if the participant completed the SIENA trial through Visit 9. Sets to 'Yes' when a participant's P6_TERM form is entered indicating study completion. Sets to 'No' for participants with Post-Rand Term status of 'Yes.'

Current Status: The participant's current study status is summarized in the following categories:

1. Enrolled in run-in (individuals who have Visit 0A data entered, no P6_TERM form, and have not yet been randomized at Visit 3)
2. Run-In term (individuals who have a P6_TERM form indicating termination prior to randomization)
3. Randomized and currently active (randomized at Visit 3 and no P6_TERM form entered)
4. Post-randomization drop-out (randomized and P6_TERM is entered and Q1000=0)
5. Completed SIENA (completed study through Visit 9; P6_TERM Q1000=1)

The bottom of the Participant Status Report gives a frequency table for the 'current status' variable for all participants at a given performance site.

2.37 Perceived Stress Scale

The following information was taken from Dr. Sheldon Cohen's write-up on the following website: http://www.mindgarden.com/products/pss.htm:

"The Perceived Stress Scale (PSS) is the most widely used psychological instrument for measuring the perception of stress. It is a measure of the degree to which situations in one's life are appraised as stressful. Items were designed to tap how unpredictable, uncontrollable, and overloaded respondents find their lives. The scale also includes a number of direct queries about current levels of experienced stress. Moreover, the questions are of a general nature and hence are relatively free of content specific to any sub-population group. The questions in the PSS ask about feelings and thoughts during the last month. In each case, respondents are asked how often they felt a certain way.

Higher PSS scores have been associated with: failure to quit smoking, failure among diabetics to control blood sugar levels, greater vulnerability to stressful life-event-elicited depressive symptoms, and more colds."

The 10-item PSS[9] (PSS-10) has been incorporated into an AsthmaNet-formatted form, the Perceived Stress Scale (PSS_10) form. AsthmaNet received approval for use of the formatted form from Dr. Sheldon Cohen, one of the scale's original authors.

Visit 3
Administer Perceived Stress Scale (PSS_10)

The administration of the PSS-10 is one of the first procedures performed at Visit 3. This timing in the visit structure is intentional so that a participant's responses are not affected by other study procedures, such as spirometry and e-diary/peak flow review. Study coordinators should observe the order of procedures as they are laid out on the visit procedure checklists to ensure that PSS results are not biased by other study activities.

The PSS-10 is completed by the participant. When administering the questionnaire, request that the participant complete the entire 10-question form and provide answers as completely and as accurately as possible. No stated or implied time limit should be set. If the participant requests help with or clarification of any question, the study coordinator should instruct the participant to reread the instructions and to give the best answer possible to each question. The study coordinator should not provide an answer to any question. Providing guidance may bias the participant's responses.

Participants should use a black or blue pen to complete the questionnaire. If the participant wishes to change a response, the original response should be crossed out

[9] Cohen, S and Williamson, G. Perceived Stress in a Probability Sample of the United States. Spacapan, S. and Oskamp, S. (Eds.) *The Social Psychology of Health.* Newbury Park, CA: Sage, 1988.

with a single line and then dated and initialed by the participant. The final response should be circled for clarification. No changes to the participant-completed form may be made by study personnel; changes may only be made by the participant.

When the participant is finished with the questionnaire, collect it and review it for completeness before proceeding with the visit. If a question has been left blank, ask the participant to do his/her best to answer it. The answers to all of the questions are necessary to score the instrument. Check that the participant's responses are clearly marked.

The participant should provide source documentation on the PSS-10 form by providing his/her initials and the date/time in the source documentation box. Review the source documentation provided by the participant to ensure that the date and time are accurate before collecting the form.

2.38 Phone Contact

Run-in Phone Contacts – Visit 1 (Week 1.5), 2 (Week 4.5)
The SIENA protocol designates 3 weeks between Visits 1 and 2, and 3 weeks between Visits 2 and 3. To ensure that the participant is taking his/her run-in Respimat®, completing e-diary questions and peak flows, to inquire as to whether any spirotel® alerts were received and to address the participant's concerns regarding his/her asthma control, formal phone contacts should be scheduled between these visits, approximately mid-way through the 3-week interval. In order for a participant to be eligible for randomization, he/she must maintain a high level of compliance with dosing from his/her run-in Respimat® and with performing e-diary and peak flow procedures, so it is important to ensure the participant is carrying out his/her home procedures correctly.

Phone contacts are documented on the SIENA Phone Contact form (P6_CONTACT_2). This is an administrative form; data are not entered into the database. Completed forms should be stored in the participant's study folder at the performance site; do not forward these forms to the DCC. Phone contact documentation is subject to audit during an AsthmaNet site visit.

Phone contacts should be scheduled according to the dates provided on the participant's Visit Scheduler Report generated at Visit 1. If multiple attempts are made to contact the participant within the range of dates given on the report and no contact is made, the coordinator should continue to try to get in touch with the participant until his/her next scheduled visit. Document all contact attempts on P6_CONTACT_2.

If the participant requires Visit 2A to perform a third sputum induction, a Visit Scheduler will be run at that visit to provide the date for the phone contact between Visit 2A and 3, and the Visit 3 date.

Post-Randomization Phone Contacts – Visit 3 (week 9), 4 (week 15), 5 (week 21), 6 (week 27), 7 (week 33), 8 (week 39)
The SIENA protocol designates 6 weeks between Visits 3 and 4 and 6 weeks between Visits 4 and 5 during treatment period 1, 6 weeks between Visits 5 and 6 and 6 weeks between Visits 6 and 7 during treatment period 2, and 6 weeks between Visits 7 and 8 and 6 weeks between Visits 8 and 9 during treatment period 3. Because of the lack of clinic contact during these periods of the study, formal phone contacts should be scheduled between these visits. Phone contacts allow the coordinator to address the participant's concerns regarding his/her asthma control and to schedule an extra clinic visit, if needed. These phone contacts also afford the coordinator an opportunity to ensure that the participant is carrying out his/her home procedures correctly, including taking study medications and completing e-diary questions and peak flows, and to inquire as to whether any spirotel® alerts were received.

Phone contacts should be scheduled around the 3-week point in the visit intervals described above (i.e., mid-way through the 6-week interval). Ideal contact dates are

listed on the Visit Scheduler Reports run at Visits 3-8. If multiple attempts are made to contact the participant within the range of dates given on the report and no contact is made, the coordinator should continue to try to get in touch with the participant until his/her next scheduled visit. Document all contact attempts on the SIENA Contact Form (P6_CONTACT/P6_CONTACT_2).

P6_ CONTACT is for participants randomized to Twisthaler; P6_ CONTACT_2 is for participants randomized to MDI.

Refer to Section 4 of this MOP for more details on how to complete this form.

2.39 Physical Exams

See Section 3 of the AsthmaNet General Manual of Operations for information regarding the physical exam clinical procedures. SIENA-specific procedures follow.

Adult Procedures

The following procedures apply to SIENA participants who are age 18 and over only.

Adult physical exams are documented on administrative forms that are not entered into the study database. Comprehensive exams are documented on the Adult Long Physical Exam form (LEXAM_ADULT) and brief exams are documented on the Adult Short Physical Exam form (SEXAM_ADULT). These forms should be completed at the applicable visits and stored in the participant's study folder at the performance site. These forms are subject to audit during an AsthmaNet site visit.

The short physical exam includes measures of resting blood pressure, pulse rate, and body temperature, as well as results of pulmonary auscultation. Short exams can be performed by study coordinators, registered nurses, physician assistants, and other individuals who are appropriately trained in these procedures and certified in the SIENA protocol.

The long physical exam includes the measurements made during a short physical exam, as well as documentation of the presence/absence of oral candidiasis and physical findings. A licensed medical practitioner (LMP) must complete the physical findings and pulmonary auscultation portions of the long exam. A LMP is defined as a physician (MD/DO), physician assistant (PA), or nurse practitioner; a registered nurse does not qualify as a LMP. If a non-physician LMP completes a required long exam at the beginning or end of a study, the participant still must have interaction with a physician during the visit. The individual performing the long exam should be certified in the SIENA protocol unless he/she is filling in temporarily for personnel who usually conduct these exams. Individuals who will provide these exams on a regular basis should possess SIENA certification (physician or coordinator exam).

In addition to regular physical exams, additional physical measurements including height and weight, and waist, hip and neck circumference, are taken for adults at various points during each study. These measurements are documented on the Adult Body Measurements form (BODYMEAS_ADULT) and entered into the AsthmaNet database. Body measurements can be made by study coordinators, registered nurses, physician assistants, and other individuals who are appropriately trained in these procedures and certified in the SIENA protocol.

Note that height will be measured at all visits for adult participants who are between the ages of 18 and 21, until the participant reaches age 21. For visits where no BODYMEAS_ADULT form is completed, the height measurement will be recorded on

the SIENA Pulmonary Procedure Checklist (P6_PULMONARYCHK). Height updates are required for adults in this age range because they may still be growing and height impacts predicted lung function estimates.

Visit 1 (or Visit 0A for Supervised Washout Participants), 9, 90A-92A
Perform Adult Long Physical Exam (LEXAM_ADULT)

A long physical exam is required at Visit 1 (or Visit 0A for Supervised Washout participants) in order to ensure that it is safe and appropriate for each participant to enroll in the SIENA study. A long exam is required at Visit 9 to ensure that the participant leaves the study in good health with plans for follow-up care, as needed. A long exam will also be performed at the participant's asthma exacerbation visit.

For the SIENA trial, participants must have interaction with a physician at Visits 1 (or Visit 0A for Supervised Washout participants), 9 and 90A-92A, even if the physician is not performing the long exam.

The LMP conducting the long physical exam should sign, date and note the time in the gray box on the LEXAM_ADULT form as source documentation.

Visit 2-8 (as well as Visits 0B, 1 for Supervised Washout Participants)
Perform Adult Short Physical Exam (SEXAM_ADULT)

A brief physical exam is conducted at Visits 2-8 (as well as Visits 0B and 1 for Supervised Washout participants).

The person conducting the physical exam should sign, date and note the time in the gray box on the SEXAM_ADULT form as source documentation.

Visit 1 (or Visit 0A for Supervised Washout Participants), 9
Complete Adult Body Measurements form (BODYMEAS_ADULT)

Follow the instructions on the form for making the various measurements. Body mass index (BMI) should be calculated and written in the gray box under Q1010. This value is not entered into the study database but it should be available for reference during the trial.

Note that height is captured on the BODYMEAS_ADULT form for adults at Visit 1 (or Visit 0A for Supervised Washout participants) and Visit 9. Individuals who are less than 21 years of age will have their heights updated at every visit until the point when they turn 21. Updated heights are recorded on the SIENA Pulmonary Procedure Checklist (P6_PULMONARYCHK) for these individuals.

Pediatric Procedures

The following procedures apply to SIENA participants who are ages 12-17 only.

Pediatric physical exams are documented on data collection forms that are entered into the study database. Comprehensive exams are documented on the Pediatric Long Physical Exam form (LEXAM_PED) and brief exams are documented on the Pediatric Short Physical Exam form (SEXAM_PED). These forms should be completed at the applicable visits and entered with the data packet.

Ages should not be rounded up when choosing to complete the pediatric or adult packet, even if a participant is very close to his/her 18th birthday. Pediatric physical exams should continue to be completed for participants who turn 18 during the course of SIENA.

The pediatric short physical exam includes measures of height and weight and assessment for oral candidiasis. Physical findings are also assessed (but are not data entered). Short exams can be performed by study coordinators, registered nurses, physician assistants, and other individuals who are appropriately trained in these procedures and certified in the SIENA protocol.

The pediatric long physical exam includes the measurements made during a short physical exam, as well as documentation of a more extensive list of physical findings. A licensed medical practitioner (LMP) must complete the physical findings and pulmonary auscultation portions of the long exam. A LMP is defined as a physician (MD/DO), physician assistant (PA), or nurse practitioner; a registered nurse does not qualify as a LMP. If a non-physician LMP completes a required long exam at the beginning or end of a study, the participant still must have interaction with a physician during the visit. In most cases the professional who performs the long physical exam should be certified in the SIENA protocol. If a LMP does physical exams for SIENA only infrequently, as a short-term replacement for the usual LMP staff, then it is not required that he/she pass the protocol exam.

Note that height will be measured at all visits for pediatric participants in an effort to update their predicted lung function values as their height and age increase.

Note that plotting of height and weight on age-appropriate growth charts is not required for the SIENA trial. This study does not include a growth failure protocol. We will use the collected heights to analyze growth trends with respect to study treatments at the end of the trial.

Visit 1 (or Visit 0A for Supervised Washout Participants), 9, 90A-92A
Perform Pediatric Long Physical Exam (LEXAM_PED)

A long physical exam is required at Visit 1 (or Visit 0A for Supervised Washout participants) in order to ensure that it is safe and appropriate for each participant to enroll in the SIENA study. A long exam is required at Visit 9 to ensure that the participant leaves the study in good health with plans for follow-up care, as needed. A long exam will also be performed at the participant's asthma exacerbation visit.

For the SIENA trial, participants must have interaction with a physician at Visits 1 (or Visit 0A for Supervised Washout participants), 9 and 90A-92A, even if the physician is not performing the long exam.

The LMP conducting the long physical exam should sign, date and note the time in the gray box on the LEXAM_PED form as source documentation.

Visit 2-8 (and Visits 0B, 1 for Supervised Washout Participants)
Perform Pediatric Short Physical Exam (SEXAM_PED)

A brief physical exam is conducted at Visits 2-8 (as well as Visit 0B and 1 for Supervised Washout participants).

The person conducting the physical exam should sign, date and note the time in the gray box on the SEXAM_PED form as source documentation.

2.40 Pregnancy Test

At protocol-defined visits, urine samples will be obtained from female participants of child-bearing potential for assessment of pregnancy by the presence of the beta subunit of human chorionic gonadotropin (HCG). Testing will be performed at the performance site during the participant's visit using the HCG combo stick test approved by each institution. The results of the pregnancy test should be recorded on the Urine Pregnancy Test (PREG_TEST) form and the participant should initial and date the source documentation box to acknowledge the results. If a participant is found to be pregnant at any point during the SIENA study, she must be terminated from study participation immediately. See additional instructions below.

Visits 1, 1 Continuation Visit, 9
Complete Urine Pregnancy Test form (PREG_TEST) form for all female participants; administer urine pregnancy test, if necessary

At the designated visits, the PREG_TEST form is required for all female participants, regardless of their child-bearing potential. A urine pregnancy test must be administered if the participant is deemed to be of child-bearing potential.

At all relevant visits, if the participant is potentially able to bear children by the information supplied on the PREG_TEST form, the pregnancy test must be performed and results reported to the participant and to the DCC. Follow local and state regulations regarding reporting of pregnancies to parents/guardians in the case of participants who are minors.

Participants who are post-menopausal (defined as at least one year since last menses) or have undergone a hysterectomy or tubal ligation do not need to be tested. Juvenile participants who are pre-menarche also do not need to be tested. The parent/guardian should provide source documentation for pre-menarche individuals. This information is documented on the PREG_TEST form.

Note that a history of infertility does not constitute a valid reason to skip the pregnancy test at a visit, nor does a participant’s insistence that she does not have heterosexual intercourse.

Note that individuals who are transgendered or are transitioning to the opposite gender should be tested for pregnancy in accordance with their biological sex. Biologically female participants who are of child-bearing potential must use birth control and provide urine for pregnancy tests as required by the protocol.

After performing a urine pregnancy test, the participant should be shown the results and asked to initial and date the source documentation box at the bottom of the form as verification that the information on the form is correct and acknowledged by her.

Source documentation should be completed even if a pregnancy test was not performed at the visit. In most cases the participant will provide the source documentation. If a participant is pre-menarche, the parent/guardian should provide the source documentation.

Visit 1 (including Continuation Visit for Methacholine Challenge)
If a participant is considered able to bear children, results of the pregnancy test must be known before she proceeds with the diluent stage of the methacholine challenge at Visit 1 Continuation Visit. Pregnant women should not perform methacholine challenges. In addition, pregnant or nursing participants are ineligible for the SIENA protocol.

Pregnancies Discovered during Study Participation
If a woman is found to be pregnant at any time during the study, either through a pregnancy test performed at a study visit or through another means, she is ineligible for continued participation. Pregnant women should be seen at the performance site and terminated from further study participation immediately. Participants who become pregnant during the study should have a SIENA Termination of Study Participation (P6_TERM) form submitted to the DCC as soon as possible recording pregnancy as the primary reason for study termination (Q1040 should be answered 'Yes' and Q1200 should be answered 'a'). Pregnancy should not be reported as an adverse event or as a serious adverse event in the SIENA database.

Boehringer Ingelheim (BI), provider of drugs for the SIENA study, requires reporting of serious adverse events that occur during pregnancy. This applies to randomized participants, as well as non-randomized participants. Participants should be asked to report serious adverse events that occur during pregnancy, and these should be reported using the BI Investigator-Initiated Serious Adverse Event Reporting Form. A locked Word version with fillable fields has been provided to ease reporting of events. This is located in the Protocols: SIENA: Documents folder. Form instructions and a brief PowerPoint overview of the form are also posted. Completed forms should be emailed to Anne-Marie Dyer (adyer@psu.edu) and Ron Zimmerman (rzimmerm@phs.psu.edu).

See Section 10 of the AsthmaNet General Manual of Operations for further details on the completion of the Urine Pregnancy Test (PREG_TEST) form.

2.41 RAND Impact of Asthma on Quality of Life SF-12 (RAND_IAQL_12)

General Instructions
Asthma questionnaires, including quality of life assessments, are generally the first procedures completed at a visit. Visits have been structured in this fashion so that participant responses will not be affected (biased) by other study procedures, such as spirometry, physical exam, and diary review. Questionnaire administration must not be moved to a different place in a study visit; it must be performed where indicated on the specific visit procedure checklist, relative to other procedures. The order of the questionnaires within a visit also should not be altered.

If a visit is partially completed and then rescheduled, and questionnaires were already completed, they must be completed anew at the beginning of the rescheduled visit. Do not allow the respondent to refer to or update his/her previously completed questionnaires. Old copies of the questionnaires should be filed in the participant's study folder or shredded; they should not be entered into the study database or forwarded to the DCC. Note that this procedure does not apply to FEV_1 re-assessment visits. For these visits, the original previously-completed questionnaires will be submitted with the visit packet.

Basic guidelines for the administration of quality of life questionnaires follow.

- Administer the questionnaire in a relaxed environment where the respondent can concentrate on the questions without distraction.
- Provide the respondent a black pen and a writing surface.
- Be available for assistance; however, be careful not to lead the respondent or influence his/her responses.
- If a respondent is unclear on what a question means, it is best simply to repeat it exactly as it is worded. If the respondent asks for an explanation, say "Whatever it means to you." Never try to interpret or reword a question. This may introduce bias in his/her responses. Instruct the respondent to answer the question(s) to the best of his/her ability.
- Do not help a participant (or respondent) select an answer. For example, if a participant asks, "Well, my shortness of breath has been pretty bad recently. Does that mean I should choose 2?" Instead of saying "Yes," say, "There is no *right* answer. Select the number that best indicates how your shortness of breath, as a result of your asthma, has been in the last X weeks." X refers to the recall window for the particular questionnaire.
- Be neutral when hearing any potential responses. Be sure that your words or manner do not imply surprise, sympathy, approval, or disapproval. For example, if a participant expresses frustration with

his/her asthma while completing the questionnaire, do not express concern or sympathy at this time. This may require you to ignore your instincts and training. Wait until after the questionnaire is complete to offer advice, encouragement or suggestions.

When the participant (or respondent) is finished with the questionnaire, collect it and review it for completeness before proceeding with the visit. If a question has been left blank, ask the respondent to do his/her best to answer it. The answers to all of the questions are very important. Check that the responses are clearly marked.

Note: The *informed administration* approach will not be used in AsthmaNet studies; the participant/respondent should not look at past responses to the questionnaire when completing the form at a given visit.

General Information

Given how pervasive and impairing asthma is, there has been increased attention to the development and use of asthma outcome measures, particularly patient-reported outcomes that may be more meaningful to patients than traditional clinical markers of asthma severity. One key outcome is disease-specific quality of life (QOL), the patient's subjective perception of the impact of a disease and its treatment on his/her life (in contrast to general QOL, a broader measure of well-being). Asthma-specific QOL can be distinguished from asthma symptoms—for example, how often one experiences wheezing—in that asthma-specific QOL is a gauge of how much symptoms bother or matter to a patient in different areas of life.

According to the expert panel report (EPR-3) released by the National Heart, Lung, and Blood Institute's (NHLBI) National Asthma Education and Prevention Program, the goals of asthma treatment include improving the QOL for people who have asthma, controlling symptoms, reducing the risk of exacerbations, and preventing asthma-related death. Because these targeted aspects of asthma may respond differently to treatment, they should be monitored separately. Yet available instruments often confound QOL with asthma control, defined as the extent to which manifestations of asthma (symptoms, functional impairments, and risks of negative events) are minimized and goals for treatment are met. QOL items are commonly combined with items measuring asthma symptoms and functional impairment (e.g., limitations in daily activities, such as housework and walking up hills) in creating total scores. Thus, no existing instrument is able to provide separate and distinct information on the impact of asthma on QOL. This key limitation of asthma-specific QOL measures was emphasized by leaders in asthma research and practice at the Asthma Outcomes Workshop convened by the NHLBI in March 2010. At this workshop, the Asthma Related Quality of Life Subcommittee declined to recommend any existing instrument as a core outcome measure of asthma-specific QOL, and instead strongly recommended that new instruments be developed that measure the impact of asthma on QOL as a construct distinct from asthma control.

To address this need, Cathy Sherbourne, Maria Orlando Edelen, Nicole Eberhart, Brian Stucky, and Marielena Lara were funded by NHLBI to develop a freely available new system for measuring the impact of asthma on QOL that avoids confounding QOL with asthma symptomatology and functional impairment. The system, referred to as The RAND Impact of Asthma on Quality of Life item bank (RAND-IAQL), contains 65 items that focus on the patient's perception of the impact or bother of asthma on his/her QOL, and includes content ranging across many domains of life important to people with asthma. They also created freely available 4-item and 12-item short forms. Their developmental process began with formative work including literature review and expert recommendations, but the majority of the item content was generated based on feedback from adults with asthma who participated in focus groups. Salient themes generated from focus group discussions included both general (e.g., enjoyment of life) and specific (e.g., sleep difficulty, affect, medication dependence and side effects, physical activity limitations, social relations, health concerns) areas of impact. From these sources they arrived at a set of items representing a wide range of content regarding the impact of asthma on QOL. These items were then field-tested in a web-based sample of 2032 ethnically diverse adults who reported that they had asthma. Using data from a large national field test of adults with asthma, they evaluated the pool of candidate items using modern psychometric methods, including item response theory (IRT) and computerized adaptive tests (CAT). When conducting an IRT analysis items are "calibrated" (or characterized) to indicate the strength of the relationship between the item and the construct being measured (here the impact of asthma on QOL) and the location on the construct's scale where the item is most informative. The collection of calibrated items is referred to as an "item bank." The item bank provides a flexible and potentially sustainable assessment environment that minimizes respondent burden without sacrificing precision. A psychometric evaluation of the RAND-IAQL item bank suggested that though the concept of asthma impact on QOL is multi-faceted, it may be measured as a single underlying construct. Subsets of items from the bank can be administered either adaptively (i.e., with computer adaptive testing), or through carefully selected fixed-length instruments (i.e., short forms) that can be tailored to achieve various measurement goals. From the final set of 65 items two short forms were developed: 1) A brief 4-item short form comprised of items measuring general aspects of the impact of asthma on QOL (reliability = .86) and 2) a 12-item short form which contains the 4 general items along with 8 additional items that measure content-specific aspects of QOL (e.g., physical activity limitations, social concerns, health concerns, and sleep (reliability = .93)). Compared to the full item bank the RAND-IAQL-4 and RAND-IAQL-12 sacrifice very little measurement precision, despite drastically reducing respondent burden.

Validity results from their field data indicate that the RAND-IAQL measures distinguish between levels of asthma control. The impact of asthma on QOL was greater in persons with indicators of more severe asthma, and in persons with comorbid medical and mental conditions and greater health care utilization.

Additional evidence is needed from clinical samples, as the initial field test was conducted in an online convenience sample of individuals with asthma. Use of a clinical

sample would ensure appropriateness of the measure for clinical use, and would enable the researchers to conduct validity analyses not only in relation to patient-reported outcomes, but also using objective physiologic measures (spirometry, methacholine challenge, sputum eosinophils, and other physiologic measures). Furthermore, it is important to examine the responsiveness of the RAND-IAQL to established and experimental treatment, and to determine a minimal clinically important difference for the outcome measure. An efficient method for gathering this important additional validity and responsiveness information is to piggy-back the new questionnaire on ongoing clinical trials, including the SIENA study.

Visits 3, 5, 7, 9
Administer Impact of Asthma on Quality of Life (RAND_IAQL_12)

The RAND IAQL-12 (12-item short form) has been incorporated in the SIENA study at visits when the other QOL questionnaires are administered. It will be self-administered and completed by the participant. This questionnaire has a 4-week recall window.

Note that this questionnaire includes a source documentation box. After reviewing the completed form for accuracy and completeness, the participant should initial, date and record the time in the source documentation box on page 2.

2.42 Randomization

Visit 3
Randomize participant, if eligible (Check box on P6_LOG)
Log/dispense Respimat® and MDI inhalers (P6_DRG_SCH_RESP, P6_DRG_SCH_MDI)
Confirm Respimat® and MDI dispensations (P6_MED)

SIENA is a three-period crossover trial during which each participant receives treatment with three different regimens over the course of his/her study participation. Each treatment period is 12 weeks long. The three treatment regimens employed during the study are:

- active tiotropium (LMA) and placebo mometasone (ICS)
- placebo tiotropium (LMA) and active mometasone (ICS)
- placebo tiotropium (LMA) and placebo mometasone (ICS)

Tiotropium dosing is 2 puffs in the morning, mometasone Twisthaler® dosing is 2 puffs BID, and mometasone MDI dosing is 1 puff BID. Due to FDA approval for the mometasone MDI in summer 2014, production of the mometasone Twisthaler® was discontinued. Therefore, participants randomized in SIENA after mm/dd/yy were randomized to the mometasone MDI device. Participants randomized to mometasone Twisthaler® prior to this date will continue to use the Twisthaler® device for the remainder of their time in SIENA.

Each participant will be randomized to a specific order of regimens to be received during the three treatment periods. The order of treatment administration is referred to as the treatment 'sequence.' For example, one treatment sequence would be: placebo tiotropium and active mometasone in period 1, placebo tiotropium and placebo mometasone in period 2, and active tiotropium and placebo mometasone in period 3.

Target sample size is 336 randomized participants Network-wide, 262 in the eosinophilic phenotype and 74 in the non-eosinophilic phenotype. The target is for 25% (84) adolescent participants as well.

Randomization balances treatment sequence assignments within the nine partnerships (i.e., Boston, Chicago, Denver, Madison, Pittsburgh, St. Louis, San Francisco, Tucson/Durham, Winston-Salem/Emory), not within a given performance site. Randomization within each partnership is stratified on eosinophil group: High (one or two measures of sputum eosinophil ≥ 2%); or Low (two measures of sputum eosinophil % < 2%) based on two acceptable sputum inductions during the run-in.

At the end of Visit 3, if the participant meets all of the eligibility requirements to date and documented on SIENA Eligibility Checklist 5 (P6_ELIG5), he/she is eligible to be

randomized. The study coordinator should access the SIENA Randomization Module on the secure AsthmaNet website and enter the appropriate visit number (i.e., 3), the participant's SIENA ID number, and the performance site at which the participant is being randomized. At this point, the system is assigning the participant's treatment sequence and allocating Respimat® and MDI inhalers that correspond to his/her assigned regimen for treatment period 1. The module will display 2 Respimat® inhaler numbers and 1 MDI number. Assigned numbers for Respimat® inhalers will have the format 300000 to 329999, for mometasone Twisthaler® inhalers will have the format 100000 to 129999, and for mometasone MDI inhalers will have the format 200000 to 229999. Respimat® inhalers will have blue labels and Twisthaler®/MDI inhalers will have white labels. **Forms and handouts will refer to these inhalers by the color of their label.** Visit 3 randomization must be performed the day of Visit 3 after eligibility has been confirmed (P6_ELIG5).

After the participant is randomized successfully, the 'randomized' box should be checked on the SIENA Participant Assignment Log (P6_LOG). The assigned Respimat® and MDI numbers should be logged on the Participant-Specific Drug Accountability Log for Post-Randomization Respimat® (P6_DRG_SCH_RESP) and Participant-Specific Drug Accountability Log for Post-Randomization MDI (P6_DRG_SCH_MDI). Information on the participant's assigned Respimat® and Twisthaler®/MDI numbers at each visit will also be included on the SIENA Participant Status Report.

In order to validate the assigned Respimat® and MDI inhaler numbers through the SIENA database, the SIENA Scheduled Medications form (P6_MED) should be completed any time a Respimat® or MDI number is generated through the randomization module to be dispensed to a participant. Remove the labels from the assigned Respimat® boxes and MDI boxes and attach them to Q3 or Q5 on the P6_MED form. This form will be data entered as part of the Visit 3 packet.

It should be noted that participants can be randomized in the SIENA randomization module at Visit 3 only if <u>all</u> of the following criteria are met:

1) The participant's SIENA ID number is enrolled in the SIENA protocol.
2) The participant's Visit 1 packet, including Visit 1 eligibility data, has been entered at the performance site (only first entry required). The Visit 1 eligibility forms (P6_ELIG1, P6_ELIG2 and P6_ELIG3) must indicate that the participant is eligible (P6_ELIG1 Q1140=1 and P6_ELIG2 Q1210=1 and P6_ELIG3 Q1130=1).
3) The participant's Visit 2 packet, including Visit 2 eligibility data, has been entered at the performance site (only first entry required). The Visit 2 eligibility form (P6_ELIG4) must indicate that the participant is eligible (P6_ELIG4 (vnum=2) Q1070=1).
4) Participant must have two acceptable sputum samples, defined by the following at a visit (either V1, V2 or V2A):

- SPUTUMCHK Q1070 = 1
- SPUTUM Q1070 = 1
- SPUTLAB Q1030 = 1
- SPUTREAD Q1010 in (1, 2, 3, 4)
- SPUTREAD Q1050 < 80
- SPUTREAD Q1090 not missing

5) No SIENA Termination of Study Participation (P6_TERM) form has been entered for the participant.

See Section 3 of this manual for details on accessing and interacting with the SIENA Randomization Module.

Note that treatment sequence and regimen assignments in the SIENA study are double-blind. That is, neither the participant, nor performance site personnel, will be aware of the contents of the participant's blinded Respimat® or Twisthaler®/MDI inhalers from Visit 3 through 9. The majority of DCC personnel are also blinded to the treatment assignments while the study is ongoing.

Visits 4-8
Generate new Respimat® and Twisthaler®/MDI inhaler numbers via Randomization Module
Log/Dispense Respimat® and Twisthaler®/MDI inhalers (P6_DRG_SCH_RESP, P6_DRG_SCH_TWIST/P6_DRG_SCH_MDI)
Confirm Respimat® and Twisthaler®/MDI dispensations (P6_MED)

At Visits 4-8, clinic personnel must utilize the SIENA Randomization Module to generate numbers for new Respimat® and Twisthaler®/MDI inhalers from which the participant will take his/her daily doses until the next regularly scheduled visit. To prepare for an upcoming visit and to provide lead time for the investigational pharmacists, the Respimat® and Twisthaler®/MDI numbers may be generated up to <u>one business day</u> ahead of Visits 4-8. Because the Twisthalers expire 45 days from the date the foil pouch is opened, and the visit windows are 6 weeks, pharmacy labeling Twisthalers on Friday for a Monday visit is not preferred. Doing so shortens the expiration window to 42 days at time of dispensation, and allows no extra days within expiration window should the participant fail to return within the visit window. Randomization can occur on Friday for a Monday visit; however, it is ideal for pharmacy to remove and label the Twisthalers Monday rather than Friday.

The study coordinator should access the SIENA Randomization Module on the secure AsthmaNet website and enter the applicable visit number from a dropdown menu, the participant's SIENA ID number, and the performance site at which he/she is being seen for the visit. The randomization module will display the participant's new Respimat® and Twisthaler®/MDI numbers. The assigned Respimat® and Twisthaler®/MDI numbers

should be logged on the Participant-Specific Drug Accountability Log for Post-Randomization Respimat® (P6_DRG_SCH_RESP) and Participant-Specific Drug Accountability Log for Post-Randomization Twisthaler® (P6_DRG_SCH_TWIST) or Participant-Specific Drug Accountability Log for Post-Randomization MDI (P6_DRG_SCH_MDI), depending on mometasone device participant was randomized to at Visit 3, for the applicable visit number. Affix labels from the Respimat® boxes and Twisthaler® pouches/MDI box for all dispensed inhalers to the P6_MED form in the visit packet. Information on the participant's assigned Respimat® and Twisthaler®/MDI numbers at each visit will also be included on the SIENA Participant Status Report.

It should be noted that the following criteria must be met at Visits 4-8 before Respimat® and Twisthaler®/MDI numbers will be displayed:

1) The participant must have been randomized via the SIENA Randomization Module at Visit 3.
2) The participant must not have been terminated from the study (i.e., no P6_TERM form has been entered).
3) The cross-over visit (i.e., visits 5, 7) must have been completed and had Respimat® and Twisthaler®/MDI inhalers assigned before the module will return numbers for subsequent visits during the same treatment period. For example, Visit 5 randomization must have taken place before Visit 6 Respimat® and Twisthaler®/MDI inhalers will be assigned.
4) Respimat® and Twisthaler®/MDI inhalers will not be assigned for a given visit number if they have already been assigned beyond that visit number. For example, if a participant had Respimat® and Twisthaler®/MDI inhalers assigned at Visit 5, no inhalers can be assigned for Visit 4. If additional Respimat® and Twisthaler®/MDI inhalers are requested for Visit 5, the coordinator will be taken through the backup assignment process as outlined below.

Backup inhalers

If a participant loses his/her blinded inhaler(s) between visits, then he/she will require the assignment of a new (backup) Respimat® and/or Twisthaler®/MDI. To generate a new Respimat® and Twisthaler®/MDI number, the study coordinator should access the SIENA Randomization Module on the secure AsthmaNet website and enter the applicable visit number (i.e., the same visit number for which the previous (lost) Respimat® and/or Twisthaler®/MDI numbers were generated) from a dropdown menu, the participant's SIENA ID number, and the performance site at which he/she is being seen for the visit. The randomization module will recognize that the participant has already had inhalers assigned for this visit number and will provide a warning message giving the coordinator a chance to cancel out of the module if a mistake has been made. If the coordinator chooses to proceed, the module will ask the coordinator to specify the number of Respimat® (zero, one or two), and Twisthaler® (zero, one, two, or three) or MDI (zero or 1) inhalers needed by checking the box beside the correct number.

The assigned Respimat® and Twisthaler®/MDI number(s) should be recorded on the Participant-Specific Drug Accountability Log for Post-Randomization Respimat® (P6_DRG_SCH_RESP), and Participant-Specific Drug Accountability Log for Post-Randomization Twisthaler® (P6_DRG_SCH_TWIST) or Participant-Specific Drug Accountability Log for Post-Randomization MDI (P6_DRG_SCH_MDI) for the applicable visit number. Information on the participant's assigned Respimat® and/or Twisthaler®/MDI backup number(s) at each visit will also be included on the SIENA Participant Status Report. A SIENA Scheduled Medications single form (P6_MED) should be completed and data entered any time one or more backup inhalers are dispensed to a study participant. Affix labels from the Respimat® box(es) and/or Twisthaler® pouch(es)/MDI box for all dispensed inhalers to the P6_MED form.

Backup randomization procedures

In the rare event that the SIENA Randomization Module is unavailable during any visit when it is required (i.e., visits 3-8 or backup dispensations for any of these visits), clinic personnel must contact the DCC for assistance. During week days (Monday through Friday) between 8 AM and 5 PM ET, calls should be made to the AsthmaNet main line at 717-531-3663. The SIENA scientific coordinator, project coordinator, or one of the data management staff will be able to assist with backup randomization procedures. After regular work hours, calls should be made to the AsthmaNet main line and the option for after-hours emergency contact for SIENA should be chosen. The SIENA scientific coordinator will answer and facilitate backup randomization procedures.

It is extremely important that blinded Respimat® and Twisthaler®/MDI inhalers are assigned using the SIENA Randomization Module. Randomly choosing an available inhaler at Visits 4-8 and assigning it to a participant in lieu of the randomization module is inappropriate, as it may not contain the participant's assigned treatment regimen for the current treatment period. If an incorrect Respimat® or Twisthaler®/MDI is dispensed to a participant, a protocol violation will be assigned.

2.43 Recruitment

SIENA visits will commence on June 15, 2014. Nine clinical center partnerships composed of 27 participating performance sites will recruit for SIENA.

A recruitment period of 16 months has been established for SIENA, with the final randomization visit occurring by the end of September 2015 in order to complete the trial by the end of June 2016.

The gender and minority status of individuals screened and enrolled at Visit 1 and individuals randomized in SIENA will be summarized by clinical center partnership and, within each partnership, by performance site on the SIENA accrual report. This report will be available on the secure AsthmaNet website in the Reports: Accrual: SIENA folder shortly after recruitment begins. Partnerships should strive to screen at least 50% female participants and 33% minority participants over the recruitment period.

Target sample sizes for each partnership are based on the number of participants who are successfully entered into the run-in, and subsequently randomized in the SIENA trial. Each of the nine clinical center partnerships is expected to randomize approximately 32 adult and 10 adolescent participants for a Network total of 384 participants. With a recruitment period of 16 months, that is equivalent to 2.62 randomized participants per partnership per month.

Approximate SIENA Timelines

June 15, 2014:	First participant screened (Visit 0A)
July 30, 2014:	First participant randomized (Visit 3)
August 1, 2015:	Final screening visit (Visit 1)
September 15, 2015:	Final randomization visit (Visit 3)
June 30, 2016:	Final participant visit (Visit 9)

2.44 Re-Enrollment

Participants who do not successfully complete the SIENA Supervised Washout or run-in for reasons that may be overcome with time or additional training (e.g., use of excluded medications, respiratory infection, borderline compliance, etc.) may be suitable candidates to re-enroll in SIENA for a second attempt. Participants who are not able to provide two acceptable sputum samples in their first enrollment should not be re-enrolled. Randomized participants who drop out early may not re-enroll in the trial.

Visit 1 Failures (or Visit 0A Failures for Supervised Washout Participants)
Participants who do not qualify for the SIENA study at Visit 1 (or Visit 0A for Supervised Washout Participants) for reasons that may be overcome with time (e.g., insufficient medication washout, respiratory infection in past 4 weeks, use of excluded medications, etc.) may be invited to repeat Visit 1 (or Visit 0A) at a later date. Data collected during the unsuccessful Visit 1 (or Visit 0A) should not be entered into the AsthmaNet database and forms should not be forwarded to the DCC regardless of whether the participant will re-enroll in the study or not. The Visit 0A packets should be stored at the performance site in a section of folders denoted as 'SIENA Visit 0A Failures,' and the Visit 1 packets should be stored at the performance site in a section of folders denoted as 'SIENA Visit 1 Failures.'

Participants who return to the performance site for a second attempt at Visit 1 (or Visit 0A) should repeat all of the Visit 1 (or Visit 0A) procedures as listed on SIENA Visit Procedure Checklist (P6_VISIT1 or P6_VISIT0A). A new visit packet should be completed.

When re-enrollment occurs, the following procedures apply:

- The participant must be given a new SIENA participant ID number from the Participant Assignment Log (P6_LOG). See the Participant Assignment Log discussion in this section and Section 4 for further details. This new ID will need to be linked to the participant through the protocol enrollment process before data can be entered into the SIENA database. For information on the protocol enrollment process, refer to Section 7 of the AsthmaNet General Manual of Operations.
- The participant and/or his/her parent/guardian must read and sign new copies of the current IRB-approved SIENA and BioLINCC informed consent/assent documents. The documents signed at the initial enrollment should reside in the folder created for the participant's original ID number. The newly signed consent documents should reside in the participant's current study folder. Informed consent documents should not be updated with a new signature and date, as this practice violates institutional procedures at some of the performance sites.
- The Adult or Pediatric Participant Contact Information (CONTACT_ADULT or CONTACT_PED) form should be reviewed and updated by the participant or

his/her parent/guardian, as necessary. A photocopy should be made and stored with the participant's original Visit 1 (or Visit 0A) packet. The original form with updates should be stored in his/her new study folder.

- A new Visit 1 (or Visit 0A) packet with the participant's new ID number should be completed and submitted to the DCC if the participant is now eligible. Do not attempt to update previously-completed forms with the participant's new information. A new study folder should be created to house the participant's forms under his/her new study ID number.

After a Successful Visit 1 (or Visit 0A for Supervised Washout Participants) and Prior to Randomization at Visit 3

Once a participant is deemed eligible at Visit 1 (or Visit 0A), he/she is formally enrolled in the SIENA study. The data collection forms from Visit 1 (or Visit 0A) should be entered into the study database and forwarded to the DCC.

If a participant withdraws consent or is deemed ineligible during the run-in (or Supervised Washout), then he/she must be formally terminated from the study. A SIENA Termination of Study Participation (P6_TERM) form should be completed and entered into the database. All of the forms completed at the termination visit should be entered into the AsthmaNet database and sent to the DCC. If any blood or sputum samples were collected during the run-in, they should be sent to the appropriate labs according to the instructions in this section of the MOP.

Such participants should not be invited to re-enroll unless their reason for withdrawing or being withdrawn was such that there is a very high probability that re-entry will result in randomization and full participation in SIENA. For example, if extenuating circumstances caused a participant to miss visits or not be able to carry out daily procedures for a period of time, then he/she may be a good candidate to re-enroll after life settles down and adequate time can be devoted to study procedures. A participant terminated at Visit 2 because he/she was not able to produce one acceptable sputum sample (or terminated at Visit 2A because he/she was not able to produce two acceptable sputum samples) should <u>not</u> be re-enrolled.

Participants who are good candidates for re-enrollment must re-enter the SIENA study starting anew at Visit 1 (or Visit 0A).

The following guidelines apply when the participant is re-enrolled:

- The participant must be given a new SIENA participant ID number from the Participant Assignment Log (P6_LOG). See the Participant Assignment Log discussion in this section and Section 4 for further details. This new ID will need to be linked to the participant through the protocol enrollment process before data can be entered into the SIENA database. For information on the protocol enrollment process, refer to Section 7 of the AsthmaNet General Manual of Operations.

- The participant and/or his/her parent/guardian must read and sign new copies of the current IRB-approved SIENA and BioLINCC informed consent/assent documents. The documents signed at the initial enrollment should reside in the folder created for the participant's original ID number. The newly signed consent documents should reside in the participant's current study folder. Informed consent documents should not be updated with a new signature and date, as this practice violates institutional procedures at some of the performance sites.
- The Adult or Pediatric Participant Contact Information (CONTACT_ADULT or CONTACT_PED) form should be reviewed and updated by the participant. A photocopy should be made and stored with the participant's original Visit 1 (or Visit 0A) packet. The original form with updates should be stored in his/her new study folder.
- The Adult Asthma and Allergy History (ASTHMA_HX_ADULT) form, Home Environment Questionnaire (HEQ), Prior Conditions for Adult Participants (PRIOR_COND_ADULT) form, Prior Conditions for All Participants (PRIOR_COND_ALL) form, and Prior Asthma/Allergy Treatment (PRIOR_TRT) form may be reused if they were completed at Visit 1 during the participant's prior enrollment. These forms must be reviewed with the participant in detail and updated appropriately. The participant's new ID number and visit date must be written on the forms. A photocopy should be made and stored with the Visit 1 (or Visit 0A) packet from the participant's original enrollment. The form with the handwritten updates should be stored in his/her new study folder and sent to the DCC.
- All study procedures must be carried out anew, with the exceptions noted above, beginning with Visit 1 (or Visit 0A). Complete and submit new data collection forms for the participant using his/her new participant ID number and current dates.
- The blood draw for genetic analysis is optional in the SIENA study; however, participants who gave a sample prior to their study termination should be asked to provide a new blood sample upon re-enrollment, if the participant is amenable. New blood and sputum samples must be obtained at the applicable visits.

After Randomization in SIENA

Participants who withdraw consent after they have been randomized in the SIENA study at Visit 3 are NOT eligible to re-enroll. Each participant can contribute only one set of data for the analysis.

2.45 Registration

At or prior to first visit
Register participant in AsthmaNet Registry

Before a participant can be enrolled in the SIENA trial, he/she must be present in the AsthmaNet Registry with 'complete' status. ACRN and CARE Network participants who completed Registry forms in those networks already will have 'complete' status in the AsthmaNet Registry. Any participants from the earlier networks who have 'incomplete' status, or individuals who are new to the NHLBI asthma networks, will need to undergo the full AsthmaNet registration process.

All individuals who are enrolled in the SIENA trial will need to have AsthmaNet label sheets and reports printed and stored with the AsthmaNet Registry documentation.

Complete Registry procedures are documented in Section 9 of the AsthmaNet General Manual of Operations.

Visit 1 (or Visit 0A for Supervised Washout Participants)
Complete Registry Checklist (REG_CHK)

Follow the procedures for completing the Registry Checklist (REG_CHK) as outlined in Section 9 of the AsthmaNet General Manual of Operations. Attach one of the participant's "Registry Checklist" labels to the gray box at the bottom of the checklist before submitting the form to the DCC. This label contains the participant's AsthmaNet master ID number and serves as a reference during the protocol enrollment process.

Include REG_CHK behind the Visit Procedure Checklist (P6_VISIT1 or P6_VISIT0A) in the participant's Visit 1 (or Visit 0A) packet.

2.46 Satisfaction Questionnaire

Participant's termination visit
Give participant AsthmaNet Satisfaction Questionnaire (SATQX) with preaddressed, postage-paid envelope

The AsthmaNet Satisfaction Questionnaire (SATQX) is a quality control tool that was developed by the AsthmaNet Quality Control Committee (QCC) to solicit feedback from participants when they leave AsthmaNet studies. The questionnaire is anonymous in that no participant or master ID number or other identifying information is recorded on the form. In addition, the participant returns the form directly to the DCC in a pre-addressed, postage-paid envelope. Performance site staff does not review the data on the form, does not see individual results, and does not data enter the information on the form. Data entry takes place solely at the DCC.

The Satisfaction Questionnaire (SATQX) is posted on the secure AsthmaNet website in the visit packet corresponding to the final study visit for a given protocol. For SIENA, it is present in the Visit 9 packet. In addition, the questionnaire is also posted appended to the single SIENA Termination of Study Participation (P6_TERM) form for use with participants who terminate from the study before Visit 9.

Postage-paid envelopes that are pre-addressed to the DCC may be obtained from the DCC as supplies are needed. At least one month's lead time should be allowed for shipment and receipt of the envelopes to ensure an adequate supply at the performance site at all times.

Only SIENA participants who successfully complete Visit 1 (or Visit 0A for Supervised Washout Participants) should be given a questionnaire at the time of their study termination.

Process: The following steps should be carried out to ensure that all participants who terminate from the SIENA trial have an equal opportunity to provide feedback on their experiences.

1. Distribute a copy of the questionnaire to any participant who successfully completes Visit 1 (or Visit 0A for Supervised Washout Participants), then terminates, whether he/she completes the study or terminates early (for his/her own reasons, due to ineligibility, or for other reasons).
2. Download the questionnaire from the secure AsthmaNet website along with the SIENA Termination of Study Participation (P6_TERM) form. Questionnaires in visit packets will have protocol number and site ID pre-completed in the key fields area of the form. Questionnaires appended to single P6_TERM forms will have only protocol number completed. Coordinators should complete the site number before distributing the questionnaire to a participant.
3. Print the questionnaire double-sided and staple the pages together to avoid loss.

4. Complete the participant's final study status in the gray box at the top of page 1 of the form. Individuals who terminate during the pre-randomization phases of the study should be coded as 'Run-in termination.'
5. Give the questionnaire to the participant at the conclusion of his/her final study visit. The participant should be given a pre-addressed, postage-paid envelope with the questionnaire.
6. Instruct the participant to complete the questionnaire, put it in the envelope, seal it, and place it in the US postal mail. If a participant elects to complete the questionnaire at the performance site, clinic personnel should not interact with him/her as the form is completed. In this case, it is preferable for the participant to drop the questionnaire in any postal box himself, but he/she may seal the questionnaire in the envelope and ask clinic personnel to mail it. The questionnaire should not be sent to the DCC with form shipments.

Note: If an individual is not present at the time he/she withdraws from the study, and he/she is unwilling to come to the performance site for a final visit, the Satisfaction Questionnaire should be mailed to his/her home address. Include instructions for completion with the questionnaire and prepaid envelope.

Personnel at performance sites who have access to the secure AsthmaNet website can generate Satisfaction Questionnaire Reports for sites to which they have been granted access in the database. The reports summarize the site's response rate, by study and overall, as well as the frequencies of responses to each of the questions on the questionnaire, by study and overall.

The DCC will provide periodic reports of the data from the questionnaires for all sites for the QCC. Response rates will be compared across the performance sites and clinical center partnerships to ensure that all sites are participating fully in the survey process.

2.47 Significant Asthma Exacerbation

Visits 1 – 9

Definition
Although all participants who experience an asthma exacerbation will also be categorized as having a treatment failure event, asthma exacerbations are more severe episodes of acute worsening, defined by meeting one or more of the following criteria:

1. Failure to respond within 48 hours to the treatment failure rescue algorithm

   Participants who experience treatment failure will be treated with open-label Asmanex® 220 mcg Twisthaler or open-label Asmanex® 200 mcg MDI (2 puffs, twice daily for 10 days), depending on Asmanex device to be randomized to at Visit 3. If the participant fails to respond within 48 hours to this treatment, he/she is categorized as having a significant asthma exacerbation.

   This criterion applies from Visit 1 on.

   See the discussion of Treatment Failure in this section for the treatment failure rescue algorithm.

2. Use of ≥ 16 puffs of PRN "as needed" albuterol per 24 hours for a period of 48 hours.

   The participant's spirotel® device has been programmed to provide an alert if he/she meets this criterion. The alert will read 'Rescue Use High/Call Clinic ASAP.' In addition, the participant should be instructed to monitor his/her rescue use on his/her SIENA Asthma Monitoring Log (P6_ASTHMA_LOG) to pick up the occurrence of this criterion.

   This criterion applies from Visit 0A on.

3. FEV_1 <50% of the baseline pre-bronchodilator FEV_1 on two consecutive spirometric measurements made on different days.

   The baseline pre-bronchodilator FEV_1 value (in liters) should be taken from Q1030 on the participant's Visit 1 Spirometry Testing (SPIRO) form. This value is used for assessing asthma exacerbation criteria for the remainder of the participant's study participation. If the participant requires a continuation visit to establish his or her study eligibility, the baseline pre-bronchodilator FEV_1 should be taken from the SPIRO form completed at the original visit.

   A participant will meet this criterion if he/she experiences pre-bronchodilator FEV_1 values that are <50% of the baseline FEV_1 value on two consecutive measurements made on different days.

   If the pre-bronchodilator FEV_1 value at a visit is <50% of the baseline pre-bronchodilator value obtained at Visit 1, and the participant does not meet other significant asthma exacerbation criteria, the participant should be given albuterol

(≤6 puffs in one hour) to assess the degree of reversibility in his/her airflow obstruction. These values must be reported to the physician responsible for the care of the participant on that day. If the physician determines that the participant's response to the bronchodilator is satisfactory, and the participant's clinical condition is stable, he/she may be released from the study visit and continue in the study, as usual, provided he/she returns to the study site in 24-96 hours (1-4 days) for repeat spirometry to assess for significant asthma exacerbation. The additional visit scheduled for repeat spirometry is referred to as an 'FEV_1 re-assessment visit.' The site coordinator or designee should telephone the participant every 24 hours to assess his/her condition in the event that asthma exacerbation conditions become evident and require immediate treatment.

At the FEV_1 re-assessment visit within the next four days, the repeat spirometric pre-bronchodilator FEV_1 value must be >50% of the baseline pre-bronchodilator value obtained at Visit 1; if not, the participant will be considered as having an asthma exacerbation at that time.

This criterion applies from Visit 2 on.

See the FEV_1 Re-assessment Visit discussion in this section for more details on FEV_1 re-assessment visits.

4. Pre-bronchodilator FEV_1 <40% of predicted on two consecutive spirometric measurements made on different days.

   The pre-bronchodilator FEV_1 % predicted value should be taken from Q1040 on the participant's Spirometry Testing (SPIRO) form for a given visit. A participant will meet this criterion if he/she experiences pre-bronchodilator FEV_1 values that are <40% of predicted on two consecutive measurements made on different days. The FEV_1 re-assessment visit described in 3 above also applies to this criterion.

   This criterion applies from Visit 2 on.

   See the FEV_1 Re-assessment Visit discussion in this section for more details on FEV_1 re-assessment visits.

5. Receives systemic corticosteroids for an exacerbation

   This criterion applies from Visit 0A on.

6. Experiencing an exacerbation of asthma in the opinion of study investigator or personal physician.

   This criterion applies from Visit 0A on.

For SIENA, every exacerbation will be categorized as a treatment failure.

Rescue Algorithm
Participants who experience worsening of asthma will be managed according to the following rescue algorithms. Rescue algorithms are based on recommendations from the NAEPP Guidelines for Diagnosis and Management of Asthma and prior ACRN trials.

Albuterol (study RESCUE ProAir®) and oral prednisone are the principal medications for rescue management. At Visit 1 (or Visit 0A for Supervised Washout participants), participants will be given RESCUE ProAir® and a course of prednisone to keep at home for rescue use. Participants will be instructed in their use for home management. Oral prednisone will be used if increased albuterol therapy does not resolve the asthma exacerbation, and only as directed by a study physician. For severe acute episodes of asthma, treatment will be administered according to the best medical judgment of the treating physician.

Once an asthma exacerbation has occurred, the participant should contact the study coordinator and/or be evaluated at the performance site or the nearest medical emergency facility as quickly as possible.

Home Care
Asthma exacerbations will be recognized by an increase in albuterol (ProAir®) use or symptoms. Participants will be educated to recognize exacerbations as early as possible to facilitate prompt treatment and to lessen morbidity.

Participants who recognize increased symptoms and/or a fall in PEF to ≤65% baseline will use albuterol by MDI, 2-4 puffs, every 20 minutes up to 60-90 minutes if needed and then every 4 hours, or less, if needed. Participants will be instructed to use the "Rescue ProAir®" inhaler for treatment.

If the PEF does not increase to >65% baseline or if symptoms are not improved after the first 60-90 min of therapy, the participant should contact the investigator, their primary physician or seek care in the emergency department. Failure of albuterol may necessitate the use of oral steroids (see below).

Physician's Office or Emergency Room Treatment
Participants will be assessed by history, physical examination, and by physiological monitoring including spirometry or PEF. If the participant's PEF and/or FEV_1 are less than 25% of predicted or if the participant shows evidence of altered mental status, cyanosis, labored breathing, or use of accessory muscles, sampling of arterial blood for respiratory gas analysis is indicated, with appropriate action taken depending on the results obtained.

When treated in the physician's office or the hospital emergency department, participants should initially be given albuterol by nebulization (0.5 cc of 0.5% solution) every 20 minutes over the first 60-90 minutes.

If the PEF increases to >65% of baseline after the first 60-90 minutes, the participant can be discharged to continue treatment at home. Prednisone may be administered at the discretion of the physician to augment therapy.

If symptoms persist and PEF remains ≤65% of baseline, nebulized albuterol should be continued as often as every 20 min at the discretion of the treating physician. Oral or parenteral corticosteroids should be considered. Monitoring of PEF or spirometry should continue every hour. Within 4 hours of treatment, a decision should be made regarding participant disposition.

If PEF increases to >65% of baseline within 4 hours, the participant can be discharged to continue treatment at home. Home treatment should include a 5-day course of prednisone (see below).

If PEF remains >40% but ≤65%, an individualized decision should be made to hospitalize the participant for more aggressive therapy or to continue therapy at home with a course of prednisone.

If PEF is ≤ 40% of baseline after repeated albuterol treatments, the participant should be admitted to the hospital unless in the physician's best judgment alternative treatment could suffice.

Prednisone Treatment

In this protocol, prednisone will be used when an asthma exacerbation, as defined above, occurs. Rescue prednisone will be given to the participant at Visit 1 (Visit 0A for Supervised Washout participants) to keep at home to be used only on the advice of study staff.

The recommended dose of prednisone used during an acute exacerbation is 2 mg/kg/day (maximum 60 mg) as a single morning dose for three days, followed by 1 mg/kg/day (maximum 30 mg) as a single morning dose for 2 days; all administered doses will be rounded down to the nearest 5 mg in children. Participants will be assessed in person and by phone on days 0, 3, 10, 14, and 21. Additional visits and treatment for exacerbations is at the discretion of the treating physician.

Adjustment of Trial Medication

Once a participant has met significant asthma exacerbation criteria during a treatment period and begins oral prednisone treatment, he/she should discontinue blinded study treatment. Open-label Asmanex®, started for a treatment failure that became a significant asthma exacerbation, should also be discontinued. Visit 9XA will be scheduled to occur 3-7 days after initiation of prednisone. At the time of the participant's 9XA (Day 3 Asthma Exacerbation) visit, he/she will crossover to the next treatment period (or have his/her final in-person visit during treatment period 3). While blinded study medication will be dispensed at Visit 5 and Visit 7, blinded study treatment should not resume until the participant has had his/her crossover visit and completed prednisone treatment for the exacerbation. The participant will take a 5-day prednisone

course, and Day 0 represents the day the participant starts prednisone. If Visit 9XA/Visit 5 or Visit 9XA/Visit 7 occurs on:

- **Day 3 or 4 –** participant should not start new study meds until Day 5;
- **Day 5, 6 or 7 –** participant should start new study meds that day.

Study Participation Following a Significant Asthma Exacerbation during Run-In and Supervised Washout

Participants experiencing an asthma exacerbation during the run-in phase of the study (or Supervised Washout) are ineligible to continue in the trial. A SIENA Termination of Study Participation (P6_TERM) form should be completed, as well as a Significant Asthma Exacerbation (P6_SIGEX) form. The P6_TERM and P6_SIGEX forms will be submitted as single forms, using the visit number of the participant's most recently entered visit packet. See the discussion of Withdrawal Due to Exacerbation in the Withdrawal section for further details.

Study Participation Following a Significant Asthma Exacerbation after Randomization

During treatment periods 1 and 2, participants who experience an asthma exacerbation will crossover to the next treatment period at the time of the participant's Visit 9XA (Day 3 Asthma Exacerbation visit). Blinded study treatment should not resume until the participant has had his/her crossover visit and completed prednisone treatment for the exacerbation. For example, if a participant experiences his/her first significant asthma exacerbation of the study between visits 5 and 6 during treatment period 2, he/she will not complete Visit 6, but instead his/her next visit will be Visit 90A/Visit 7. This participant should be scheduled for Visit 90A/Visit 7 to crossover into treatment period 3 3-7 days after initiation of prednisone. Visit 6 should be marked missing in the SIENA database. The participant should not begin taking his/her new blinded medication until finishing prednisone treatment. See Adjustment of Trial Medication on previous page for further details.

In treatment period 3, participants who experience an asthma exacerbation will have his/her last in-person visit at the time of the participant's Visit 9XA (Day 3 Asthma Exacerbation visit). For example, if a participant experiences his/her second significant asthma exacerbation of the study between visits 7 and 8 of treatment period 3, he/she will not complete Visit 8, but instead his/her next visit will be Visit 91A/Visit 9. This participant should be scheduled for Visit 91A/Visit 9 3-7 days after initiation of prednisone. Visit 8 should be marked missing in the SIENA database. The participant's blinded medications and open-label Asmanex® will be returned at the visit. The participant will continue to be followed for 21 days after prednisone start, so the Termination of Study Participation (P6_TERM) form should not be completed until Visit 91D.

Handling Visit Data

If a participant meets significant asthma exacerbation criteria during a visit in the randomized treatment period, no additional visit procedures will be performed. Instead, forms completed at the initial Asthma Exacerbation phone contact, or Visit 9X (AAAQ,

WPAI_ASTHMA, WURSS-21), will be completed and the Asthma Exacerbation visit scheduler will be run. At the time of the Asthma Exacerbation visit (Visit 9XA) which will occur 3-7 days of after initiation of prednisone, the participant will cross over to the next treatment period (or have his/her final visit). In other words, the Asthma Exacerbation visit will coincide with the participant's crossover/last visit. Prompts to complete Asthma Exacerbation visit forms are included on the V5, V7 and V9 checklists, and should be followed.

For asthma exacerbations determined at Visits 4, 6 and 8, forms completed prior to knowing the participant experienced a significant asthma exacerbation, with exception to P6_COMPLY, will be entered with the original visit packet. This includes the ACT, ASUI, CMED, AECLIN, P6_TXFAIL_CHK, SEXAM_PED, P6_PULMONARYCHK, and SPIRO forms. If an FEV1 re-assessment visit was performed, the P6_PULMONARYCHK and SPIRO forms completed during the re-assessment visit will be entered as single forms with the visit number of the initial visit. P6_SIGEX will be entered with the Asthma Exacerbation visit packet (Visit 9XA) and P6_COMPLY will be entered with the crossover visit packet. See Compliance Monitoring below for details on handling spirotel® data.

For Visits 5, 7 and 9, only the P6_PULMONARYCHK, SPIRO, P6_TXFAILCHK and SEXAM_PED (for 12-17 only) forms for the initial visit and re-assessment visit will be entered. These forms will all be single forms, with the visit number prior to the cross-over visit. No other forms from the initial visit should be entered. See Compliance Monitoring below for details on handling spirotel® data.

Compliance Monitoring (P6_COMPLY)
Participants who experience a significant asthma exacerbation, causing him/her to not complete the middle visit of the treatment period (Visits 4, 6 or 8), should have the visit number of the cross-over/last visit (5, 7 or 9) for the entire period's spirotel® data. Following download and conversion of the spirotel® data, the visit ID should be updated in Breeze before the crossover/last visit occurs and reports are run at the crossover/last visit.

Significant Asthma Exacerbation Protocol
In SIENA, when a Significant Asthma Exacerbation takes place during the randomized treatment phase and prednisone is started, an Asthma Exacerbation protocol will begin. A brief description of the forms and visits during the Asthma Exacerbation protocol is as follows:

Visit 90-92 (Day 0, phone contact at start of prednisone)
Activate Asthma Exacerbation kit and review instructions (P6_ASTHMA_EXAC)

- ➔ Instruct participant to complete Acute Asthma Assessment Questionnaire (AAAQ)
- ➔ Instruct participant to complete Asthma-Specific Work Productivity and Activities Impairment Questionnaire (WPAI_ASTHMA)

➔ Instruct participant to complete Wisconsin Upper Respiratory Symptom Survey – 21

If a participant is determined to have an Asthma Exacerbation at the time of a study visit during the randomized treatment phase, and begins prednisone treatment that day, Visit 9X forms (AAAQ, WPAI_ASTHMA, WURSS-21) should be completed at the visit. In addition, the participant should be scheduled to return to the clinic for Visit 9XA in 3-7 days. If, due to participant availability, Visit 9XA cannot be scheduled within 5 days, the participant should be called on Day 3 as a safety check. See Study Participation Following an Asthma Exacerbation after Randomization above and the Visit Window discussion in this section for further information on Asthma Exacerbation visit windows.

Visit 90A-92A (Day 3, Visit 3 days after prednisone start)

Complete Change in Scheduled Study Medications (P6_CHANGE_MEDS) to document discontinuation of study medication while on prednisone for asthma exacerbation

Administer Acute Asthma Assessment Questionnaire (AAAQ)

Complete Significant Asthma Exacerbation (P6_SIGEX) form

Distribute Asthma Exacerbation forms to be completed at phone contacts, as well as an extra copy to replenish the kit

- ➔ Acute Asthma Assessment Questionnaire (AAAQ) (4 copies)
- ➔ Asthma-Specific Work Productivity and Activities Impairment Questionnaire (WPAI_ASTHMA) (4 copies)

As noted, Visit 9XA should be scheduled 3-7 days after the participant starts prednisone to treat an asthma exacerbation. However, should participant availability not allow the participant to be seen within 5 days, the participant should be called on Day 3 as a safety check.

For Significant Asthma Exacerbations that occur during the randomized treatment phase, the P6_SIGEX form will be a packet form and part of the Visit 9XA packet. The exacerbation date is recorded in Q1070. It should correspond to the date exacerbation criteria were confirmed for the current event. If multiple criteria for exacerbation are met, record the earliest date any of the applicable criteria were met. Visit 9XA will coincide with the participant's crossover/last visit.

Visit 90B-92B, 90C-92C, 90D-92D (Day 10, 14 and 21, Phone Contact 10, 14 and 21 days after prednisone start)

Instruct participant to complete Acute Asthma Assessment Questionnaire (AAAQ)

Instruct participant to complete Asthma-Specific Work Productivity and Activities Impairment Questionnaire (WPAI_ASTHMA)

Complete SIENA Significant Asthma Exacerbation Follow-Up (P6_SIGEX_FOLLOW) form

Complete Change in Scheduled Study Medications (P6_CHANGE_MEDS) form to document resumption of study medication following prednisone treatment

Note: If no additional care was sought or medications started since last contact and the participant is doing fine, physician narrative and signature can be left missing on P6_SIGEX_FOLLOW.

At the participant's next regular visit following a significant asthma exacerbation, collect completed Asthma Exacerbation kit forms, and distribute the number of Wisconsin Upper Respiratory Symptom Survey – 21 Daily Symptom Report (WURSS_21) forms required to replenish the participant's supply.

Documentation
Once the significant asthma exacerbation has been confirmed, in addition to the forms completed above, the following forms should also be completed:

- Clinical Adverse Events (AECLIN)

  All significant asthma exacerbations should be documented on AECLIN using ICD-9 code 493.92.

  The start date recorded should correspond to the date exacerbation criteria were confirmed. For example, if a participant is deemed a non-responder after 48 hours of open-label Asmanex® (two puffs, twice daily) for treatment failure, the date corresponding to the second day of open-label Asmanex® treatment should be recorded as the exacerbation date. If multiple criteria for asthma exacerbation are met, record the earliest date any of the applicable criteria were met.

- Concomitant Medications for Asthma/Allergy and Adverse Events (CMED)

  Oral prednisone and any non-study medications used to treat the exacerbation event should be recorded on the CMED form. Examples include parenteral corticosteroids and nebulized beta-agonist administered in a physician's office or other care facility.

  Medications used for treatment of exacerbations and listed on the CMED form should be linked to the exacerbation adverse event recorded on the AECLIN form.

- SIENA Change in Scheduled Medications (P6_CHANGE_MEDS)

  When a participant experiences an asthma exacerbation, his/her scheduled Respimat® and Twisthaler®/MDI should be discontinued and he/she should start oral prednisone. Discontinuation of the scheduled medications should be recorded on the P6_CHANGE_MEDS form, along with the date the change is effective. Q1000 should be answered 'Adverse Event' and the exacerbation event recorded on AECLIN should be provided in Q1010. This should be completed at Visit 9XA.

  When the participant begins treatment with the blinded scheduled medications again, another P6_CHANGE_MEDS form should be submitted. In this case

Q1020 should be answered 'Resumed' along with the date the change is effective. This should be completed at Visit 9XB.

- SIENA Significant Asthma Exacerbation (P6_SIGEX)

  P6_SIGEX must be completed any time the participant meets the criteria for an asthma exacerbation.

  The significant asthma exacerbation date is recorded in Q1070. It should correspond to the date exacerbation criteria were confirmed for the current event. If multiple criteria for exacerbation are met, record the earliest date any of the applicable criteria were met. Guidelines by exacerbation criterion follow:

  - Failure to respond within 48 hours to the treatment failure rescue algorithm

    If the participant failed to respond to treatment failure rescue within 48 hours, the significant asthma exacerbation date should be the date when 48 hours have elapsed.

  - Use of ≥ 16 puffs of PRN "as needed" albuterol per 24 hours for a period of 48 hours.

    If the participant used ≥ 16 puffs of PRN "as needed" albuterol per 24 hours for a period of 48 hours, the significant asthma exacerbation date should be the second day the participant uses ≥ 16 puffs per 24 hours.

  - FEV_1 <50% of the baseline pre-bronchodilator FEV_1 on two consecutive spirometric measurements made on different days.

    If the participant experiences an FEV_1 <50% of the baseline (Visit 1) pre-bronchodilator FEV_1 on two consecutive spirometric measurements made on different days, the significant asthma exacerbation date should be the date of the second FEV_1 measurement.

  - FEV_1 <40% of predicted on two consecutive spirometric measurements made on different days.

    If the participant experiences an FEV_1 <40% of predicted on two consecutive spirometric measurements made on different days, the significant asthma exacerbation date should be the date of the second FEV_1 measurement.

  - Receives systemic corticosteroids for an exacerbation

    If the participant received systemic corticosteroids for an exacerbation, the significant exacerbation date should be the date the participant started the systemic corticosteroids.

  If a participant meets asthma exacerbation criteria during the run-in (between Visit 0A and Visit 3), P6_SIGEX should be completed as a single form and data entered. Use the number of the last regular visit completed as the visit number on the form. In this situation, the participant is ineligible and must be terminated from further study participation.

If a participant meets asthma exacerbation criteria during the post-randomization phase of the trial, P6_SIGEX should be completed as a packet form as part of the Visit 9XA packet.

- SIENA Treatment Failure Checklist (P6_TXFAIL_CHK)

  If a significant asthma exacerbation has occurred and is not associated with a recent treatment failure, the P6_ TXFAIL_CHK form should be completed to indicate that the participant meets treatment failure as a result of significant asthma exacerbation.

  The treatment failure (i.e. asthma exacerbation) date is recorded in Q1070 on P6_TXFAIL_CHK. It should correspond to the date significant asthma exacerbation criteria were confirmed for the current event. If multiple criteria for significant asthma exacerbation were met, record the earliest date any of the applicable criteria were met.

- SIENA Significant Asthma Exacerbation Follow-up (P6_SIGEX_FOLLOW) form

  Additional medications and treatment sought for asthma exacerbation conditions since last clinic contact (visit or phone contact) are documented on this form.

- Serious Adverse Event Reporting Form (SERIOUS)

  If a participant is hospitalized due to a significant asthma exacerbation event, or the event is considered to be life-threatening or meets other criteria in the definition of a serious adverse event (SAE), a SERIOUS form should be completed. SERIOUS forms should be submitted to the DCC within 72 hours of the notification of a SAE. See the Adverse Events discussion in this section for further details.

2.48 Sinonasal Questionnaire

Rhinitis and sinusitis are common in patients with asthma. These conditions represent a disease continuum referred to as sinonasal disease. Because sinonasal disease may lead to poorly controlled asthma, evaluation and documentation of this condition is important for the SIENA trial.

The Sinonasal Questionnaire (SNQ)[10] is a simple five-item questionnaire that screens for chronic sinonasal disease. Participants are asked how often, on average, over the last 3 months, they have had each of five symptoms. The SNQ has been shown to be sensitive, specific and highly reproducible. It has been validated for participants ages 18 and older. The SNQ has been incorporated in an AsthmaNet-formatted form, the Sinonasal Questionnaire (SNQ) form. AsthmaNet received approval for use of the formatted form in SIENA from Dr. Anne Dixon, one of the instrument's original authors.

Visits 3, 5, 7, 9
Administer Sinonasal Questionnaire (SNQ)

The administration of the SNQ is one of the first procedures performed at the visit. This timing in the visit structure is intentional so that a participant's responses are not affected by other study procedures, such as spirometry and e-diary/peak flow review. Study coordinators should observe the order of procedures as they are laid out on the visit procedure checklists to ensure that SNQ results are not biased by other study activities.

If a given visit has been partially completed and then rescheduled for a later date because of the participant's time constraints, a new SNQ form must be completed at the beginning of the rescheduled visit. Do **not** allow the participant to refer to or update his/her previously completed questionnaire. Old copies of the questionnaires should be filed in the participant's study folder and clearly marked as such; they should not be entered into the study database or forwarded to the DCC. Note that this procedure does not apply to FEV_1 re-assessment visits. For these visits, the original previously-completed questionnaires will be submitted with the visit packet.

The SNQ is completed by the participant. When administering the questionnaire, request that the participant complete the entire 5-question form and provide answers as accurately as possible. Only one box should be checked for each question. No stated or implied time limit should be set. If the participant requests help with or clarification of any question, the study coordinator should instruct the participant to reread the instructions and to give the best answer possible to each question. The study coordinator should not provide an answer to any question. Providing guidance may bias the participant's responses.

[10] Dixon AE, Sugar EA, Zinreich SJ, Slavin RG, Corren J, Naclerio RM, Ishii M, Cohen RI, Brown ED, Wise RA, Irvin CG. Criteria to screen for chronic sinonasal disease. Chest 2009; 136:1324-1332.

Participants should use a black or blue pen to complete the questionnaire. If the participant wishes to change a response, the original response should be crossed out with a single line and then dated and initialed by the participant. The final response should be circled for clarification. No changes to the participant-completed form may be made by study personnel; changes may only be made by the participant.

When the participant is finished with the questionnaire, collect it and review it for completeness before proceeding with the visit. If a question has been left blank, ask the participant to do his/her best to answer it. The answers to all of the questions are necessary to score the instrument. Check that the participant's responses are clearly marked.

The participant should provide source documentation on the SNQ form by writing his/her initials and the date/time in the source documentation box. Review the source documentation provided by the participant to ensure that the date and time are accurate before collecting the form.

2.49 Shipping – ImmunoCAP/Total IgE

Sample Shipping
ImmunoCAP/IgE samples will be shipped priority overnight to ADx Labs at National Jewish Health in Denver. Only samples for randomized participants should be shipped for analysis. Shipments will take place on the second Tuesday of April and October. Scheduled shipment dates follow:

2014: October 14
2015: April 14 and October 13
2016: April 12 and October 11
2017: April 11

The DCC will send a reminder to the coordinators approximately one week ahead of each scheduled shipment. If a performance site has a conflict with a particular shipment date, arrangements should be made with ADx lab staff to ship the samples on an alternate date. Samples should not be held at the site until the next 6-month shipment. Samples should not be shipped on alternate dates without first clearing the dates with lab staff to ensure that they are available to receive and process the shipment.

Preparing ImmunoCAP/IgE Samples for Shipment to Denver Lab
To create a shipment, scan the barcodes for all samples available to ship into the AsthmaNet BST system. Include a shipment comment detailing the contents of the shipment (i.e., human serum). Each shipment (from each site) will receive a unique shipment ID number. A shipment inventory will be generated that contains: date of shipment, shipping tracking number, site of origination, shipment ID, and an inventory detailing all the tubes in the shipment with their barcode numbers and participant information (study ID number, initials, visit number and blood draw date). Print the shipment inventory for inclusion in the shipment.

Once the shipment is confirmed in the BST module, an e-mail will automatically be sent to the Denver Lab. The e-mail will include an export file from the database that shows the information from the shipment inventory. A summary of the shipment will be included in the body of the e-mail message.

Packaging ImmunoCAP/IgE for Shipment to Denver Lab
Before packaging available samples for shipment, they must be scanned into the BST system and an inventory of the shipment generated and printed as described above. After the samples have been scanned and the shipment has been confirmed by the performance site, the samples should be packaged for shipment. The following materials are required:

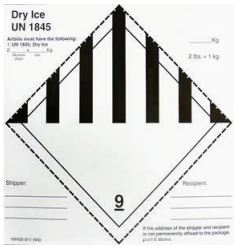
Item	Vendor	Catalog #	# Per Shipment
ThermoSafe Styrofoam mailer in corrugated carton	Fisher Scientific	03-525-36	1
FisherBrand Biohazard Polyethlene Transport Bag 8x8" (or larger)	Fisher Scientific	01-800-07 (8x8")	1
FisherBrand Biohazard Wipes, standard absorbency (4x4")	Fisher Scientific	06-670-35	2
Packaging tape	Staples	380107	
Exempt Human Specimen labels Therapak 2.5"x2"	Fisher Scientific	22-130-070	1
Therapak Dry Ice Label – UN1845 (5.5x5.5")	Fisher Scientific	221-30-065	1
Shipment inventory from BST			1

The instructions for assembling shipments below meet the minimum federal standards. Each performance site's institution may have additional guidelines. Sites should follow their institutional guidelines as long as they are in compliance with the minimum federal standards.

Assembly instructions:

1. Only ImmunoCAP samples for randomized participants will be shipped for analysis. Samples for non-randomized participants should be removed and placed in another chipboard box.
2. Place one sheet of absorbent material on top of the samples inside the chipboard box to be shipped. Close the box.
3. Place the closed box into the plastic transport bag.
4. Place a second sheet of the absorbent material in the plastic transport bag.
5. Seal the transport bag tightly.
6. Fill the bottom of the Styrofoam shipper with approximately 1 inch of cubed/chipped dry ice.
7. Place the plastic transport bag containing the samples on top of the ice layer.

8. Cover the transport bag with more crushed dry ice so that the box of tubes cannot be seen. Continue to fill the Styrofoam box with as much dry ice as possible. Do not ship more than one fiberboard storage box in a Styrofoam shipper.
9. Place a copy of the shipment inventories for each sample type (in a plastic Ziploc bag) on top of the dry ice and close the Styrofoam mailer tightly.
10. Seal the Styrofoam mailer with tape. Do not completely seal the box so that it is airtight. Carbon dioxide from the dry ice must be allowed to escape.
11. Place the Styrofoam mailer inside a cardboard mailing sleeve (the specified shipper in the table above comes with a cardboard mailer).
12. Attach one “Exempt Human Specimen” sticker and one “DRY ICE – UN 1845” label to the cardboard carton. Mark the appropriate weight of dry ice in kg on the label.



13. Address the shipment to:

    Advanced Diagnostic Laboratories at National Jewish Health
    ATTN: Client Services
    1400 Jackson Street
    Room M013
    Denver, CO 80206
    Phone: (303) 270-2663

14. Specify FedEx priority overnight shipment (AM receipt not required). No other form of shipping is acceptable.

ADx Laboratory Contacts
Michael Aron
National Jewish Health
Advanced Diagnostics Laboratories
E-Mail: AronM@njhealth.org
Phone: (303) 270-2578

2.50 Shipping – Periostin

Sample Shipping
Periostin samples will be shipped priority overnight to UCSF at the end of the study.

Preparing Periostin Samples for Shipment to UCSF
A few days prior to shipment, e-mail UCSF to notify them of the shipment:
Kelly Norsworthy (Kelly.Norsworth@ucsf.edu)
Sheena Kerr (Sheena.Kerr@ucsf.edu)

To create a shipment, scan the barcodes for all samples available to ship into the AsthmaNet BST system. Include a shipment comment detailing the contents of the shipment (i.e., human serum). Each shipment (from each site) will receive a unique shipment ID number. A shipment inventory will be generated that contains: date of shipment, shipping tracking number, site of origination, shipment ID, and an inventory detailing all the tubes in the shipment with their barcode numbers and participant information (study ID number, initials, visit number and blood draw date). Print the shipment inventory for inclusion in the shipment.

Once the shipment is confirmed in the BST module, an e-mail will automatically be sent to UCSF. The e-mail will include an export file from the database that shows the information from the shipment inventory. A summary of the shipment will be included in the body of the e-mail message.

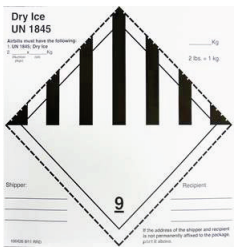
Packaging Periostin for Shipment to UCSF
Before packaging available samples for shipment, they must be scanned into the BST system and an inventory of the shipment generated and printed as described above. After the samples have been scanned and the shipment has been confirmed by the performance site, the samples should be packaged for shipment. The following materials are required:

Item	Vendor	Catalog #	# Per Shipment
ThermoSafe Styrofoam mailer in corrugated carton	Fisher Scientific	03-525-36	1
FisherBrand Biohazard Polyethlene Transport Bag 8x8” (or larger)	Fisher Scientific	01-800-07 (8x8”)	1
FisherBrand Biohazard Wipes, standard absorbency (4x4”)	Fisher Scientific	06-670-35	2

Packaging tape	Staples	380107	
Exempt Human Specimen labels Therapak 2.5”x2”	Fisher Scientific	22-130-070	1
Therapak Dry Ice Label – UN1845 (5.5x5.5”)	Fisher Scientific	221-30-065	1
Shipment inventory from BST			1

Assembly instructions:

1. Periostin samples will be shipped in chipboard box.
2. Place one sheet of absorbent material on top of the samples inside the chipboard box to be shipped. Close the box.
3. Place the closed box into the plastic transport bag.
4. Place a second sheet of the absorbent material in the plastic transport bag.
5. Seal the transport bag tightly.
6. Fill the bottom of the Styrofoam shipper with approximately 1 inch of cubed/chipped dry ice.
7. Place the plastic transport bag containing the samples on top of the ice layer.
8. Cover the transport bag with more crushed dry ice so that the box of tubes cannot be seen. Continue to fill the Styrofoam box with as much dry ice as possible.
9. Place a copy of the shipment inventories for each sample type (in a plastic Ziploc bag) on top of the dry ice and close the Styrofoam mailer tightly.
10. Seal the Styrofoam mailer with tape. Do not completely seal the box so that it is airtight. Carbon dioxide from the dry ice must be allowed to escape.
11. Place the Styrofoam mailer inside a cardboard mailing sleeve (the specified shipper in the table above comes with a cardboard mailer).
12. Attach one “Exempt Human Specimen” sticker and one “DRY ICE – UN 1845” label to the cardboard carton. Mark the appropriate weight of dry ice in kg on the label.



13. Address the shipment to:

    Attention: Sheena Kerr
    University of California, San Francisco
    Health Sciences East, Room 1350
    513 Parnassus Avenue
    San Francisco, CA 94143-0130
    (415) 476-0752

14. Specify FedEx priority overnight shipment (AM receipt not required). No other form of shipping is acceptable.

2.51 Spirometry

Spirometry procedures are carried out at all SIENA visits. Pulmonary function data are very important, as they confirm the participant's eligibility for the study, provide data for assessment of significant asthma exacerbation criteria and for the composite primary outcome that determines which treatment(s) is (are) superior for each participant.

General Instructions
AsthmaNet utilizes the MedGraphics spirometry system. The Spirometry Manual of Operations is located in Appendix 1 of the AsthmaNet General Manual of Operations.

Individuals performing spirometry must be AsthmaNet-certified in pulmonary function testing or, at a minimum, observed and supervised by an AsthmaNet-certified technician. If an uncertified individual is performing any spirometry procedures at a visit, a supervisor ID must be recorded on the applicable form(s), including the Spirometry Testing (SPIRO) form, Post-Albuterol (4 puffs) Spirometry Testing (PALB4_SPIRO) form, and Post-Ipratropium (4 puffs) Spirometry Testing (PIPRA4_SPIRO) form, as applicable at a given visit.

A participant's prior spirometry results should not be reviewed with him/her at the current visit. Knowledge of past test results can influence current expectations and bias the resulting data.

In general, before a participant can proceed with spirometry testing, he/she must meet all of the medication and substance holds specified on the SIENA Pulmonary Procedure Checklist (P6_PULMONARYCHK) with "gray box" exclusions. If a participant has taken any of the listed substances within the specified washout period prior to a visit, he/she generally may not proceed with spirometry testing at the visit. In this case, the visit should be rescheduled within the visit window for appropriate washouts to be met. If the participant has almost met a required washout period, contact the SIENA scientific coordinator at the DCC. An exception may be allowed. Note that this does not apply to FEV_1 re-assessment visits. For these visits, an ineligible participant may proceed with spirometry if this is a re-assessment visit for evaluation of a significant asthma exacerbation.

If an exception is granted through the DCC, Q1140 on P6_PULMONARYCHK should be marked 'Yes' even though one or more of the 'gray boxes' corresponding to drug or substance washouts is completed. This conflict will result in a data error which the coordinator should mark unresolvable; the exception should be explained in a comment.

eNO Testing in Relation to Spirometry
Since spirometry testing is known to affect eNO measures, eNO testing must be performed after the SIENA Pulmonary Procedure Checklist is completed and prior to spirometry at Visits 1, 2 and 2A. See the Exhaled Nitric Oxide discussion in this section for further details.

Demographics
Care must be taken to enter the participant's identification (i.e., participant ID number with leading '0', initials, etc.) and demographic information into the spirometry software correctly. A technician ID must also be included for each test that is performed.

Height
Participants who are less than 21 years old (i.e., participants who have not yet had their 21st birthday) will have their height measured and recorded at each visit until they turn 21. Height is recorded on different data forms depending on the participant's age.

Age 18 and over: Heights for individuals who are age 18-20 will be recorded in Q1150 on the P6_PULMONARYCHK form at all spirometry visits with the exception of Visits 0A, 1 (for those not in Supervised Washout) and 9, at which height is recorded for all adult participants on the Adult Body Measurements form (BODYMEAS_ADULT). Participants who are at least 21 years old at enrollment will have their height measured and updated in the spirometry system only twice during the study at Visit 1 (or Visit 0A for those in Supervised Washout) and Visit 9. Once a participant is over the age of 21, he/she should not be re-measured until Visit 9. Height values should be updated in the spirometry system each time they are measured.

Age 12-17: Heights for adolescents who are age 12-17 will be measured at each visit and recorded on the applicable Physical Exam form (LEXAM_PED or SEXAM_PED) at the visit. These forms are data entered. Height values should be verified and updated in the spirometry system each time spirometry is performed on participants in these age tracks.

Race/Ethnicity
The participant's spirometry race/ethnicity designation should be retrieved from his/her AsthmaNet Registry Report. The participant's spirometry race/ethnicity category corresponds to the primary racial designation that he/she supplied in Q1150 on the Registry (REGISTRY) form. Individuals who specified 'American Indian/Alaskan Native' or 'Other' will use Caucasian predicted lung function equations. Always use the spirometry race/ethnicity designation listed on the participant's Registry report in the MedGraphics software. Race/ethnicity has a large influence on a participant's predicted lung function values.

Gender
Individuals who are transgendered or transitioning to the opposite gender should have their biological sex entered into the AsthmaNet Registry (under 'gender'). Biological sex should be entered into the MedGraphics software for purposes of calculating predicted lung function values.

Visits 1 (or Visit 0A for Supervised Washout Participants)
Complete Pulmonary Procedure Checklist (P6_PULMONARYCHK)
Perform Spirometry Testing (SPIRO)

Baseline spirometry at Visits 0A (for Supervised Washout participants) and Visit 1 are used to determine study eligibility. These results are recorded on the Spirometry Testing (SPIRO) form and are referenced on SIENA Eligibility Checklists (P6_ELIG0A, P6_ELIG3) at the respective visit. At Visit 1, if the participant does not qualify for the study based on reversibility, spirometry at the V1 continuation visit will be used to qualify the participant for methacholine challenge.

Visits 2-8 (as well as Visit 0B, 1 for Supervised Washout Participants)
Complete Pulmonary Procedure Checklist (P6_PULMONARYCHK)
Verify/update height on MedGraphics machine (using height recorded on SEXAM_PED for 12-17, and height recorded on P6_PULMONARYCHK for 18-20)
Perform Spirometry Testing (SPIRO)

Baseline spirometry at Visits 0B and 3 are used to determine study eligibility. These results are recorded on the Spirometry Testing (SPIRO) form and are referenced on SIENA Eligibility Checklists (P6_ELIG0B, P6_ELIG3) at the respective visit.

At Visits 3-8, FEV_1 from spirometry will be used to evaluate the third tier in the composite primary outcome to determine superiority among treatments for a given individual and as a longitudinal secondary outcome measure.

Visits 9
Complete Pulmonary Procedure Checklist (P6_PULMONARYCHK)
Verify/update height on MedGraphics machine (using height recorded on LEXAM_PED for 12-17, and height recorded on BODYMEAS_ADULT for 18-20)
Perform Spirometry Testing (SPIRO)

At Visit 9, FEV_1 from spirometry will be used to evaluate the third tier in the composite primary outcome to determine superiority among treatments for a given individual and as a longitudinal secondary outcome measure.

Visits 90A-92A
Complete Pulmonary Procedure Checklist (P6_PULMONARYCHK)
Verify/update height on MedGraphics machine (using height recorded on LEXAM_PED for 12-17, and height recorded on P6_PULMONARYCHK for 18-20)
Perform Spirometry Testing (SPIRO)

Visit 1, 2A
Administer 4 puffs of albuterol, wait 10-15 minutes, and perform post-bronchodilator testing
Perform Post-Albuterol (4 puffs) Spirometry Testing form (PALB4_SPIRO)

At Visit 1, post-albuterol spirometry is used to determine study eligibility and eligibility for sputum induction. To qualify the participant, he/she should perform baseline spirometry, then be given 4 puffs of albuterol and be allowed to rest for **10-15 minutes**. A spacer should <u>not</u> be used. The first two puffs of albuterol should be given while

assessing pre-education inhalation technique using the MDI Technique Checklist. If pre-education score is not perfect, post-education technique should be assessed while participant takes two additional puffs of albuterol. After the 10-15 minute wait, spirometry should be repeated and the results recorded on the PALB4_SPIRO form. All participants should complete the pre/post spirometry sessions at Visit 1, regardless of whether or not they provided source documentation from a previous pre/post spirometry test to support their eligibility. If participant reverses ≥ 12%, he/she is eligible to continue with Visit 1. If not, the participant should be scheduled for a continuation visit to perform methacholine challenge.

If a continuation visit is required, new SIENA Pulmonary Procedure Checklist (P6_PULMONARYCHK), Exhaled Nitric Oxide (ENO) and Spirometry Testing (SPIRO) forms must be completed with the current date (using the same visit number as the prior visit). The P6_PULMONARYCHK, ENO and SPIRO forms from the continuation visit should be entered into the SIENA database as single forms (in addition to the regular packet forms). A single METHA_RPT should be printed to document the values on the single SPIRO and METHA forms. All data collected on the P6_PULMONARYCHK, ENO and SPIRO forms for both parts of the visit should be entered into the study database.

Note: When the participant returns for the continuation visit, the first procedure performed is the pregnancy test followed by eNO testing and spirometry. Do not have the participant redo previously completed questionnaires at this visit; the questionnaires completed on the original visit date will be submitted with the visit packet.

For pre/post spirometry, participants should dose from albuterol (ProAir®) inhalers taken from bulk supply at Visit 1. This should be logged on SIENA Drug Dispensing Log: ProAir® (RESCUE) Inhaler (P6_DRG_RESC). Actuators should be sterilized between participants, allowing for multiple participant use.

At Visit 2A, participants will be assessed for eligibility to perform sputum induction. To qualify the participant, he/she should perform baseline spirometry, then be given 4 puffs of albuterol and allowed to rest for **10-15 minutes**. After the 10-15 minute wait, spirometry should be repeated and the results recorded on the Post-Albuterol (4 puffs) Spirometry Testing (PALB4_SPIRO) form. Results of the post-bronchodilator spirometry session will be used to qualify the participant for sputum induction.

Participants should dose from their albuterol (RESCUE ProAir®) inhalers for this test at Visit 2A.

Albuterol puffs taken as part of the pre/post spirometry testing procedure should not be included in the RESCUE puffs the participant records in his/her spirotel® device the evening after the visit.

Visit 2

Administer 4 puffs of ipratropium, wait 30 minutes, and perform post-bronchodilator testing

Complete Post-Ipratropium (4 puffs) Spirometry Testing form (PIPRA4_SPIRO)

At Visit 2, post-ipratropium spirometry is used to characterize the study population and to assess eligibility to perform sputum induction. The participant should perform baseline spirometry, then be given 4 puffs of ipratropium and be allowed to rest for **30 minutes**. A spacer should not be used. After the 30 minute wait, spirometry should be repeated and the results recorded on the PIPRA4_SPIRO form.

For pre/post spirometry, participants should dose from ipratropium (Atrovent®) inhalers provided by the DCC. Actuators should be sterilized between participants, allowing for multiple participant use.

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2.52 Spirotel®

The spirotel® is a peak flow meter and electronic diary (e-diary) combined into one device. The SIENA trial will use the spirotel® II, which is an upgraded version of the spirotel® device used in the VIDA and INFANT studies. Participants will be given a device and trained in its use at their first visit (either Visit 1 or Visit 0A for Supervised Washout participants). Participants will be expected to complete scheduled AM and PM sessions daily for the duration of the study. A scheduled session includes answering a set of questions in the e-diary and performing three peak flow maneuvers. Data collected in the device between visits will be downloaded to the MedGraphics database during each visit to the performance site. After the most recent data have been downloaded, clinical personnel will generate and print reports to review with the participant.

This section covers SIENA-specific spirotel® information. For additional information on the spirotel® device, refer to Appendix 6 of the AsthmaNet General Manual of Operations.

Participant Instruction

Visit 1 (or Visit 0A for Supervised Washout Participants)
Instruct participant in use of spirotel® (use demo device) (HTSPIROTEL, P6_SPIROTEL_REF_2)

The DCC will provide each performance site one or two demonstration (demo) devices loaded with the BARD, SIENA and STICS demo programs. These devices are only to be used for instructional purposes; they should not be dispensed to participants for use during the trial. Demo devices do not store data.

BARD/SIENA/STICS Demo devices have been programmed with the SIENA e-diary questions (AM and PM) and four alerts, which are described in more detail below:

- “Take puffs from Study inhalers” Alert
- “Peak flow is low. Call Clinic ASAP.” Alert
- “Rescue use high; Call Clinic ASAP.” Alert
- “E-diary data indicates you need YELLOW inhaler. Call clinic ASAP.”

At Visit 1 (or Visit 0A) when the spirotel® is first introduced to the participant, performance site personnel should review the information on the “How to Use Your Spirotel® Electronic Diary and Peak Flow Meter” handout (HTSPIROTEL). Version 2.0 of this handout must be referenced so that directions correspond to the Spirotel® II device. The participant should be educated on the steps for completing scheduled morning and evening assessments and on the expectation that these sessions are to be completed twice a day, every day, during the study. The participant should also be educated on how to use the device to perform unscheduled (extra) peak flows

throughout the day, if needed to monitor lung function and to aid in determining if the participant needs to seek additional care for his/her asthma.

After the participant has reviewed the HTSPIROTEL handout, performance site personnel should introduce him/her to the BARD/SIENA/STICS demo device. When the device is turned on, three options appear: BARD, SIENA or STICS. Select “SIENA”. Two additional options will appear: English or Spanish. Most participants should choose the English option. After making this choice, three new options will appear: AM, PM and PEF. Select “AM” to take the participant through a scheduled morning session with e-diary questions and peak flow maneuvers. The participant should be instructed to perform three peak flow maneuvers during each scheduled session. The number of maneuvers performed will be stored in the device’s memory. Select “PM” to take the participant through a scheduled evening session with e-diary questions and peak flow maneuvers. Select “PEF” to take the participant through an unscheduled peak flow maneuver-only session. Reinforce to the participant that all data entered into the device will be stored for download and review at his/her next visit to the performance site.

In addition to the HTSPIROTEL handout that covers the spirotel® procedures in general, a SIENA-specific handout (SIENA Spirotel® Reference Card (P6_SPIROTEL_REF/ P6_SPIROTEL_REF_2)) has been created to fit into the spirotel®’s case for quick reference by the participant at home during a session. P6_ SPIROTEL_REF is for participants randomized to Twisthaler; P6_ SPIROTEL_REF _2 is for participants randomized to MDI. This reference includes each question abbreviation (i.e., the limited representation the participant sees on the device), along with the longer text question that it represents. The reference also supplies clarification for certain questions, such as the difference between preventive albuterol puffs and rescue puffs, as well as explanations for the symptom scores. Clinical personnel should show the participant this reference and review it upon dispensing his/her device. It should also be emphasized that bronchodilator puffs taken as part of visit procedures should not be counted when reporting rescue use values.

Spirotel® Performance Check

Visit 1 (or Visit 0A for Supervised Washout Participants)

Complete Spirotel® Performance Checklist (SPIROTEL_PERF, P6_ELIG0A, P6_ELIG3)
(use SIENA demo device)

After the participant has had a chance to experiment with the BARD/SIENA/STICS demo device, he/she should undergo a formal spirotel® performance assessment using the steps on the Spirotel® Performance Checklist (SPIROTEL_PERF). Version 2.0 of this form should be used to correspond to the spirotel® II used in the SIENA trial. The participant must pass the performance check with a score of 13 to remain eligible for the study. Results of the performance check are recorded in Q1180 on P6_ELIG0A for Supervised Washout participants and Q1040 on SIENA Eligibility Checklist 3 (P6_ELIG3).

If a participant fails to perform all the steps on the performance checklist correctly, he/she may be retrained and undergo another assessment. There is no limit on the number of times the participant may attempt to pass the checklist. Store all completed SPIROTEL_PERF forms in the participant's SIENA study folder at the performance site; they should not be forwarded to the DCC. This documentation may be subject to audit during an AsthmaNet site visit.

Preparing the SIENA Spirotel® for Participant Use

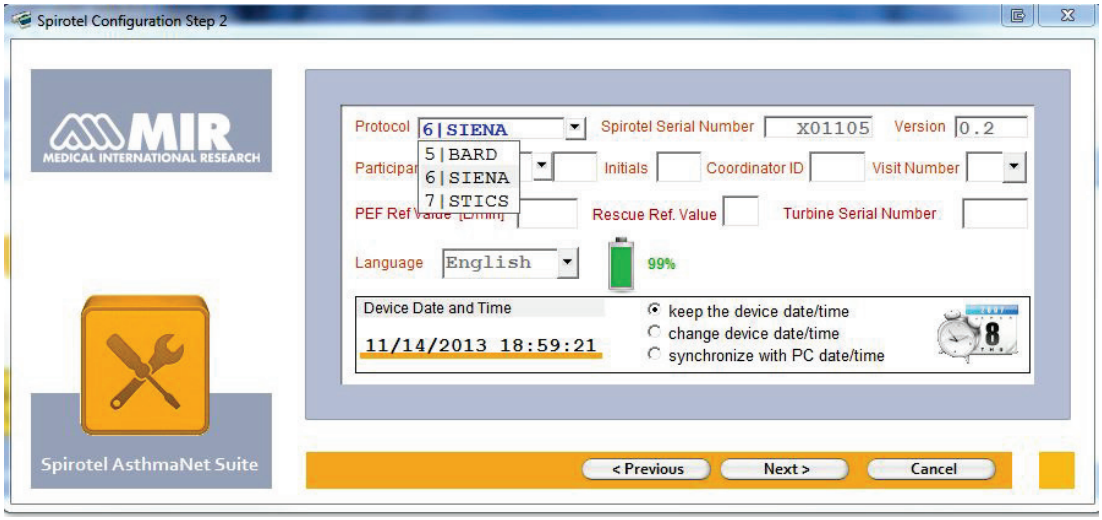
Visit 1 (or Visit 0A for Supervised Washout Participants)

Program spirotel® with participant's information, including baseline peak flow and rescue use

Visit 2 (and Visit 0B, 1 for Supervised Washout Participants)

Update baseline peak flow, rescue use and return visit number in spirotel®

Determine which spirotel® device will be assigned to the participant. Configure the device for the participant. The following setup screen will appear. Choose SIENA from the protocol drop-down list. The device serial number, software version number, and first digit of the participant ID (6) will auto-populate. Check the device date/time to be sure they are set to local date/time. Choose the language option that is desired (English, which is the default option, or Spanish) from the drop-down menu.



Several participant-specific pieces of information must be entered by clinical personnel, including:

- Participant ID: This is the participant's assigned SIENA ID number. The ID is broken into three sections: protocol number (6 pre-completed), performance site number, and ID number. Clinical personnel must complete the site number and ID number portions.
- Participant initials: This is the set of initials by which the participant will be referenced during the study. These initials must match those used when entering

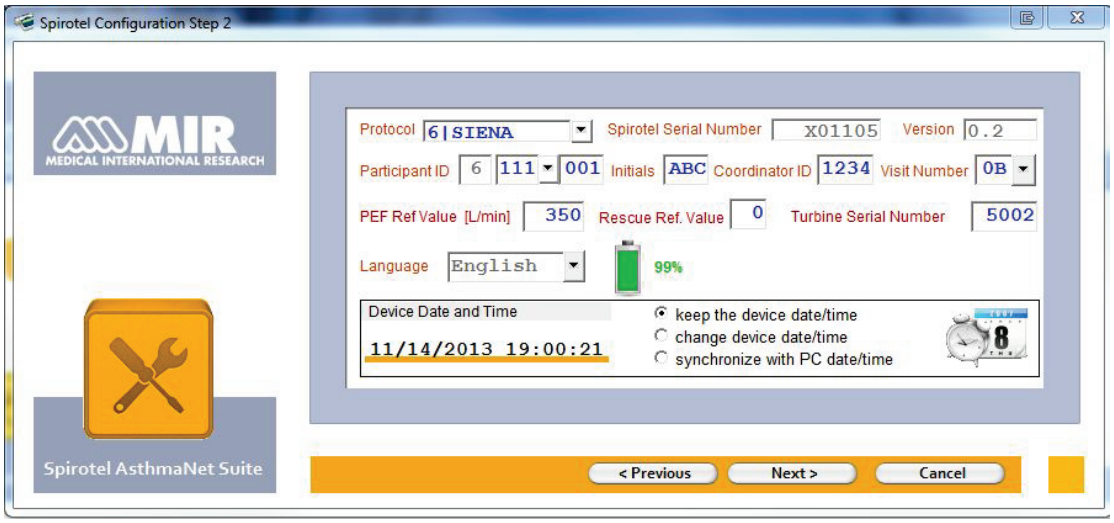
the participant into the AsthmaNet Registry. If a participant's initials have changed since the time he/she was registered, current initials should be entered into the spirotel® and a Registry Data Correction form (REG_CORRECT) should be submitted to the DCC. See the AsthmaNet Registry Manual of Operations in Section 9 of the General MOP for details.

- Coordinator ID: This is the 4-digit identification number belonging to the person who is setting up the participant's device
- Visit Number: The return visit number should be entered. At Visit 0A, the return visit number should be specified as 0B if participant is undergoing 2-Step Supervised Washout. If participant is undergoing 1-Step Supervised Washout, visit number should be specified as 1 at Visit 0A. At Visit 1 the return visit number should be specified as 2. At Visit 2, the return visit number should be specified as 3 even if participant is returning for Visit 2A. The visit number will be updated by clinical personnel at each regular visit.
- PEF Ref Value [L/min]: This is the participant's peak flow (PEF) reference value. At the participant's first visit, he/she does not have any collected data on which to base the calculation of a reference PEF, so this will be calculated from spirometry at the visit (Visit 1, or Visit 0A for Supervised Washout participants). Refer to Q1000 on the SIENA Baseline PEF and Rescue Use (P6_BASELINE) form for this value at the participant's first visit. For Supervised Washout participants, the SIENA Spirotel® Baseline Report (P6_BASELINE) will be used to update this value at Visits 0B and 1. For all other participants, the SIENA Spirotel® Baseline Report (P6_BASELINE) will be used to update this value at Visit 2.

  See the Baseline Peak Flow and Rescue Use discussion in this section for details on the PEF reference value. Note that the reference peak flow itself is being entered/updated, not the 65% Baseline Peak Flow.
- Rescue Ref Value: This is the participant's baseline rescue use value. At the participant's first visit, he/she does not have any collected data on which to base the calculation of a reference PEF, so this will be based on participant self-report. Refer to Q1010 on the SIENA Baseline PEF and Rescue Use (P6_BASELINE) form for this value at the participant's first visit. For Supervised Washout participants, the SIENA Spirotel® Baseline Report (P6_BASELINE) will be used to update this value at Visits 0B and 1. For all other participants, the SIENA Spirotel® Baseline Report (P6_BASELINE) will be used to update this value at Visit 2.

  See the Baseline Peak Flow and Rescue Use discussion in this section for details on the rescue use reference value.
- Turbine Serial Number: This is the number etched in the turbine that has been installed in the device.

A sample completed setup screen with information for participant 6-111-001 ABC at Visit 1 follows.



Visit 1 (and Visit 0A for Supervised Washout Participants)
Have participant do one unscheduled PEF maneuver on his/her spirotel®.

At Visit 1 (as well as Visit 0A for Supervised Washout Participants), the participant will need to do one unscheduled PEF on his/her spirotel® to define the Visit 1 (and Visit 0A) date for spirotel® reports.

Visit 0B-8
Update return visit number in spirotel®

When a participant returns to the performance site and completes a visit, the Visit Number in his/her device must be manually changed to the next return visit number. Choose the appropriate return visit number from the dropdown menu. For example, if a participant is at the site and completes Visit 2 and will be scheduled for Visit 3, the visit number setting in his/her device must be incremented to 3 before he/she leaves the visit. If participant is returning for Visit 2A, the visit number setting should still be 3. This setting ensures that all stored data will be associated with the correct visit number.

Note that if a participant is having the interval between Visit 2 and 3 extended due to treatment failure, the Visit Number in his/her device should remain 3. Before a participant leaves a visit, ensure that the device is set up appropriately for the next visit he/she will complete.

If a participant experiences two treatment failures in the same treatment period, he/she will proceed to the next treatment period 14 days following completion of open-label Asmanex® (YELLOW) inhaler or prednisone. If a participant experiences a significant asthma exacerbation in a treatment period, he/she will cross over to the next treatment period 3-7 days after initiation of prednisone. If the participant has not had the mid-point

visit of that period (Visit 4 in Period 1, Visit 6 in Period 2, and Visit 8 in Period 3), the return visit number for all data collected in the period should be that of the cross-over/last visit number (Visit 5, 7 or 9). For example, if the participant experiences two treatment failures between Visits 5 and 6 during treatment period 2, he/she will not complete Visit 6, but instead his/her next visit will be Visit 7. All spirotel® data downloaded since Visit 5 should have visit ID 7.

Spirotel® Quality Control Procedures

Visit 0A-9
Perform spirotel® QC (SPIROTELQC)

Perform a quality control test on the unit following the directions in the spirotel® Manual of Operations (Appendix 6 of the AsthmaNet General Manual of Operations). Once the combination unit consisting of the device and turbine passes the quality control process, print the Spirotel® Quality Control report (SPIROTELQC) for inclusion in the visit packet and data entry. Forms for failed device/turbine combinations should be printed and stored in the participant's study folder at the performance site; do not enter or forward them to the DCC.

Spirotel® quality control procedures may be performed in advance of the Visit 1 (or Visit 0A) date to prepare the device for the visit.

Logging Dispensation and Return of Spirotel® Equipment

Visit 1 (or Visit 0A for Supervised Washout Participants)
Log/dispense spirotel® (SPIROTEL_DEVICE, SPIROTEL_TURBINE)

Visit 9 or whenever a participant leaves the study or returns faulty equipment
Collect/Log spirotel® (SPIROTEL_DEVICE, SPIROTEL_TURBINE)

Each time a spirotel® device or turbine is assigned to a participant, the Spirotel® Device Log (SPIROTEL_DEVICE) or Spirotel® Turbine Log (SPIROTEL_TURBINE) must be completed. At the time of dispensation, complete the device or turbine serial number, the participant's SIENA ID number, the date the device or turbine is being dispensed, and the initials of the person dispensing the materials to the participant.

Each time a spirotel® device or turbine is returned by a participant at the end of his/her study participation or because of equipment failure, SPIROTEL_DEVICE and SPIROTEL_TURBINE must be updated to reflect receipt of these items. At the time of collection, complete the date the device and turbine are being returned, the initials of the person collecting the materials, and information regarding whether the device and/or turbine failed quality control testing. If the device and/or turbine failed QC testing, or they are otherwise malfunctioning, note the date the device and/or turbine was shipped back to the DCC. The DCC will test the defective units and will work with Respitech to secure replacements, as needed.

If a device and/or turbine fails quality control testing at a regular visit, update the applicable log accordingly for return of the defective materials. Create a new record on the appropriate log indicating the dispensation of new materials to the participant.
If a device and turbine are lost during the study, enter this information into the logs in the comment column. All turbines and devices must be accounted for at all times.

SIENA Asthma Monitoring Log (P6_ASTHMA_LOG)
The Asthma Monitoring Log (P6_ASTHMA_LOG) is an administrative form that was created to give participants a centralized location to record their scheduled peak flows and rescue use (in puffs) each day. The spirotel® device does not allow participants to scroll back to view data entered for previous days; the P6_ASTHMA_LOG is the only reference the participant will have to assess how his/her lung function and RESCUE ProAir® use may have changed over recent days, possibly signaling the onset of treatment failure or significant asthma exacerbation. The log also includes space to record unscheduled peak flows, nighttime awakenings, any non-study medications that are taken between visits, and any medical problems the participant experiences.

See the Asthma Monitoring Log discussion in this section for further details.

Downloading the spirotel®

Visit 0B-9
Download spirotel® and convert data using DBTools

At each visit to the performance site, the data stored in the participant's spirotel®'s memory will be downloaded to the local machine, converted, and uploaded to the MedGraphics database. Once the data have been downloaded successfully, they will no longer be available on the participant's device. Data must be downloaded from a device before it can undergo the quality control process at a visit.

Note that data must be downloaded prior to generating reports at a visit.

If the participant forgets to bring his/her spirotel® to a visit (other than Visit 3), arrange for him/her to bring it to the clinic as soon as possible for download and change in return visit number. The longer a participant keeps the spirotel® at home, the more likely the device will run low on memory or battery, possibly resulting in data loss. Data will also continue to accumulate in the device under an incorrect visit number, resulting in the need for substantial data corrections following download. Participants must be reminded to bring their devices with them to every study visit. Visit 3 is an exception to this; a participant cannot be randomized at Visit 3 without his/her spirotel device.

General e-Diary and Peak Flow Compliance Assessments

Visit 0B-9
Print and review Spirotel® Participant Compliance Report (P6_COMPLY_RPT)

The e-diary questions serve as a daily log that should be completed by the participant twice a day, every day, during his/her study participation. Peak flows should also be performed twice a day, on schedule, throughout the study. Compliance with these procedures is especially important because increases in symptoms (recorded in the e-diary) determine treatment failure, which represents the first tier comparison between treatments for the primary composite outcome variable.

Participants cannot perform the scheduled peak flow maneuvers without first having completed all of the AM or PM e-diary questions. Participants who do not meet high standards of compliance with measurement of peak flow and completion of e-diary questions will not be eligible to continue with screening for SIENA or to become randomized at Visit 3. If a participant's compliance begins to decline during the trial, he/she should be counseled regarding the importance of carrying out his/her home procedures, including e-diary procedures. Compliance percentages less than 75% are considered unacceptable.

At each Visit 0B-9, the participant's spirotel® device will be downloaded to the local PC, converted, and uploaded to the MedGraphics database. The Spirotel® Participant Compliance Report for the current visit should be generated through the BreezeSuite software. This report includes all data collected between the previous visit number and the current visit number. If multiple downloads were performed between visits and the return visit number was correctly specified, all data from the combined downloads will be used in the compliance assessment. This report is not download-specific.

The Spirotel® Participant Compliance Report serves as source documentation for the SIENA Compliance Checklist (P6_COMPLY), and includes the following information:

- Q1000: Number of full days since the last visit: This value does not include the current visit date or the date of the previous visit. Only days since the last visit when the participant should have completed both AM and PM scheduled sessions are included/counted.
- Q1010: Number of days where AM and PM scheduled sessions are complete: A complete session is defined as a scheduled session where all e-diary questions have been answered and at least one peak flow maneuver has been completed. Note that participants are generally expected to do three peak flow maneuvers at each session, but they will be considered compliant for this report if they perform at least one. For a given day to be considered 'compliant', all AM and PM e-diary questions must be answered and at least one AM peak flow maneuver and at least one PM peak flow maneuver must be present in the dataset. This compliance definition is more stringent than the requirements for eligibility during the run-in for randomization. See the Eligibility Criteria discussions in this section for more information.
- Q1020: Percent compliance: This value is computed as the number of e-diary complete days divided by the number of full days x 100, or (Q1010/Q1000) x 100.

Cleaning Requirements

To ensure that the participant's device will function properly over the duration of his/her study participation, the turbine must be removed from the device and cleaned thoroughly at Visits 3, 5, and 7 (and Visit 1 for Supervised Washout participants). This timing during the study was chosen because these visits mark the beginning of a new treatment period and they cannot be missed. Minimal cleaning requirements have been specified; more frequent cleaning may be performed at the discretion of clinical personnel.

For complete instructions on cleaning spirotel® turbines, refer to the Spirotel® Manual of Operations in Appendix 6 of the AsthmaNet General Manual of Operations.

Visits 3, 5, 7 (and Visit 1 for Supervised Washout Participants)
Remove turbine from spirotel® device and clean
Replace cleaned turbine into spirotel® device and perform spirotel® QC (SPIROTELQC); return device to participant

Near the beginning of Visits 3, 5 and 7 (and Visit 1 for Supervised Washout participants), remove the turbine from the participant's spirotel® device and initiate the cleaning process. Other study procedures should be performed while the turbine is in the cleaning solution.

Near the end of the visit, reassemble the device and then perform quality control procedures on the unit. Follow normal quality control procedures in the event that the unit does not pass the quality control process.

Charging Requirements

Visits 2-9 (and Visits 0B, 1 for Supervised Washout Participants)
Charge spirotel® device

Coordinators should ensure that the spirotel® is completely charged prior to dispensing it to the participant at Visit 1 (or Visit 0A).

At subsequent visits, to ensure that the participant's device will have enough battery power to make it until the next visit, the spirotel® should be charged. Near the beginning of the visit, attach the participant's device to a "USB Type A Male to USB Micro Type B Male" cable and plug it in. Allow the battery to charge fully while the visit is taking place.

Cables will not be provided for participants to charge their spirotel® devices at home; however, some may have the correct type of cable for other electronics. If a participant has the correct cable at home (any charger with a micro USB end), he/she may charge the spirotel®, if desired, between visits.

For complete instructions on charging spirotel® devices, refer to the Spirotel® Manual of Operations in Appendix 6 of the AsthmaNet General Manual of Operations.

SIENA Spirotel® Alerts

Several alert messages have been programmed into the SIENA spirotel® device in an effort to improve participant compliance with taking study medications, and recognizing treatment failure and significant asthma exacerbation events. Alerts appear following a completed scheduled AM or PM session (after the last PEF maneuver) when certain criteria are met. If multiple alerts apply, a 5 second pause will occur between alerts. Alert definitions follow.

- "Take puffs from Study inhaler(s)" Alert

  This alert appears after every scheduled AM and PM session is complete, including three peak flow maneuvers. This alert applies throughout the study starting at Visit 1.

- "Peak flow is low. Call Clinic ASAP." Alert

  This alert appears after a completed scheduled AM or PM session when the participant's highest PEF (best of three blows) is <65% of the current peak flow reference value. This alert applies throughout the study.

- "Rescue use high; Call Clinic ASAP." Alert

  This alert appears when the participant has taken ≥ 16 albuterol puffs for symptoms (Q19) for two consecutive days. This qualifies as a significant asthma exacerbation, and should be treated accordingly. This alert applies throughout the study. See the discussion of Significant Asthma Exacerbation in this section for further information.

- "E-diary data indicates you need YELLOW inhaler. Call clinic ASAP."

  This alert appears when the participant's e-diary meets any of the following criteria (for treatment failure):

  - Awakening from asthma three or more times in a two-week period or on two consecutive nights

    Q1 >= 1 for 2 consecutive sessions OR for 3 or more sessions in any 14 consecutive calendar days

  - Using albuterol for relief of symptoms four or more times/day for two or more consecutive days

    Q20 >= 4 for 2 or more consecutive sessions

  - Albuterol relieving symptoms for less than four hours after each treatment

    Q21 = 1

- Using albuterol for relief of symptoms daily for seven days, and this use exceeds two times the weekly use of albuterol in the baseline period

  Q20 >= 1 for 7 or more consecutive sessions AND sum of Q19 over 7 consecutive days > rescue reference value x 14

- Regular exercise has caused severe shortness of breath 2 or more days over a 7 day period

  Q17 = 1 for 2 or more sessions in 7 consecutive days

For explanation of treatment failure criteria, see Treatment Failure discussion in this section.

Spirotel® Traffic Light Settings

The spirotel® device has red, yellow, and green zones on its display. Zones have been defined as follows for the SIENA study:

Green:	Highest PEF > 80% of reference PEF
Yellow:	65 ≤ Highest PEF ≤ 80% of reference PEF
Red:	Highest PEF <65% of reference PEF

Following the third peak flow maneuver during a scheduled morning or evening session, the participant's 'Highest PEF (L/M)' will appear on the spirotel®'s screen. This value will be accompanied by an indicator in the green, yellow, or red zone that corresponds to the above defined zones. The indicator will appear in the center of the appropriate zone; it does not vary its location based on how low or high the actual peak flow is relative to the participant's current reference value.

If the participant's highest peak flow during a scheduled session is in the red zone, he/she should be cognizant of possible asthma exacerbation conditions and the need for treatment. A spirotel® alert will appear telling the participant his/her peak flow is low and to contact the clinic.

Note that the traffic light indicator does not appear during a scheduled session until the participant has completed his/her third maneuver and the 'Highest PEF (L/M)' has appeared.

Also note that the traffic light indicator is not applicable to individual unscheduled peak flows the participant performs, unless he/she performs more than one measurement within a 20 minute period. In that case, a 'Highest PEF (L/M)' will show after the second (or third, etc. maneuver) with the traffic light indicator.

Handling participant travel

If a participant takes a trip during his/her study participation that requires sleeping for one or more nights in a new time zone, e-diary answers and peak flow measurements should be made within the specified time windows using "local" time. For example, if a

participant from the Boston performance site travels to San Francisco for a five-day business meeting, then he/she should perform e-diary and peak flow procedures in the protocol time windows using local San Francisco time. This assumes that the participant will adjust his/her sleep/wake habits from Eastern Time to Pacific Time.

To assure that the spirotel® device will accommodate the participant's measurements in the alternate time zone, and to ensure that times reflect when activities were actually performed during the participant's day, the time setting in the device must be changed by clinical personnel just prior to the participant leaving on the trip. Refer to the Spirotel® Manual of Operations in Appendix 6 of the AsthmaNet General Manual of Operations for options and instructions for handling participant travel.

The participant should be asked to note the measurements that were affected by travel on his/her SIENA Asthma Monitoring Log (P6_ASTHMA_LOG) as another source of information when reviewing spirotel® reports at a visit.

2.53 Spirotel® Reports

Visit 2-9 (and Visit 0B, 1 for Supervised Washout Participants), 90A-92A
Print and review SIENA Spirotel® Participant Visit Report (P6_SPIROTEL_RPT)

Visit 2-9 (and Visit 0B, 1 for Supervised Washout Participants)
Print and review SIENA Spirotel® Participant Compliance Report (P6_COMPLY_RPT, P6_COMPLY)

Visit 2 (or Visit 0B, 1 for Supervised Washout Participants)
Print and review SIENA Spirotel® Baseline Report (P6_BASELINE)
Complete header information on SIENA Spirotel® Baseline Report (P6_BASELINE)

Visit 3 (and Visit 0B, 1 for Supervised Washout Participants)
Print and review SIENA Spirotel® Eligibility Report (P6_ELIG_RPT)

Four spirotel® reports will be generated and consulted during the SIENA trial. Reports are accessed through the MedGraphics BreezeSuite software after a participant's spirotel® data are downloaded and converted at a given visit by doing the following:

1. Open the BreezeSuite software. The 'Open Patient' screen will display.
2. Select the SIENA checkbox and select Refresh.
3. Double-click on the applicable participant ID, or select the applicable participant ID and click on the 'Open' button. A list of visits for this participant will appear.
4. Double-click on the desired visit, or select the desired visit and click on the 'Open Visit' button.
5. Select 'Quick Print' and 'Spirotel SIENA Reports' from the toolbar.
6. Five options are available for printing: Participant Visit Report, Participant Compliance Report, Eligibility Report (available only at Visits 0B, 1, 3), Baseline Report (available only at Visits 0B, 1, 2), and All Reports. The "All Reports" option should not be used to print because it does not allow you to save every report.

Descriptions of the SIENA reports follow.

- Spirotel® Participant Visit Report (P6_SPIROTEL_RPT):

  This report serves as a 'data dump' of all the information the participant entered into his/her e-diary/peak flow device between visits.

  The top part of the report shows device configuration data. Variables include: participant ID and initials, visit number, coordinator ID, reference peak flow value, reference rescue value, turbine and device serial number, and download date. If

multiple downloads occur between visits, data from each download are summarized separately.

The body of the report shows all the data entered into the device sorted by trial date and the time each trial started. Variables include: trial date, trial type (AM session, PM session, extra PEF), time trial started (military time), SIENA diary questions Q1-Q22, number of peak flow maneuvers completed during a session, FVC, FEV_1, PEF, FEF25-75, and FET. SIENA diary questions correspond to the order in which the participant answers them in the device. Refer to the SIENA Spirotel® Coordinator Reference Card (P6_SPIROTEL_CREF) when reviewing the report with a participant. Questions and their possible responses are listed below:

Q1: Number of times the participant woke up last night due to asthma (0-9)
Q2: *(Visits 2-9 only)* Number of puffs the participant will take from his/her BLUE study inhaler this morning (0-9)
Q3: *(Visits 4-9 only)* Number of puffs the participant will take from his/her WHITE study inhaler this morning (0-9)
Q4: Has the participant taken any puffs from his/her RED RESCUE albuterol inhaler during the past 4 hours? (1=yes, 0=no)
Q5: Shortness of breath score overnight (0,1,2,3)
Q6: Chest tightness score overnight (0,1,2,3)
Q7: Wheezing score overnight (0,1,2,3)
Q8: Cough score overnight (0,1,2,3)
Q9: Phlegm/mucus score overnight (0,1,2,3)
Q10: *(Visits 4-9 only)*Number of puffs the participant will take from his/her WHITE study inhaler tonight (0-9)
Q11: Has the participant taken any puffs from his/her RED RESCUE albuterol inhaler during the past 4 hours? (1=yes, 0=no)
Q12: Shortness of breath score since waking this morning (0,1,2,3)
Q13: Chest tightness score since waking this morning (0,1,2,3)
Q14: Wheezing score since waking this morning (0,1,2,3)
Q15: Cough score since waking this morning (0,1,2,3)
Q16: Phlegm/mucus score since waking this morning (0,1,2,3)
Q17: Did your regular exercise cause unusually severe shortness of breath during the past 24 hours? (1=yes, 0=no, 9=n/a)
Q18: Number of RED RESCUE albuterol puffs taken in the past 24 hours to prevent symptoms (for example: before exercise, before smoke exposure, or before exposure to pets) (0-40)
Q19: Number of RED RESCUE albuterol puffs taken for asthma symptoms or low peak flow during past 24 hours (0-40)
Q20: Number of times used RED RESCUE albuterol inhaler for asthma symptoms during past 24 hours (0-40)
Q21: Did RED RESCUE albuterol relieve symptoms for less than 4 hours after treatment during past 24 hours? (1=yes, 0=no)

Q22: Was the participant seen by a healthcare provider (doctor's office, ER, urgent care, study site) for an unscheduled visit in the past 24 hours due to asthma symptoms? (1=yes, 0=no)

The Spirotel® Participant Visit Report should be reviewed with the participant at each visit, starting with Visit 2 (or Visit 0B), to ensure that he/she is following study procedures.

Coordinators should review the participant's answers to Q18 and Q19 (rescue albuterol use information) to ensure that the participant is using albuterol for primary treatment of asthma symptoms appropriately, and to confirm that he/she understands the difference between the two questions (i.e., preventive versus symptom-related use) and how to calculate each.

Coordinators should review Q19 and Q20 to ensure the participant is recording number of puffs taken and number of times albuterol inhaler used appropriately.

Coordinators should review Q2, Q3 and Q10 (study inhaler use) at each visit to ensure that the participant is following instructions for Respimat® (starting at Visit 2) and Twisthaler®/MDI (starting at Visit 4) dosing as dictated by the protocol.

The last page of the report summarizes treatment failure and significant asthma exacerbation alerts based on the spirotel data. The coordinator should review the spirotel data and report with the participant.

If a participant is seen for an exacerbation or treatment failure between regular visits, the Spirotel® Participant Visit Report should be generated and reviewed at that time. The visit number on the report will be the number of the next regular visit which was pre-programmed into the device. The report should be filed in the participant's study folder; it will not be forwarded to the DCC. At the next regular visit, following downloading of the participant's data, a new report should be generated. This report will show the data from both downloads and should be submitted to the DCC with the regular visit packet.

If a participant has experienced two treatment failures or an exacerbation between regular visits and is seen at the clinic, the Spirotel® Participant Visit Report should be generated and reviewed at that time. If the participant will be skipping visits in the treatment period and coming in for the next cross-over (Visit 5 or 7) or last visit (Visit 9), data in the download performed at the visit should have visit number changed to the number of the next cross-over visit/last visit. After the visit number is changed in Breeze, the report should be rerun and stored in the participant's folder; do not forward it to the DCC. When the participant arrives for the cross-over/last visit, the report should be regenerated to contain data from multiple downloads. The updated report should be forwarded to the DCC with the cross-over visit packet.

This report is cumulative in that it shows all data associated with a given visit number, even if multiple downloads take place.

- Spirotel® Participant Compliance Report (P6_COMPLY_RPT):

  This report summarizes a participant's compliance with completing his/her e-diary questions and peak flows in the interval between visits. For a day to be compliant, both AM and PM must be complete (all e-diary questions were answered and at least 1 PEF was done). If multiple downloads are done between visits, all data corresponding to a given visit number will be included in one summary report.

  The top of the report shows the participant's SIENA ID number, initials, and run-in visit number.

  See the spirotel® discussion in this section for further details on the compliance calculations on this report.

- Spirotel® Eligibility Report (P6_ELIG_RPT):

  This report is used at Visits 0B, 1, and 3 to determine if the participant's e-diary/peak flow compliance and symptoms meet the SIENA eligibility criteria.

  The top of the report shows the participant's SIENA ID number, initials, and run-in visit number.

  Visit 0B Eligibility Symptoms for Q1000, Q1020, and Q1040 on P6_ELIG0B:
  This section of the report summarizes the participant's symptoms between Visit 0A and 0B if in Supervised Washout. Mild cough does not count towards daily symptoms. Values provided should be used to complete Q1000, Q1020 and Q1040 on P6_ELIG0B.

  Visit 1 Eligibility Symptoms for Q1070, Q1090, and Q1110 on P6_ELIG1:
  This section of the report summarizes the participant's symptoms between Visit 0B and 1 if in Supervised Washout. Mild cough does not count towards daily symptoms. Values provided should be used to complete Q1070, Q1090 and Q1110 on P6_ELIG1.

  Visit 3 Eligibility Symptoms for Q1080-Q1090 on P6_ELIG5:
  This section of the report summarizes the participant's symptoms during the run-in (between Visit 1 and Visit 3). Values provided should be used to complete Q1080 and Q1090 on P6_ELIG5.

  Visit 3 Spirotel® Compliance for Q1100 on the P6_ELIG5:
  The next section of the report summarizes the participant's e-diary and PEF compliance for purposes of qualifying for randomization. This calculation is

different from that provided on the generic Spirotel® Participant Compliance Report described above. It looks at the prior 3 weeks of data only and computes the number of full days elapsed and the number of AM and PM scheduled sessions the participant has completed (a session is considered complete if all e-diary questions were answered and at least 1 PEF was done) in past 3 weeks. The compliance percentage is calculated as:
(# Complete AM Sessions + # Complete PM Sessions) / (2 x # Full Days) * 100%
This value is interpreted as the percentage of sessions the participant completed. The SIENA protocol requires a minimum session completion percentage of 75% for the participant to be eligible for randomization.

- Spirotel® Baseline Report (P6_BASELINE): This report is used at Visits 0B, 1 and 2 to determine the participant's baseline peak flow (PEF) and rescue use value to be programmed into his/her spirotel® . The baseline PEF is used to define the participant's green-yellow-red zones to aid in identifying worsening of asthma. The baseline rescue use is used to identify one of the treatment failure criteria (weekly rescue use more than twice baseline weekly rescue use.) This report doubles as a data collection form which is included in the visit packets for these visits.

  The report calculates baseline PEF by taking the average of PEF values during the two weeks prior to the visit. If a participant took albuterol within 4 hours of a PEF, that measurement is not included in the calculation. Baseline rescue use is calculated by taking the average number of albuterol puffs for asthma symptoms during the two weeks prior to the visit. For more information on the calculations see the discussion of Baseline Peak Flow and Rescue Use in this section.

  The top of the Baseline Report shows the participant's SIENA ID number, initials, visit number, visit date, and coordinator ID. The coordinator should complete the visit date and coordinator ID.

  Q1000 contains the computed baseline PEF value (in liters/minute). This value should be programmed in the participant's spirotel® at the current visit.

  Q1010 contains the computed baseline Rescue Use value (in liters/minute). This value should be programmed in the participant's spirotel® at the current visit.

Supervised Washout Participants who require Visit 1 Continuation
For Supervised Washout participants who require a Visit 1 Continuation visit, the P6_ELIG_RPT generated at the original Visit 1 visit (containing just the spirotel® data since Visit 0B) should be entered into the database (and used for the P6_ELIG1 form) and sent to the DCC. For the P6_COMPLY_RPT and P6_BASELINE form, only the spirotel reports generated at the Visit 1 Continuation visit (containing all of the Visit 1 spirotel® data) should be entered into the database and sent to the DCC.

2.54 Split Visit 1

For those participants who meet reversibility criteria, Visit 1 may be split due to its length. Day 2 of split visit should try to be scheduled to take place within 1-2 days of Day 1, and within 7 days maximum.

Exclusion criteria assessed at the initial Visit 1 apply to the continuation Visit 1 as well (i.e. respiratory infection in past 4 weeks, medication exclusions, etc.). Review Eligibility Checklist 1 and 2 to ensure nothing has changed, and the participant still meets eligibility criteria.

On Day 1 of the split Visit 1, visit procedures through post-albuterol spirometry should be performed. On Day 2 of the split Visit 1, the visit should begin with completion of the Pulmonary Procedure Checklist (P6_PULMONARYCHK), FeNO testing (ENO), Spirometry testing (SPIRO) and Post-Albuterol Spirometry testing (PALB4_SPIRO). The latter is done as preparation for sputum induction only; reversibility results from Day 1 qualify the participant. These forms will be entered as Visit 1 single forms. Completion of Section 1 of Eligibility Checklist 3 and the Sputum Induction Checklist (SPUTUMCHK) will follow, along with sputum induction and the remaining Visit 1 procedures as given on the Visit Procedure Checklist 1 (P6_VISIT1 or P6_VISIT1_SUP).

Supervised Washout Participants
For Supervised Washout who perform a Split Visit 1, cleaned turbine will need to be replaced in spirotel® device and spirotel® QC performed before participant leaves clinic. spirotel® device should be returned to participant with return visit number (1) and baseline reference values unchanged. Asthma Monitoring Log (P6_ASTHMA_LOG) should also be returned to participant.

2.55 Sputum Induction

Visit 1, 2, 2A
Complete Sputum Induction Checklist (SPUTUMCHK)
Perform Sputum Induction (SPUTUM)
Complete Additional Treatment Post Sputum Induction (SPUTUM_ADD_TRT), if needed
Enter sputum sample data into Biological Sample Tracking module

Sputum induction is required for the SIENA study. A participant must provide at least two acceptable sputum samples to be randomized. Participants have up to three attempts to provide two acceptable samples at Visits 1, 2 and 2A. If after Visit 2, the participant does not have two acceptable slides, Visit 2A will be performed on the scheduled Visit 3 date at which time he/she will perform a third sputum induction. Sputum results will be displayed on the SIENA Participant Status Report. If the participant has two "Acceptable" sputums, he/she is then eligible to proceed to Visit 3.

The Sputum Induction Manual of Operations is located in Appendix 7 of the AsthmaNet General Manual of Operations. Individuals performing sputum induction must be AsthmaNet-certified in this procedure.

Pre-sputum induction spirometry
Participants must undergo reversal with 4 puffs of albuterol to be assessed for procedure eligibility. At Visit 1, participants should dose from albuterol (ProAir®) inhalers taken from bulk supply at Visit 1. This should be logged on SIENA Drug Dispensing Log: ProAir® (RESCUE) Inhaler (P6_DRG_RESC). Actuators should be sterilized between participants, allowing for multiple participant use. Participants should dose from their albuterol (RESCUE ProAir®) inhalers for this test at Visit 2A. At Visit 2, participants will perform reversal with 4 puffs ipratropium rather than albuterol, sterilizing actuators between participants like albuterol at Visit 1.

Visit 1, 2A
For participants with reversibility ≥ 12% and those requiring a Visit 2A, results of the reversal testing are recorded on the Post-Albuterol (4 puffs) Spirometry Testing form (PALB4_SPIRO). The Spirometry Report generated through the MedGraphics system (Pre/Post report) provides the % predicted value needed to complete the Sputum Induction Checklist (SPUTUMCHK) and assess the participant for eligibility for the sputum induction procedure. The FEV_1 value (in liters) after reversal prior to sputum induction is recorded in Q1030 and the corresponding % predicted value in Q1040 on the SPUTUMCHK form. The % predicted value must be at least 50% for the participant to continue with sputum induction at the visit.

Visit 1 Continuation Visit (Participants requiring PC_{20} for eligibility)
For participants requiring a continuation visit to qualify with $PC_{20,}$ results of standard reversal are recorded on the Methacholine Challenge Testing (METHA) form. If the participant requires additional treatment to reverse to ≥ 90% of his/her baseline (pre-

challenge) FEV_1 value, these results are recorded on the Additional Treatment Post Methacholine Challenge Testing (METHA_ADD_TRT) form. The final FEV_1 attained after all post-challenge treatment should be used to qualify the participant for sputum induction. The Spirometry Report generated through the MedGraphics system (Metha report) provides the % predicted value needed to complete the Sputum Induction Checklist (SPUTUMCHK) and assess the participant for eligibility for the sputum induction procedure. Note that the Methacholine Report obtained through the MedGraphics system does not include FEV_1 % predicted values which are needed to assess the participant for the minimum 50% of predicted value required to proceed with sputum induction at the visit. To compute FEV_1 % predicted values, locate the FEV_1 value (in liters) from the final reversal treatment and divide it by the predicted FEV_1 value (in liters) from the top of the 'FEV_1 absolute' column on the Methacholine Report. Multiply the result by 100 and round to the nearest %.

Visit 2

At Visit 2, participants will perform reversal with 4 puffs ipratropium rather than albuterol. Results of the reversal testing are recorded on the Post-Ipratropium (4 puffs) Spirometry Testing form (PIPRA4_SPIRO). The Spirometry Report generated through the MedGraphics system (Pre/Post report) provides the % predicted value needed to complete the Sputum Induction Checklist (SPUTUMCHK) and assess the participant for eligibility for the sputum induction procedure. The FEV_1 value (in liters) after reversal and prior to sputum induction is recorded in Q1030 and the corresponding % predicted value in Q1040 on the SPUTUMCHK form. The % predicted value must be at least 50% for the participant to continue with sputum induction at the visit.

Sputum processing criteria

In order for the resulting sputum sample to be processed, its volume must be deemed adequate for processing by the technician processing the sputum induction and the duration of the procedure (not including spirometry maneuvers) must be at least 4 minutes. No minimum volume is required for processing. If the duration of the procedure was less than 4 minutes, the sample must not be processed. No exceptions are allowed.

The processing of induced sputum to make sputum slides, pellets, and supernatant is explained in the Sputum Induction Manual of Operations. Samples MUST be processed immediately in order to ensure that the slides are of acceptable quality.

Sputum "Acceptable" Criteria

A participant's sputum will be considered acceptable if:

- he/she was eligible to proceed with sputum at the visit,
- the sputum sample was adequate
- the sputum sample was processed within 4 hours
- the sputum slide is readable with squamous count < 80%

Sputum shipments to San Francisco

Slides

For the SIENA trial, slides must be read as soon as possible to determine eligibility for randomization. As a result, slides will be shipped priority overnight to San Francisco every Tuesday and Thursday.

Supernatant, pellets

For the SIENA trial, sputum supernatant and pellets will be shipped to San Francisco every 6 months for overnight receipt. Supernatants and pellets for samples with ≥ 80% squamous cells should NOT be shipped. Shipments will take place on the second Tuesday of April and October. Scheduled shipment dates follow:

2014: October 14
2015: April 14 and October 13
2016: April 12 and October 11
2017: April 11

If a performance site has a conflict with a particular shipment date, arrangements should be made with San Francisco lab staff to ship the samples on an alternate date. Do not ship on an alternate date without first clearing it with lab personnel. There may not be anyone available to accept the shipment.

See the Sputum Induction Manual of Operations located in Appendix 7 of the AsthmaNet General Manual of Operations for further details on packaging and shipping.

Inter-Site Sputum Procedures

Several participating SIENA performance sites have indicated that they plan to use an alternate site within their clinical center partnership to perform tasks related to the sputum induction procedure. These sites do not have sputum induction equipment or certified personnel to conduct the procedure and do not wish to receive such equipment and training, or they do not have someone on staff certified in the processing aspect of the procedure. This section provides guidelines for completion of visits when two sites are involved due to the sputum induction procedure. "Home site" refers to the site where the participant normally completes his/her study visits. "Sputum induction site" refers to the site performing the sputum induction procedure and/or processing the sputum sample.

For sites referring their participants to an alternate site for sputum induction, the following alterations in procedures should be followed:

Pre-Sputum Induction

- Sputum Induction Site: If the site coordinator does not already have access to the home site's data in the SIENA database, the lead coordinator from the sputum induction site should modify an AsthmaNet User Account Checklist requesting access. This step must be completed before the sputum induction site

can insert sputum samples into BST or enter the Sputum Induction Lab form (SPUTLAB).

- Home Site: Unlike BARD, it is preferable that the participant return to the Home Site following sputum induction for drug-related tasks, blood samples, and scheduling. Since sputum induction is required to SIENA, it is possible that a participant may not qualify based on inability to perform induction.

- Home Site: Just before transporting the participant to the sputum induction site, baseline spirometry, administration of albuterol, post-albuterol/-ipratropium spirometry, and completion of the Sputum Induction Checklist (SPUTUMCHK) should be performed.

  The SPUTUMCHK form will include a tech/coordinator ID corresponding to staff at the participant's home site.

  Note: Baseline and post-albuterol/-ipratropium spirometry must be completed on the same MedGraphics computer.

  Note: The coordinator should ensure that baseline spirometry takes place at a time that will be consistent with timing of baseline spirometry at subsequent visits. A +/-3 hour spirometry window relative to timing of baseline spirometry at Visit 1 has been established. See the discussion of Visit Schedule and Visit Windows in this section for details.

  Note: Sputum induction must be completed within 2 hours (maximum window) of dosing with albuterol/ipratropium prior to the post-albuterol/-ipratropium spirometry session. Home site personnel should ensure that minimal time elapses between qualifying the participant for sputum induction and the induction procedure itself.

  Home Site: Accompany the participant to the sputum induction site. The home site coordinator should take the following information to the sputum induction site:

  - Copy of the Sputum Induction Checklist (SPUTUMCHK): For qualifying FEV_1 in Q1030 and Q1040
  - Participant's demographics (ID number, initials, date of birth, spirometry race/ethnicity, gender, height, weight) for use in MedGraphics system

<u>Sputum Induction Procedure</u>

The following procedures will be completed by the sputum induction site.

- Set up the participant in the MedGraphics computer. His/her demographics, including the most recent height measurement, should be provided by the home site's coordinator. The home site's coordinator should verify that the information has been entered into the system correctly.

- Have participant complete three technically acceptable peak flows using a demo spirotel® device, as usual. Complete the top of the Sputum Induction Worksheet (SPUTUM_INDUCTION_WKS) using the best PEF and post-albuterol FEV_1 information supplied by home site.
- Complete Sputum Induction (SPUTUM). This form will have a tech/coordinator ID corresponding to someone from the sputum induction site.
- Complete Additional Treatment Post Sputum Induction form (SPUTUM_ADD_TRT), if needed. This form will have a tech/coordinator ID corresponding to someone from the sputum induction site.
- Add a note to the post-sputum spirometry session indicating that maneuvers were done post-sputum induction. Print the sputum induction spirometry report (SI_RPT).
- Upload the participant's spirometry session immediately following completion of the induction procedure. The overreader will check the post-sputum induction spirometry for technical acceptability, but the maneuvers will not be scored.
- Make copies of the SPUTUM and SPUTUM_ADD_TRT forms and the SI_RPT. Give the originals to the coordinator from the home site. Home site personnel will be responsible for entering these data and submitting forms to the DCC with the visit packet.
- Maintain a folder that includes the following sputum documentation:
    - Participant's demographic data
    - SPUTUMCHK copy
    - SPUTUM copy
    - SPUTUM_ADD_TRT copy
    - SPUTUM_INDUCTION_WKS original
    - SI_RPT copy

Following sputum induction, the participant will return to the home site to complete the visit.

Sputum Processing/Labeling

The following procedures will be completed by the sputum induction site. These procedures also apply if the home site performs the induction procedure and the sputum induction site is only performing sputum processing tasks.

- Generate sputum labels using normal procedures. Barcode numbers will be associated with the sputum induction site, not the participant's home site.
- Process the sputum sample. Complete the Sputum Processing Worksheet (SPUTUM_PROCESS_WKS).
- Complete the Sputum Induction Lab Values form (SPUTLAB). This form will have a technician ID corresponding to the sputum induction site.

- Enter the samples into Biological Sample Tracking. The sputum induction site must have been granted access to the home site's data to complete this step.
- Enter the SPUTLAB form into the SIENA database. The sputum induction site must have been granted access to the home site's data to complete this step.
- Make a copy of SPUTLAB and forward the original to the DCC.
- Store the sputum samples. The sputum induction site will be responsible for shipping samples to San Francisco on the designated dates. The home site's samples will be included in the same shipment (and on the same BST shipment log) as samples collected for participants originating at the sputum induction site. This is possible because barcodes generated for the sputum induction site will be used for all sputum samples regardless of the site from which a participant originates.
- File SPUTLAB and SPUTUM_PROCESS_WKS in the folder referenced above. As per usual procedures, a copy of the processing worksheet should be forwarded to UCSF with the sputum slides.

Sputum-related Queries

- The home site will be responsible for answering any queries related to the SPUTUMCHK form.
- The sputum induction site will be responsible for answering any queries related to the SPUTUM, SPUTUM_ADD_TRT, and SPUTLAB forms. The sputum induction site must have been granted access to the home site's data to answer these queries.

Note: It is the home site's responsibility to contact the sputum induction site to alert the appropriate personnel when sputum-related queries are generated that they need to address. Sputum induction site personnel should not be expected to monitor the query load at the home site to determine when their input is necessary.

Sputum Quality Control Reports

Sputum quality data for samples processed by an alternate site will be included in the reports generated for the alternate site.

Sputum Slide Results

As stated above, sputum slides will be shipped to UCSF every Tuesday and Thursday to be read. The Participant Status report, found on the AsthmaNet secure website, should be run to determine whether the Visit 1, 2 and 2A sputum samples are acceptable. The Visit 2 results must be received prior to moving forward with a Visit 2A (to attempt a third sputum induction) or Visit 3 (to randomize). The intention is for results to be posted within one week of shipment.

2.56 Study Handout Folder

At the end of the first visit, SIENA study participants will be given several handouts related to study procedures. Each handout contributes to increased adherence in areas such as dosing with study medications, using the spirotel® device, and monitoring for treatment failure and significant asthma exacerbation. Participants should be given an AsthmaNet folder to use for carrying and storing the handouts. The participant should store the study folder in a convenient location, as it will serve as a reference throughout his/her SIENA participation. The folder should be brought to each study visit so that clinical personnel can review and/or update handouts, as necessary.

SIENA Study Handout Folder Contents

- SIENA Daily Activities (Visit 0A – 1-Step) (P6_DAILYACT0A_1STEP) – distributed at Visit 0A
- SIENA Daily Activities (Visit 0A – 2-Step) (P6_DAILYACT0A_2STEP) – distributed at Visit 0A
- SIENA Daily Activities (Visit 0B) (P6_DAILYACT0B) – distributed at Visit 0B
- SIENA Daily Activities (Visits 1-3) (P6_DAILYACT1) – distributed at Visit 1
- SIENA Daily Activities (Visits 3-9) (P6_DAILYACT3/P6_DAILYACT3_2) – distributed at Visit 3

“Daily Activities” handouts contain simple summaries of the activities the participant should carry out each day during the SIENA study. Other handouts provide details on the execution of these activities. The “Daily Activities” handouts also list the participant’s 65% Baseline PEF and Weekly High Rescue Use reference values (P6_DAILYACT1 and P6_DAILYACT3/P6_DAILYACT3_2). They prompt the participant to contact clinical personnel when they may be experiencing increased symptoms or an asthma exacerbation. See the Daily Activities Handout discussion in this section for further details.

P6_DAILYACT3 is for participants randomized to Twisthaler; P6_DAILYACT3_2 is for participants randomized to MDI.

- If Your Asthma Gets Worse (P6_ASWORSE_SUP)

This reference facilitates the identification of asthma exacerbations by the participant. The P6_ASWORSE_SUP handout is introduced at Visit 0A for Supervised Washout participants and reviewed at Visit 0B. It contains criteria and treatment for an exacerbation, as well as instructions on when and where to seek emergency treatment. See Significant Asthma Exacerbation discussion in this section for further details.

- If Your Asthma Gets Worse (P6_ASWORSE)
- Participant Identification Card (P6_ID/P6_ID_2)

These references facilitate the identification and treatment of treatment failure, as well as asthma exacerbations according to the protocol, both by the participant and by

healthcare providers. The P6_ASWORSE handout is introduced at Visit 1 and reviewed at subsequent visits, as needed. P6_ID/P6_ID_2 is introduced at Visit 1. Both contain criteria, reference values and treatment for treatment failure and asthma exacerbations, as well as instructions for emergency treatment. It should be carried in the participant's wallet so that it is available at all times. See the Participant Identification Card, Treatment Failure and Significant Asthma Exacerbation discussions in this section for further details.

P6_ID is for participants randomized to Twisthaler; P6_ID_2 is for participants randomized to MDI.

- How to Use Your Metered Dose Inhaler (HTMDI)

This is a standard handout that provides information on MDI closed-mouth inhalation technique and instructions for cleaning the inhaler. It is introduced at Visit 1 (or Visit 0A for Supervised Washout participants) along with the albuterol RESCUE (ProAir®) inhaler.

- How to Use Your Respimat® (HTRESP)

This is a standard handout that provides information on how to use the Respimat®. It is introduced at Visit 1 along with Respimat® Inhalation Technique training.

- How to Use Your Twisthaler® (HTTWIST)

This is a standard handout that provides information on how to use the Twisthaler®. It is introduced at Visit 1 along with Twisthaler® Inhalation Technique training. Participants to be randomized to MDI rather than Twisthaler® at Visit 3 will not receive this handout.

- SIENA Visit Preparation Checklist (P6_VISPRP/P6_VISPRP_2)

This handout is a tool for improving the participant's adherence with respect to keeping scheduled visits and preparing for the visits appropriately. The handout should be photocopied/printed two-sided. The P6_VISPRP/P6_VISPRP_2 handout includes a checklist on one side that itemizes the medications and other study materials the participant should bring to each visit. The participant should check off each item as he/she prepares for each visit to ensure that nothing is overlooked. If clinical personnel notice that the participant is not using the checklist, and he/she is not always prepared for visits, use of the checklist should be reinforced. This handout is introduced at Visit 1 (or Visit 0A for Supervised Washout participants) and should be referenced throughout the participant's study participation.

P6_ VISPRP is for participants randomized to Twisthaler; P6_ VISPRP_2 is for participants randomized to MDI.

- SIENA Visit Scheduler Report

A copy of the current Visit Scheduler Report should be included in the participant's handout folder for personal reference. Old versions should be discarded to avoid confusion. See the Visit Schedule discussion in this section for further details.

- SIENA Asthma Exacerbation Kit Instructions

This handout describes how and when the forms in the Asthma Exacerbation kit they are given at Visit 3 should be completed. See the discussion of Asthma Exacerbation Kit in this section for further detail.

2.57 Study Medications

A general description of the SIENA study medications is given below. See the SIENA Pharmacy MOP for procedures related to drug preparation, logging, and dispensation for clinic staff and pharmacists.

Rescue medications

Visit 1 (or Visit 0A for Supervised Washout Participants)
Log/dispense albuterol (RESCUE) inhaler (P6_DRG_RESC)
Log/dispense rescue prednisone (P6_DRG_PRED)

Visits 2-8 (and Visit 0B, 1 for Supervised Washout Participants)
Log/dispense albuterol (RESCUE) inhaler, if needed (P6_DRG_RESC)

Visit 9
Collect/log albuterol (RESCUE) inhaler (P6_DRG_RESC)

During the SIENA trial, all participants will receive the following study rescue medications:

- Albuterol rescue drug (ProAir®), an inhaled beta-agonist to be used as-needed throughout the SIENA trial to treat asthma symptoms as described on the "If Your Asthma Gets Worse" handout (P6_ASWORSE_SUP or P6_ASWORSE).

  ProAir® rescue drug will be labeled with a red label supplied by the DCC that includes the SIENA study name and space for the visit number, current date, expiration date, participant initials and participant ID number. ProAir® will be dispensed from bulk supplies provided by the DCC at the participant's first visit, and as needed thereafter. Pediatric participants may be dispensed multiple rescue inhalers if school nurses or daycare workers need to keep a supply on-site. This inhaler will be referred to as the RED inhaler (color of label) on participant handouts and in the spirotel®.

- Rescue prednisone, an oral corticosteroid to be used only in emergencies and under the direction of clinical staff to treat an asthma exacerbation.

  Rescue prednisone will be obtained through the individual performance site pharmacies and dispensed to each participant at their first visit. Packaging should be childproof. See the Significant Asthma Exacerbation discussion in this section for further details regarding use of prednisone for treatment of a significant asthma exacerbation.

Run-in medication

Visits 1, 2, 2A
Log/dispense run-in Respimat® (P6_DRG_RUNIN)

Visits 2, 2A, 3
Collect/log run-in Respimat® (P6_DRG_RUNIN)

To qualify for randomization, participant compliance will be evaluated on single-blind placebo tiotropium Respimat® supplied by Boehringer Ingelheim. This inhaler will be referred to as the BLUE inhaler (color of label) on participant handouts and in the spirotel®. The Respimat® device and cartridge will be packaged in a white box with a "Run-in" label. Codes for the run-in Respimat® will have the format 9__ __ __ __ __. Each Respimat contains 60 actuations, and the "Do not use after" date is 3 months after cartridge insertion.

Before giving the Respimat® to the participant, the coordinator should complete the labels as instructed below, insert the cartridge and prepare the Respimat® for first use according to "How to Use Your Respimat® (First Use)" (HTRESP). The coordinator should walk the participant through the steps so he/she is prepared to do it on his/her own if and when needed.

Labeling Run-in Respimat Box - Cover page of booklet (label text)*:*

205.522/AsthmaNet SIENA
Med No.:_____(prefilled by packaging vendor)
Exp. Date:_____(prefilled by packaging vendor)
Lot No.:_____(prefilled by packaging vendor)
Investigator:_____ (completed by pharmacy)
Visit#: _____ (completed by pharmacy)
Date: _____ (completed by pharmacy)
Participant Initials: _____ (completed by pharmacy)
Participant ID: 6- _____ (completed by pharmacy)
Date of cartridge insertion:_____ ***(coordinator completes during visit)***
Do not use after:_____ ***(coordinator completes during visit)***

Labeling Respimat Inhaler – 1st page of booklet (label text):

Visit#_____ Date:_____ (completed by pharmacy)
Participant Initials: _____ (completed by pharmacy)
Participant ID: 6-_____ (completed by pharmacy)
Date of cartridge insertion: _____*(coordinator completes during visit)*
Do not use after:_____ ***(coordinator completes during visit)***

Open-label Asmanex® Twisthaler®

Visits 1
Log/dispense YELLOW Asmanex® 200 mcg MDI (P6_DRG_YELLOW_MDI)

Visits 2, 2A, 3
Log/dispense YELLOW Asmanex® 200 mcg MDI, ONLY IF NEEDED (P6_DRG_YELLOW_MDI)

Visits 4-8

Log/dispense YELLOW Asmanex® 220 mcg Twisthaler or YELLOW Asmanex® 200 mcg MDI (ONLY IF NEEDED), depending on device randomized to at Visit 3 (P6_DRG_YELLOW/P6_DRG_YELLOW_MDI)

Visits 9

Collect/log YELLOW Asmanex® 220 mcg Twisthaler or YELLOW Asmanex® 200 mcg MDI (P6_DRG_YELLOW/P6_DRG_YELLOW_MDI)

Participants who experience treatment failure during the run-in or randomized treatment phase will receive open-label Asmanex® 220 mcg Twisthaler or Asmanex® 200 mcg MDI, depending on device randomized to at Visit 3, two puffs, twice a day for 10 days. See the Treatment Failure discussion in this section for further details.

Each Twisthaler® contains 60 actuations and the "Do not use after" date is 45 days from the date the foil pouch is opened. The coordinator will remove the Twisthaler® from the foil pouch at the time of the visit. At the time the Twisthaler® is removed from the foil pouch, the coordinator must record the "Do not use after" information on the outside of the foil pouch and complete the label text on the actuator contained in the pouch.

Labeling Twisthaler Foil Pouch:

SIENA Asmanex® 220 mcg/puff 60 count Twisthaler®
Do not use after _____(date) ***(coordinator completes during visit)***
Store in a dry place at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F)
Caution: New drug limited by Federal law to investigational use.
Sponsor: AsthmaNet, 500 University Drive, CH79, Hershey, PA 17003.

Labeling Twisthaler canister/actuator:

SIENA Asmanex® 220 mcg/puff 60 count Twisthaler®
Visit#: _____ Date: _____ ***(coordinator completes during visit)***
Do not use after _____(date) ***(coordinator completes during visit)***
Participant Initials: _____ Participant ID: 6-_____ ***(coordinator completed)***
Inhale 2 puffs by mouth between 5-10 AM and 2 puffs by mouth between 5-10 PM.
Caution New drug limited by Federal law to investigational use.
Sponsor: AsthmaNet, Hershey, PA 17003

Labeling MDI White Box:

SIENA Asmanex® HFA 200 mcg/puff 120 count inhaler
Store in a dry place at 20-25°C (68-77°F); excursions permitted to 15°-30°C (59°-86°F). Store inhaler with mouthpiece down.
Rinse mouth after each use.
Caution: New drug limited by Federal law to investigational use.
Sponsor: AsthmaNet, 500 University Drive, CH79, Hershey, PA 17033.

Labeling MDI canister/actuator:

SIENA Asmanex® HFA 200 mcg/puff 120 count inthaler
Visit#: _____ Date: _____ ***(coordinator completes during visit)***

Participant Initials: _____ Participant ID: 6-_____ ***(coordinator completed)***
Inhale 2 puffs by mouth between 5-10 AM and 2 puffs by mouth between 5-10 PM.
Caution New drug limited by Federal law to investigational use.
Sponsor: AsthmaNet, 500 University Drive, CH79, Hershey, PA 17033

This inhaler will be referred to as the YELLOW inhaler (color of label) on participant handouts and in the spirotel®. Open-label Asmanex® 220 mcg Twisthaler will arrive in a silver/gray pouch, have a pink base, and be dispensed from bulk supplies. Open-label Asmanex® 200 mcg MDI will arrive in a white box, have a blue actuator with a pink cap, and be dispensed from bulk supplies.

Double-blind treatment period medications

Visit 3
Log/Dispense Respimat® and MDI inhalers (P6_DRG_SCH_RESP, P6_DRG_SCH_MDI)

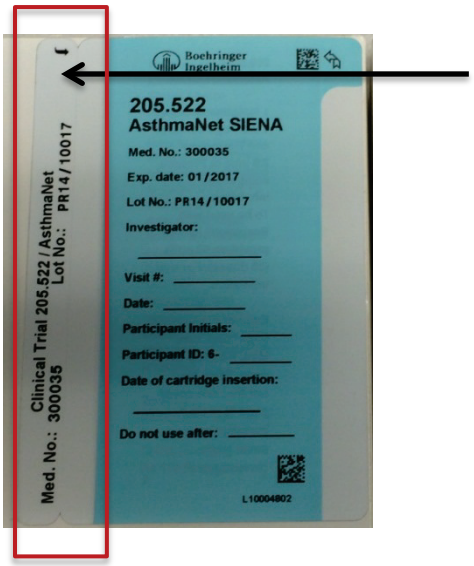
Visits 4-8
Log/Dispense Respimat® and Twisthaler®/MDI inhalers (P6_DRG_SCH_RESP, P6_DRG_SCH_TWIST/P6_DRG_SCH_MDI)

Visits 4-9
Collect/Log Respimat® and Twisthaler®/MDI inhalers (P6_DRG_SCH_RESP, P6_DRG_SCH_TWIST/P6_DRG_SCH_MDI)

Treatment period medications are double-blind. Participants, performance site staff, and DCC personnel involved in day to day decision-making for the study and statisticians on the project will not know what treatment regimen the participant is receiving during any of the three treatment periods.

<u>Respimat</u>
All blinded Respimat® devices will arrive in a white box, containing a Respimat inhaler and cartridge which contains either tiotropium or placebo. Blinded Respimat® devices and cartridges containing placebo and tiotropium will appear identical. Blinded Respimat® will dose two puffs in the morning. Each Respimat contains 60 actuations, and the “Do not use after” date is 3 months after cartridge insertion. Individual blinded Respimat® boxes will be identified by a code number that is associated with their randomized treatment assignment in the SIENA database. Codes for the blinded Respimat® will have the format 3__ __ __ __ __. This inhaler will be referred to as the BLUE inhaler on participant handouts and in the spirotel®.

The white box in which the Respimat® inhaler and cartridge arrive will include a booklet label with a documentation sticker. This sticker should be peeled and placed on the P6_MED form at the time of dispensation. Sticker is white, and is located along the edge of the booklet label.



Documentation sticker

Before giving the Respimat® to the participant, the coordinator should complete the labels as instructed above (for the Run-in Respimat®), insert the cartridge and prepare the Respimat® for first use according to "How to Use Your Respimat® (First Use)" (HTRESP). The coordinator should demonstrate how to insert the canister and prepare the Respimat for first-time use. The Respimat should be prepared so that the indicator arrow lines up with the notch by 60, and participants should be instructed to do the same.

Twisthaler

All blinded Twisthaler® devices will arrive in a silver/gray pouch, be white with a red base, and will contain either mometasone110 mcg/puff or placebo. Blinded Twisthaler® devices containing placebo and mometasone will appear identical. Blinded Twisthaler® will dose two puffs, twice a day. Each blinded Twisthaler® contains 60 actuations and the "use by" date is 45 days from the date the foil pouch is opened. The "Do not use after" date should also be recorded on the Participant-Specific Drug Accountability Log: Post-Randomization Twisthaler (P6_DRG_SCH_TWIST). Codes for the blinded Twisthaler® devices will have the format 1__ __ __ __ __. This inhaler will be referred to as the WHITE inhaler on participant handouts and in the spirotel®.

Blinded Twisthaler® devices will arrive at the clinic labeled by the pharmacy. The label on the silver/gray pouch is perforated so that a portion of the label may be removed. This portion of the label should be removed and placed on the P6_MED form at the time of dispensation.

MDI

All blinded MDI devices will arrive in a white box, have a blue actuator with a green cap, and will contain either mometasone 200 mcg/puff or placebo. Blinded MDI devices containing placebo and mometasone will appear identical. Blinded MDI will dose **one** puff, twice a day. Each blinded MDI contains 120 actuations. Codes for the blinded MDI devices will have the format 2__ __ __ __ __. This inhaler will be referred to as the WHITE inhaler on participant handouts and in the spirotel®.

The label on the white box is perforated so that a portion of the label may be removed. This portion of the label should be removed and placed on the P6_MED form at the time of dispensation.

Dispensing multiple inhalers

During the double-blind treatment period, and potentially during the run-in, multiple inhalers will be dispensed to the participant at a visit. The following sticker has been provided to identify the order in which the inhalers should be used:

When dispensing two Respimat® devices at a visit, the sticker should be placed on each box, with one sticker indicating "1 of 2" and the other indicating "2 of 2". The participant should be instructed to start with Respimat® inhaler #1, and switch to Respimat® inhaler #2 when #1 is empty. When dispensing three Twisthaler® devices at a visit, the sticker should be placed on each inhaler, with one sticker indicating "1 of 3", another indicating "2 of 3", and the other indicating "3 of 3". The participant should be instructed to start with Twisthaler® #1, switching to Twisthaler® #2 and #3 when the current inhaler is empty.

Dispensing additional inhaler(s) due to Washout

Participants receiving treatment for treatment failure (or experiencing a respiratory infection in the run-in) may need additional medication to last the 3-week washout (or 4-week washout for respiratory infection in run-in) required prior to Visits 3, 5, 7 and 9. Whether a participant returns to the clinic for study medication will depend on the amount of time until his/her next visit.

- Run-in: Recommendation is one Respimat® be dispensed at the participant's last visit before Visit 3. If the extended run-in requires 3 to 4 weeks between the participant's last visit and Visit 3, the participant should not need an additional Respimat® beyond the one Respimat® given at the last visit. If the extended run-in requires 5 or more weeks between the participant's last run-in visit and Visit 3, the participant will require another Respimat®. It is recommended that the participant be contacted by phone at 10 days, and return to clinic 3 weeks following last visit to receive a new Respimat® and open-label Asmanex® 200 mcg MDI, if needed.
- Randomized treatment phase: Twisthaler® devices dispensed at a regular visit will last a maximum of 45 days, so most extensions to the treatment period will require additional Twisthaler® device(s) be given to the participant (unless extension is 3 days or fewer). Respimat® and MDI devices dispensed at a regular visit will last a maximum of 60 days, so extension of treatment period may or may not require additional Respimat® device(s) or MDI device be given to the participant. In general, if the extended treatment period requires 8 or more weeks between the participant's last visit and Visits 5, 7 or 9, it is recommended that the

participant return to the clinic to receive new blinded Twisthaler®/MDI and Respimat® devices necessary to meet washout, and open-label Asmanex® 220 mcg Twisthaler or Asmanex® 200 mcg MDI if needed (depending on device randomized to at Visit 3). If the extended treatment period requires 6 to 7 weeks between the participant's last visit and Visits 5, 7 or 9, medication necessary to meet washout can be mailed to the participant.

See Extra Visit due to Washout in this section for further details on participant returning to clinic for additional medication.

Inhaler colors

Given that the Respimat is recognized as the blue inhaler and the Asmanex MDI has a blue actuator with green cap, this may cause confusion as to which is the blue inhaler. To prevent confusion, ancillary dots have been provided to al pharmacies. The Pharmacy MOP instructs AsthmaNet pharmacists to add a white dot to the blinded Asmanex, a blue dot to the blinded Respimat, a red dot to the albuterol inhaler and a yellow dot to the open-label Asmanex to re-inforce the color assignments. The dot color matches the AsthmaNet label color, which is the color that identifies the inhaler in the spirotel and in SIENA handouts. Inhaler color should be reviewed at each visit.

2.58 Study Treatment Questionnaires

Visit 5, 7, 9 (or last post-randomization contact during a treatment period)
Have participant complete Participant Study Treatment Questionnaire (P6_PARTTXQX/P6_PARTTXQX_2)
Complete Coordinator Study Treatment Questionnaire (P6_CTXQX)

The study treatment questionnaires are used to assess how well the masking of the scheduled inhalers was carried out. The Participant Study Treatment Questionnaire (P6_PARTTXQX/P6_PARTTXQX_2) was developed to evaluate the blind from the participant's perspective. The Coordinator Study Treatment Questionnaire (P6_CTXQX) was developed to evaluate the blind from the study coordinator's perspective. Under normal circumstances, each questionnaire is completed at the participant's final study visit of each of the three double-blind treatment periods (Visits 5, 7 and 9). Questions on the forms address the treatment the participant/guardian or study coordinator thought the participant received since starting blinded, randomized treatment at the beginning of that treatment period.

P6_ PARTTXQX is for participants randomized to Twisthaler; P6_ PARTTXQX_2 is for participants randomized to MDI.

If a participant withdraws from the study following randomization and prior to Visit 9, both questionnaires should be completed at the time of the participant's final contact with the performance site. If the final contact is by phone, the coordinator may administer the P6_PARTTXQX/P6_PARTTXQX_2 questionnaire over the phone. In this case, no source documentation will be recorded. Single forms will need to be completed if the participant withdraws in the middle of a treatment period.

If a participant experiences two treatment failures during a treatment period or the physician decides the participant should stop the current treatment period, both questionnaires should be completed at the time the participant begins YELLOW open-label Asmanex® or prednisone. These questionnaires will be single forms in the database. The packet forms at the next cross-over visit should be marked missing; the participant/coordinator should not complete them again.

Participant Study Treatment Questionnaire
Near the conclusion of Visits 5, 7 and 9, the participant should complete a Participant Study Treatment Questionnaire (P6_PARTTXQX/P6_PARTTXQX_2). This form is designed to determine how well the blind on the SIENA inhalers performed with respect to the participant's perceptions of the study medications he/she received during that treatment period. Clinical personnel should explain the purpose of the questionnaire to the participant and confirm that the participant understands that the form references only the medication taken from his/her blinded study inhalers (blinded Twisthaler®/MDI and blinded Respimat®), not the RED ProAir® RESCUE inhaler or YELLOW open-label Asmanex® inhaler used for treatment failure.

This questionnaire is completed by the participant or his/her parent or guardian. It is relatively short and should take no longer than five minutes to complete. Study personnel should not help the participant/guardian to answer questions on the form, as such assistance could influence the responses and result in bias. Participants/guardians should be asked to answer all questions to the best of their ability; they should not leave any blank. When the form is complete, the participant/guardian should initial and date the source documentation box on page 2. Coordinators should check the completed questionnaire to ensure that it has been completed correctly.

Coordinator Study Treatment Questionnaire
Near the end of Visits 5, 7 and 9, the study coordinator who was primarily responsible for the participant's SIENA study visits during that treatment period should complete a Coordinator Study Treatment Questionnaire (P6_CTXQX). This form is designed to determine how well the blind on the SIENA inhalers performed with respect to the coordinator's perceptions of the study medications the participant received during that treatment period. The coordinator should complete this form before reviewing the participant's questionnaire (P6_PARTTXQX/P6_PARTTXQX_2) and before entering the participant's form into the study database. The participant should not review the coordinator's form, and the coordinator should not discuss his/her perceptions of the study treatment with the participant.

When the P6_CTXQX form is complete, the coordinator should initial and date the source documentation box at the bottom of the page. If the primary study coordinator in charge of the participant's visits over the past treatment period is unavailable during the final visit of the treatment period or the participant's early withdrawal visit, the P6_CTXQX form should be completed as soon as possible on his/her return to the performance site, preferably within 1 week of the visit. Only one coordinator should complete the form, and only one form should be submitted per participant per treatment period.

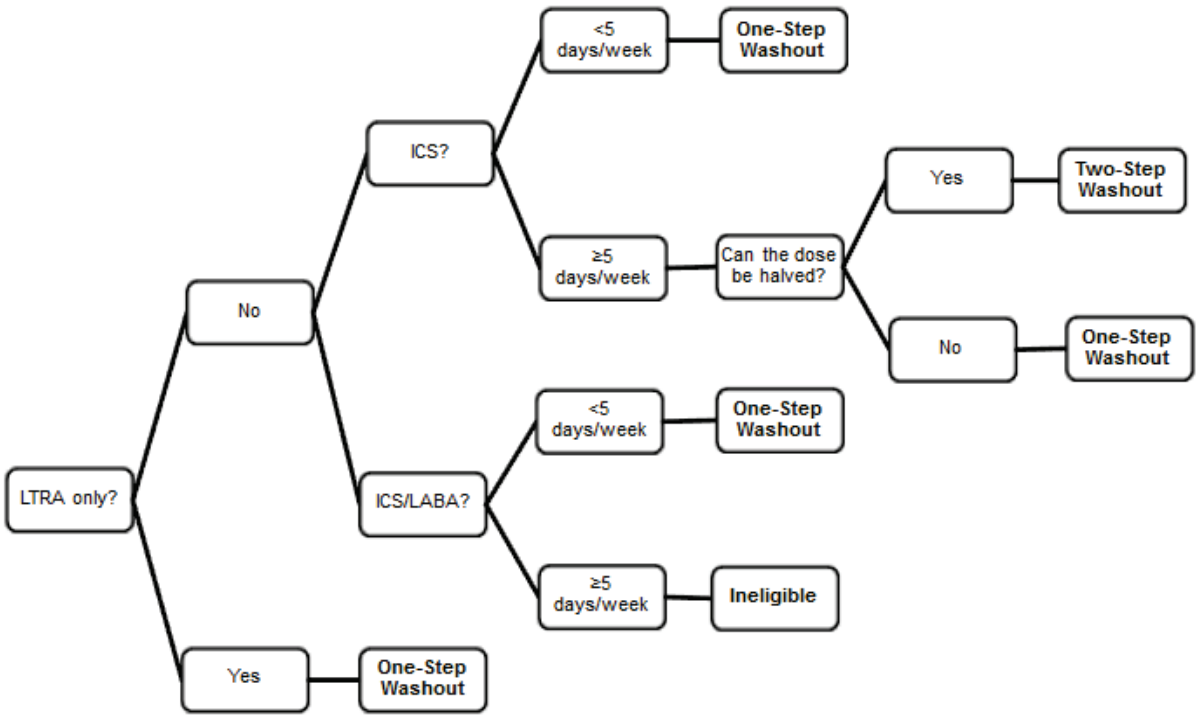
If a randomized participant is lost to follow-up or withdraws early and is unavailable to complete the P6_PARTTXQX/P6_PARTTXQX_2 form, the study coordinator still should complete a P6_CTXQX form, as long as the participant had at least one follow-up visit during the double-blind treatment period. In this case the P6_CTXQX form should be submitted as a single form.

See Section 4 in this manual for further details regarding the completion of the P6_CTXQX and P6_PARTTXQX/P6_PARTTXQX_2 forms.

2.60 Supervised Washout

Participants who are well-controlled and who are taking low-dose ICS (equivalent of BDP 80-240 mcg/day, see P6_ICS_EQUIV reference card), intermittent ICS (<5 days week), intermittent ICS/LABA (<5 days/week) or LTRA may be withdrawn from their asthma controller medication prior to enrollment into the SIENA Run-in. Visit 0A assesses the participant's eligibility for the Supervised Washout and also screens for Visit 1 eligibility. If the participant meets all of the eligibility criteria on SIENA Eligibility Checklist 0A (P6_ELIG0A), the participant will either undergo a 1-Step or 2-Step Washout. Participants on low-dose ICS whose dose can be halved, adhering to the standard recommended BID or QD dosing schedule (i.e., BID for all except mometasone which may be BID or QD), will enter the 2-Step Washout. In the 2-Step Washout, the participant's current ICS dose will be cut in half, the participant will be given a spirotel®, and will return to the clinic in three weeks for Visit 0B. If the participant remains eligible at Visit 0B (based on criteria on SIENA Eligibility Checklist 0B (P6_ELIG0B), the participant's ICS will be discontinued and he/she will return to the clinic in three weeks for Visit 1. Participants on low-dose ICS that cannot be halved, intermittent ICS, intermittent ICS/LABA or LTRA will enter the 1-Step Washout. In the 1-Step Washout, the participant's medication will be discontinued at Visit 0A, the participant will be given a spirotel®, and will return to the clinic in three weeks for Visit 1. At the time of Visit 1, the participant must not have taken ICS, ICS/LABA or LTRA within the previous 3 weeks.

Visit 0A
Review SIENA Washout Flowchart (P6_WASH_FLOW) to determine 1-Step or 2-Step Washout.



SIENA Washout Flowchart (P6_WASH_FLOW)

Adjustment of Participant's Medication - 2-Step Washout

Visit 0A

For participants in the 2-Step Supervised Washout, his/her current ICS dose will be halved at Visit 0A adhering to the standard recommended BID or QD dosing schedule (i.e., BID for all ICS except mometasone which may be BID or QD). If the participant is taking 2 puffs BID of his/her current inhaler at the time of Visit 0A, the participant's new daily dose should be 1 puff BID from his/her current inhaler. If a participant is taking 1 puff Flovent 100 mcg BID at the time of Visit 0A, the participant's new daily dose should be 1 puff Flovent 50 mcg BID. If a participant is taking 1 puff BID of his/her Asmanex® 110 mcg inhaler at the time of Visit 0A, the participant's new daily dose should be 1 puff Asmanex® 110 mcg QD from his/her current inhaler.

Visit 0B

Two weeks following Visit 0A, the participant will return for Visit 0B. At Visit 0B, if the participant remains eligible to continue in the Supervised Washout, he/she will discontinue ICS and return to the clinic in 3 weeks for Visit 1.

Adjustment of Participant's Medication - 1-Step Washout

For participants in the 1-Step Supervised Washout, their asthma controller medication (low-dose ICS that cannot be halved, intermittent ICS, intermittent ICS/LABA, LTRA) will be discontinued and he/she will return to the clinic in 3 weeks for Visit 1.

2.61 Transfer Participants

Transfer participants are defined as individuals who are enrolled in a trial and successfully complete at least one study visit at one performance site, then transfer to another performance site for a set number of visits or for the remainder of their study participation. General database procedures related to transfer participants are outlined in Section 7.5.2 of the AsthmaNet General Manual of Operations. SIENA-specific considerations follow.

- Participant Assignment Log: Complete the participant ID number and other information on the Participant Assignment Log (P6_LOG) (Not Pre-Filled) version. Maintain this log with the site-specific SIENA log. The participant should retain his/her original ID that was assigned at the originating site.
- Registry Report: Generate a copy of the participant's Registry Report to obtain demographics needed for spirometry and MedGraphics reports.
- spirotel®: The originating site should note in the Comments section of the Spirotel® device and turbine logs (SPIROTEL_DEVICE, SPIROTEL_TURBINE) that the participant's materials went with him/her to the new site. The device/turbine will continue to be used by the participant until he/she completes the study. The device/turbine will not be returned to the originating site (unless the participant returns to the originating site). The new site should record the device/turbine information on its spirotel® device and turbine logs and consider the equipment part of their supply. The new site should notify the DCC of the new location of the supplies by e-mailing the details to the AsthmaNet_SIENA_DM@phs.psu.edu alias.

  The new site should download the participant's spirotel® data to the site's BreezeSuite database and upload spirotel® data to the central database at MedGraphics following normal procedures. Depending on where the participant is in the trial, the applicable Spirotel® reports may not run correctly (because the participant's prior data is not located on the local machine). Contact the DCC for assistance before the first visit is completed at the new site. Arrangements will be made to copy the spirotel® files from the originating site's laptop to the new site's laptop so that all reports generate correctly at the time of the visit. At least 2 weeks' notice should be given to accomplish this task before the participant is seen at the new site. If the participant returns to his/her home site, the same process will need to be carried out to ensure that the home site has the most recent spirotel® data available on the local laptop.
- Randomization: In the SIENA Randomization Module, enter the participant ID and select the location where the randomization is taking place (i.e., 'new' site). If the enrollment site is chosen by mistake, the Randomization Module will return blinded inhaler numbers that are physically located at the transfer participant's

enrollment site, not the site of the current visit. If this occurs, the DCC should be contacted immediately.

- Study ID Card: A new study ID card should be distributed to the participant (with updated study personnel and primary physician information completed, as necessary).
- Current Dosing Information and Asthma Exacerbation/Treatment Failure History: The originating site should supply the new site details of the participant's current study treatment (either blinded medications, prednisone or open-label Asmanex®). The originating site should supply the new site a summary of all asthma exacerbation and treatment failure events the participant has experienced in the study, along with their dates and any ongoing treatment (primarily prednisone for an asthma exacerbation or open-label Asmanex® for a treatment failure). The new site may view the data collection forms from the enrollment site within the Participant Data module if appropriate database permissions have been requested/granted.
- Baseline Reference Values: The originating site should provide the new performance site a photocopy of their last Baseline PEF and Rescue Use (P6_BASELINE) form. In addition, the originating site should confirm the participant's baseline (Visit 1) FEV_1 value.
- Physical Measurements: For participants ≥ 21 years old, the new performance site may use the Participant Data module to view the Adult Body Measurements (BODYMEAS_ADULT) form completed at Visit 1 (or Visit 0A for Supervised Washout participants). The height and weight recorded on this form should be referenced when entering participant characteristics into the MedGraphics PC.

  For participants under age 21, the originating site should supply the new site a copy of the most recent form that contains the participant's height measurement (SEXAM_PED, LEXAM_PED or P6_PULMONARYCHK).
- Genetics Blood: If the genetics blood draw was deferred to a later visit and has not yet been completed, the originating site should notify the new site. The new site should confirm the participant's consent for participating in the genetics blood draw based on his/her responses on the local consent documents.
- Visit Schedule: The originating site should supply the new site a copy of the most recently generated Visit Scheduler Report.
- Prednisone Supply: The new site should verify that the participant has a supply of rescue prednisone on hand. If he/she does not, a new supply should be dispensed.

2.62 Treatment Failure

Visits 1-9
Assess participant for treatment failure (P6_TXFAIL_CHK, P6_TXFAIL)

Visits 90A-92A
Complete Treatment Failure Checklist (P6_TXFAIL_CHK)

Definition
The treatment failure definition is applicable to the run-in and post-randomization treatment phase; it does not apply during the Supervised Washout.

A participant will have experienced a treatment failure event if he/she meets at least one of the following criteria:

1. Awakening from asthma three or more times in a two-week period or on two consecutive nights

   If participant woke up during the night to use bathroom, get a drink, etc. and noticed asthma symptoms, that does not count as a nighttime awakening because asthma symptoms did not cause participant to wake up.
2. Using albuterol for relief of symptoms four or more times/day for two or more consecutive days
3. Albuterol relieving symptoms for less than four hours after treatment

   Treatment is as specified on RESCUE inhaler label. Criterion is met if RED RESCUE did not relieve symptoms for a full 4 hours after taking it. In other words, treatment relieved symptoms initially, but symptoms returned or got worse less than 4 hours later.
4. Using albuterol for relief of symptoms daily for seven days, and this use exceeds two times the weekly use of albuterol in the baseline period
5. Regular exercise has caused severe shortness of breath 2 or more days over a 7 day period

   Regular exercise is exercise the participant does routinely, not an activity tried for the first time. Only regular exercise activity that leads to unusually severe shortness of breath would result in this criterion being met.
6. Participant experienced a significant asthma exacerbation

   See the discussion of Significant Asthma Exacerbation in this section for the definition of an asthma exacerbation for the SIENA trial, as well as the Asthma Exacerbation protocol.

For criteria 1-5, the participant's spirotel® device is programmed to provide an alert if he/she meets any one of the criterion (with exception to #6). The alert will read 'E-diary

indicates you need YELLOW inhaler. Call Clinic ASAP.' See SIENA spirotel® Reference Card (P6_SPIROTEL_REF/P6_SPIROTEL_REF_2) for additional explanation of spirotel® questions.

The SIENA Spirotel® Participant Visit Report (P6_SPIROTEL_RPT) and Asthma Monitoring Log (P6_ASTHMA_LOG) will be reviewed at the time of each visit to identify treatment failure. The last page of the Participant Visit Report summarizes treatment failure alerts based on the spirotel data. The report lists each day the participant meets a treatment failure criterion. The coordinator should review the spirotel data and report with the participant to determine if participant experienced treatment failure and if so, the appropriate treatment failure date.

Note that in SIENA, when a participant experiences a significant asthma exacerbation, he/she will also meet the criteria for treatment failure. Further details are provided below.

Adjustment of Trial Medication

Once a participant has met treatment failure criteria during the run-in or the post-randomization treatment phase (not as a result of significant asthma exacerbation), he/she should start taking YELLOW open-label Asmanex® (2 puffs, twice daily for 10 days). The participant will continue taking his/her blinded scheduled medications while receiving treatment for treatment failure. There will be no adjustment to trial medication.

Treatment failure events that are identified retrospectively, have resolved completely, and are more than 1 week in the past generally do not need to be treated. A physician should assess the participant's condition to determine if additional treatment is warranted. Historically identified events should be reported on the treatment failure forms (P6_TXFAIL_CHK, P6_TXFAIL). The participant should be reminded to monitor his/her symptoms and rescue use at home and to alert the study coordinator if he/she has met treatment failure criteria between visits. This is important for the participant's safety, as well as for the integrity of the study data.

Study Participation Following Treatment Failure during Run-In

Participants experiencing a treatment failure during the run-in phase of the study will have the run-in extended such that three weeks transpire between completion of treatment with YELLOW open-label Asmanex® and Visit 3 (randomization). If treatment failure is ongoing or is not completely resolved, Visit 3 should not proceed until treatment failure has resolved completely. With exception to requiring 3 weeks between end of YELLOW open-label Asmanex® treatment and Visit 3, and complete resolution of treatment failure event at time of Visit 3, run-in study visits can proceed as usual (i.e., no open-label Asmanex® washout required for Visits 2 or 2A). Whether a participant returns to the clinic for study medication will depend on the amount of time between participant's last visit and 3-week washout date. See Extra Visit due to Washout and Study Medications discussion in this section for further details on whether participant needs to return to clinic for study medication (or it can be shipped), and what visit procedures should be performed when participant returns.

If a participant experiences two treatment failures in the run-in, he/she is ineligible to continue in the trial. A SIENA Termination of Study Participation (P6_TERM) form should be completed, as well as a Treatment Failure Checklist (P6_TXFAIL_CHK) form. If determined at a visit, the P6_TXFAIL_CHK form will be submitted as a packet form, and if determined between visits, it will be submitted as a single form, using the visit number of the participant's most recently entered visit packet. If the treatment failure occurred recently or has not resolved and the participant did not start the yellow inhaler, a physician should assess the participant's condition to determine if additional treatment is warranted.

Study Participation Following Treatment Failure after Randomization
Participants who experience their first treatment failure of a treatment period within the final three weeks of the 12-week period will delay the start of the following treatment period (or final visit during period 3) so that 3 weeks transpire between completion of YELLOW open-label Asmanex® (2 puffs, twice daily for 10 days) and crossover (or final visit during period 3) visit. As stated above, participants will continue taking his/her blinded scheduled medications while receiving open-label Asmanex® for treatment failure.

Whether a participant returns to the clinic for study medication will depend on the amount of time between participant's last visit and 3-week washout date. See Extra Visit due to Washout and Study Medications discussion in this section for further details on whether participant needs to return to clinic for study medication (or it can be shipped), and what visit procedures should be performed when participant returns.

If a participant experiences two treatment failures in the same treatment period, he/she will proceed to the next treatment period (or final visit during period 3) 14 days following completion of YELLOW open-label Asmanex®. For example, if the participant experiences two treatment failures between visits 5 and 6 during treatment period 2, he/she will not complete Visit 6, but instead his/her next visit will be Visit 7. This participant should be scheduled for Visit 7 (cross-over into treatment period 3) 14 days after completing open-label Asmanex®. Visit 6 should be marked missing in the SIENA database.

Note: If a treatment failure is determined at the time of a crossover/last visit, the participant is not completing a combined V5/V7/V9 and V9XA visit due to asthma exacerbation, FEV1 ≥ 50% of baseline AND ≥ 40% of predicted, the visit should be stopped and the P6_TXFAIL_CHK entered as a single form along with a P6_TXFAIL form, using the visit number of the participant's most recently entered visit packet. P6_PULMONARYCHK and SPIRO forms should also be entered as single forms with the visit number of the participant's most recently entered visit packet. Follow instructions above depending on whether this is the first or second treatment failure in the current treatment period.

If a treatment failure is determined at the time of a crossover/last visit, the participant is not completing a combined V5/V7/V9 and V9XA visit due to asthma exacerbation, FEV_1 < 50% of baseline OR < 40% of predicted, AND participant does not meet any other significant asthma exacerbation criteria, stop visit and schedule him/her for repeat spirometry (i.e., FEV_1 Re-assessment visit to determine if significant asthma exacerbation criteria have been met). If participant meets significant asthma exacerbation criteria, see Study Participation Following a Significant Asthma Exacerbation after Randomization and Handling Data in Significant Asthma Exacerbation discussion in this section. Otherwise, follow instructions above depending on whether this is the first or second treatment failure in the current treatment period.

If neither of the two cases above applies, following clinical assessment and appropriate medical management, regular study visits will continue in accordance with the participant's visit schedule.

Medication Supply

Participants receiving treatment for treatment failure may need additional medication to last the 3-week washout required prior to Visits 3, 5, 7 and 9. Whether a participant returns to the clinic for study medication will depend on the amount of time between participant's last visit and 6-week washout date. See Extra Visit due to Washout and Study Medications discussion in this section for further details on whether participant needs to return to clinic for study medication (or it can be shipped), and what visit procedures should be performed when participant returns.

Documentation

Treatment failure events are determined by the SIENA Treatment Failure Checklist (P6_TXFAILCHK). Once the treatment failure has been confirmed, the following forms should be completed:

- Clinical Adverse Events (AECLIN)

  All treatment failure events should be documented on AECLIN using ICD-9 code 000.00. Separate entry for a related significant asthma exacerbation should be recorded using code 493.92.

  The start date recorded for the treatment failure event should correspond to the date treatment failure criteria was confirmed. The start dates for entries for an event that meets both treatment failure and asthma exacerbation criteria may differ depending on the criteria that were met.

- Concomitant Medications for Asthma/Allergy and Adverse Events (CMED)

  Open-label Asmanex® used to treat the treatment failure event (2 puffs, twice daily for 10 days) should be recorded on the CMED form. The code for mometasone is 301021. Nebulized beta-agonist treatments administered in a physician's office or other care facility should also be captured on the CMED form.

Participants will continue to take blinded scheduled medications in addition to the open-label Asmanex® for treatment failure (2 puffs, twice daily for 10 days).

RESCUE ProAir® inhaler puffs should not be recorded on CMED; these are documented by the participant in his/her daily e-diary responses.

Open-label Asmanex® used for treatment of treatment failure events (2 puffs, twice daily for 10 days) and listed on the CMED form should be linked to the applicable adverse event recorded on the AECLIN form.

- SIENA Treatment Failure Checklist (P6_TXFAIL_CHK)

  The P6_TXFAIL_CHK form captures the criteria the participant meets for treatment failure. It is completed at each regular visit, starting at Visit 2, and is submitted with the visit packet, even if no treatment failure criteria are met. This documentation ensures that the study coordinator thoroughly assesses the participant for the occurrence of treatment failure at all regular study visits.

  When reviewing the Participant Visit Report, the coordinator may determine that the participant misunderstood a spirotel question, causing an erroneous treatment failure alert. If this happens, answer 'No' to the corresponding question on the P6_TXFAIL_CHK form and provide a thorough explanation in Q6000 (i.e., participant misunderstood spirotel Q21 on 2/28, albuterol relieved symptoms for 4 hours). Review the question with the participant to be sure he/she understands the question.

  The treatment failure date is recorded in Q1070. This date is critical for analysis of time to treatment failure. It should correspond to the date treatment failure criteria were confirmed for the current event. For example, if a participant requires ProAir® for relief of symptoms four or more times/day for two or more consecutive days, the second day should be recorded as the treatment failure date. If multiple criteria for treatment failure are met, record the earliest date any of the applicable criteria were met.

  If treatment failure is confirmed between visits, P6_TXFAIL_CHK should be completed as a single form and data entered. Use the number of the last regular visit completed as the visit number on the form. At the next regular visit, treatment failure should be assessed from the conclusion of the previous treatment failure. If participant has updates to treatment failure event that occurred between visits (for which P6_TXFAIL_CHK and P6_TXFAIL have already been completed), updates should be made to the single forms completed at the time of the event.

- SIENA Treatment Failure Information (P6_TXFAIL)

P6_TXFAIL is completed only when a participant meets treatment failure criteria as recorded on P6_TXFAIL_CHK and the participant has not experienced treatment failure as a result of a significant asthma exacerbation. P6_TXFAIL records details of the medical care the participant received, whether open-label Asmanex® was taken as specified for treatment failure conditions, as well as any other medications taken. P6_TXFAIL is always a single form.

Compliance Monitoring (P6_COMPLY)

Participants who experience two treatment failure events or a significant asthma exacerbation, causing him/her to skip the middle visit of the treatment period (Visits 4, 6 or 8), should have the visit number of the cross-over/last visit (5, 7 or 9) for the entire period's spirotel® data. Following download and conversion of the spirotel® data, the visit ID should be updated in Breeze before the crossover/last visit occurs and reports are run.

2.63 Visit Schedule

Visits 0A, 0B, 1, 2A, 3, 4, 5, 6, 7, 8, 90-92
Run SIENA Visit Scheduler
Review planned visit schedule

A visit scheduler program has been included on the AsthmaNet secure website to allow clinical personnel to create a Visit Scheduler Report for a given participant's SIENA study visits. The visit scheduler is run at Visits 1, 2A (if necessary), 3, 4, 5, 6, 7 and 8. The visit scheduler creates the participant's visit and phone contact schedule at:

- Visit 1, based on the Visit 1 date, for Visits 2 and 3;
- Visit 2A, based on the Visit 2A date, for Visit 3;
- Visit 3, based on the Visit 3 date, for Visits 4;
- Visit 4, based on the Visit 4 date, for Visits 5;
- Visit 5, based on the Visit 5 date, for Visits 6;
- Visit 6, based on the Visit 6 date, for Visits 7;
- Visit 7, based on the Visit 7 date, for Visits 8;
- Visit 8, based on the Visit 8 date, for Visits 9;
- Visit 90-92, based on the Visit 90-92 date, for Visits 90A-90D, 91A-91D, and 92A-92D

The 1-Step and 2-Step Supervised Washout schedulers are only run for participants in the Supervised Washout. The visit scheduler for the Supervised Washout is located on the AsthmaNet website under Reports: Visit Scheduler: SIENA in the link titled "SIENA 1-Step or 2-Step Supervised Washout Scheduler". It is an Excel file that calculates appropriate windows for the 1-Step and 2-Step Washout based on the Visit 0A and Visit 0B dates. The 1-Step Washout scheduler creates the participant's schedule, based on the Visit 0A date, for Visit 1. The 2-Step Washout scheduler creates the participant's schedule, based on the Visit 0A date, for Visit 0B and the participant's schedule, based on the Visit 0B date, for Visit 1. Visit 1 must occur at least 3 weeks after Visit 0B (or after Visit 0A for 1-Step Supervised Washout participants) to meet the 3 week washout requirement.

The visit scheduler at Visit 1 creates the participant's schedule, based on the Visit 1 date, for Visits 2 and 3 as well as the between visit phone contacts. If continuation Visit 1 (to perform methacholine challenge for eligibility purposes) or split Visit 1 is performed, date of continuation visit or second half of visit (when Visit 1 sputum induction is performed) should be used in Visit 1 scheduler. Should a participant require a third sputum induction (Visit 2A), Visit 2A will be performed on the scheduled Visit 3 date, and the Visit 2A scheduler will be run to provide dates for the phone contact and new Visit 3.

The Visit 3-8 schedulers create the participant's visit and phone contact schedule for the following visit during the randomized double-blind treatment phase. For example, the

Visit 3 scheduler provides dates for the scheduled phone contact between Visit 3 and 4, as well as Visit 4. Due to the visit window constraints imposed by the Twisthaler expiration (45 days after pouch opened), a visit scheduler cannot be run for an entire treatment period. Each treatment period is 12 weeks long, with Visits 4, 6 and 8 occurring halfway through periods 1, 2 and 3, and Visits 5, 7 and 9 occurring at the end of 12 weeks.

The Visit 90-92 schedulers create the participant's visit and phone contact schedule for the Asthma Exacerbation visits. This scheduler will be run the day the participant starts prednisone for treatment of an asthma exacerbation. The participant's actual visit date (90-92) will be entered so that ideal dates and visit windows for all subsequent visits (90A-90D, 91A-91D, and 92A-92D) can be calculated and displayed on the report.

Visit Scheduler Reports should be run near the end of the applicable visits (0A, 0B, 1, 3, 4, 5, 6, 7 and 8) and reviewed with the participant or parent/guardian. Reports are customized for each participant in that his/her actual visit dates (0A, 0B, 1, 3, 4, 5, 6, 7 and 8) are entered so that ideal dates and visit windows for all subsequent visits can be calculated and displayed on the report.

Instructions for accessing and generating the SIENA Visit Scheduler Reports on the AsthmaNet secure website can be found in Section 3 of this manual.

Copies of the SIENA Visit Scheduler Reports should be included in the participant's study handout folder for personal reference. An additional copy should be placed in the participant's study folder at the performance site. As Visit Scheduler Reports are updated at appropriate visits, be sure to discard outdated copies.

2.64 Visit Windows

The table below summarizes the regular and extended windows allowed around the ideal visit date for each of the SIENA study visits. The run-in is 6-9 weeks long. Run-in visits occur approximately every 3 weeks with phone contacts mid-way between visits. The randomized treatment phase is 36 weeks long and includes three periods, each 12 weeks long, during which the participant will receive different treatment regimens. Post-randomization visits occur approximately every 6 weeks with phone contacts at the mid-point between visits.

Note that there is no requirement that the run-in be 6 weeks long, or that 3 weeks must pass after Visit 2A before randomization. Visit scheduler was designed so that sputums performed at Visit 1, Visit 2 and Visit 2A (if needed) are about 3 weeks apart, as well as to allow adequate time for slide shipment, reading and entering of results prior to the randomization visit. However, a participant can be scheduled for Visit 3 as soon as he/she has 2 acceptable sputums, provided Visit 3 is not delayed due to open-label Asmanex® treatment for treatment failure, respiratory infection or compliance.

Participants who are well-controlled and who are taking low-dose ICS (equivalent of beclomethasone dipropionate, or BDP, 80-240 mcg/day), intermittent ICS (<5 days week), intermittent ICS/LABA (<5 days/week) or LTRA may be withdrawn from asthma controller medication prior to enrollment into the SIENA Run-in (Visit 1). For participants on daily low-dose ICS that can be halved adhering to the standard recommended BID or QD dosing schedule (i.e., BID for all ICS except mometasone which may be BID or QD), the washout will be 5 weeks. The participant's ICS dose will be cut in half at Week 0 and discontinued at Week 2. At Week 5, if eligible, the participant will complete Visit 1 and begin the run-in. For participants on low-dose ICS that cannot be halved, intermittent ICS, intermittent ICS/LABA, or LTRA, their asthma controller medication will be discontinued at Week 3. At Week 3, if eligible, the participant will complete Visit 1 and begin the run-in. Regular and extended windows for the Supervised Washout are also summarized below.

Visits should be scheduled on the ideal date whenever possible. When this is not possible, the regular windows should be used. The extended windows should be used only to accommodate extenuating circumstances when a visit will otherwise be missed. When extreme scheduling conflicts arise and the extended windows do not provide enough flexibility, the SIENA scientific coordinator at the DCC should be consulted before scheduling the visits to ensure that analysis- and drug-related repercussions of any mistimed visits have been considered. If a visit is being delayed to meet washout requirements, e-mail the details, including participant ID number and visit number, to the SIENA scientific coordinator at the DCC. Such exceptions to the visit schedule are granted automatically.

Visit windows for SIENA are constrained by the Twisthaler expiration. Once removed from the foil pouch, the Twisthaler must be used within 45 days. As a result, the post-

randomization visits have no regular or extended upper window. Instead, the visit window is 37-42 days. Should the participant need to re-schedule his/her visit outside of 45 days, a backup Twisthaler will need to be mailed to the participant.

Note that in addition to the visit windows, the time of day of the visits should also be considered. Because of the circadian variability associated with lung function, all subsequent visits should be scheduled such that baseline spirometry at the visit occurs within +/-3 hours of baseline spirometry (+/- 3 hours of Visit 1 spirometry for run-in visits, +/- 3 hours of Visit 1 spirometry for post-randomization visits if randomized on or before September 8, 2015 OR +/- 3 hours of Visit 3 spirometry for post-randomization visits if randomized after September 8, 2015). If the participant requires a continuation visit to establish his or her study eligibility, spirometry completed at the original Visit 1 is baseline. If a participant cannot be scheduled in the spirometry windows, contact the SIENA scientific coordinator at the DCC to seek an exception.

Regular and Extended Windows for SIENA 1-Step Supervised Washout

Visit Number	Study Week	Regular Window (days) Lower	Regular Window (days) Upper	Extended Window (days) Lower	Extended Window (days) Upper
0A	-3	-	-	-	-
1	0	-	+ 3 days	-	+ 5 days

Regular and Extended Windows for SIENA 2-Step Supervised Washout

Visit Number	Study Week	Regular Window (days) Lower	Regular Window (days) Upper	Extended Window (days) Lower	Extended Window (days) Upper
0A	-5	-	-	-	-
0B	-3	- 3 days	+ 3 days	-	+ 5 days
1	0	-	+ 3 days	-	+ 5 days

Regular and Extended Windows for SIENA Study Visits

Visit Number	Study Week	Regular Window (days) Lower	Regular Window (days) Upper	Extended Window (days) Lower	Extended Window (days) Upper
1	0	-	-	-	-
1 PC	1	- 3 days	+ 3 days	-	-
2	3	- 3 days	+ 3 days	- 5 days	-
2 PC	4	- 3 days	+ 3 days	-	-
3[1]	6	- 3 days	+ 3 days	-	+ 5 days
3 PC	9	- 3 days	+ 3 days	- 5 days	+ 5 days
4	12	- 3 days		- 5 days	
4 PC	15	- 3 days	+ 3 days	- 5 days	+ 5 days
5	18	- 3 days		- 5 days	
5 PC	21	- 3 days	+ 3 days	- 5 days	+ 5 days
6	24	- 3 days		- 5 days	
6 PC	27	- 3 days	+ 3 days	- 5 days	+ 5 days
7	30	- 3 days		- 5 days	
7 PC	33	- 3 days	+ 3 days	- 5 days	+ 5 days
8	36	- 3 days		- 5 days	
8 PC	39	- 3 days	+ 3 days	- 5 days	+ 5 days
9	42	- 3 days		- 5 days	

[1] If the participant requires a third sputum induction, Visit 2A will be performed on the scheduled Visit 3 date, and a scheduler run to create visit schedule for phone contact and new Visit 3. The Visit 2A PC and V3 will have the same visit windows as V2 PC and V3.

Visit 3 marks the end of the SIENA run-in phase.

Visits 5, 7 and 9 mark the end of each randomized treatment period. Ideally, each treatment period will be 12 weeks.

The following table includes the lower and upper windows for the Asthma Exacerbation visit and phone contacts.

Regular Windows for Asthma Exacerbation Visit and Phone Contacts

AE Visit	Days after AE	Regular Window (days) Lower	Upper
AE	-		
Day 3 Visit	3 days		+ 4 days
Day 10 PC	10 days	- 2 days	+ 2 days
Day 14 PC	14 days		+ 3 days
Day 21 PC	21 days		+ 3 days

Ideal visit dates and regular and extended visit windows have been programmed into the SIENA Visit Scheduler Reports for ease of scheduling participant visits. See the Visit Schedule discussion in this section and Section 3 for further details on these reports.

If a participant routinely fails to keep scheduled visits, he/she should be counseled by the performance site coordinator. If the problem persists, the local investigator should talk with the participant. Participants who have unusual scheduling conflicts or miss/reschedule run-in visits multiple times may not be good prospects for randomization, as most of the SIENA study visits cannot be missed. If counseling by the site coordinator during the run-in phase does not seem to improve the situation, the coordinator should consider terminating the participant from further study participation by filing a SIENA Termination of Study Participation form (P6_TERM).

2.65 Washout for Treatment Failure

Run-in (Visits 1-3)
If the participant experiences a treatment failure during the run-in, the participant will receive open-label Asmanex® mcg (two puffs, twice daily for 10 days) and the run-in will be extended 3 weeks from completion of open-label Asmanex® treatment. At the time of randomization (Visit 3), three weeks must have passed since the completion of treatment for treatment failure. With exception to requiring 3 weeks between end of open-label Asmanex® treatment and Visit 3, Visits 2 and 2A (if necessary) can proceed as usual. Additional blinded run-in medication should be dispensed, as necessary, such that the participant has adequate Respimat® inhalers on hand to take until his/her next visit. Whether a participant returns to the clinic for study medication (or it can be shipped) will depend on the amount of time between participant's last visit and 3-week washout date. See Extra Visit due to Washout and Study Medications discussion in this section for further details on whether participant needs to return to clinic for study medication (or it can be shipped), and what visit procedures should be performed when participant returns.

If the participant experiences a significant asthma exacerbation or two treatment failures during the run-in, he/she is ineligible and must be terminated.

Cross-over (5, 7) and Final (9) Visits
Visits 5, 7 and 9 mark the end of a double-blind treatment period. Should a participant experience a treatment failure during a treatment period, the treatment period will be extended, if necessary, such that ≥ 3 weeks elapse before the participant's cross-over/final visit. At the time of the cross-over/final visit, three weeks must have passed since the completion of treatment for treatment failure (open-label Asmanex® 220 mcg Twisthaler or open-label Asmanex® 200 mcg MDI, depending on device randomized to at Visit 3, two puffs, twice daily for 10 days). Whether a participant returns to the clinic for study medication (or it can be shipped) will depend on the amount of time between participant's last visit and 3-week washout date. See Extra Visit due to Washout and Study Medications discussion in this section for further details on whether participant needs to return to clinic for study medication (or it can be shipped), and what visit procedures should be performed when participant returns.

If a participant experiences two treatment failures during a treatment period, his/her cross-over/last visit should occur at least 14 days following completion of open-label Asmanex® for treatment failure.

If a participant experiences a significant asthma exacerbation during a treatment period, his/her crossover/last visit should occur 3-7 days after initiation of prednisone treatment. This visit will coincide with the participant's Asthma Exacerbation visit (V9XA). There will be no washout prior to cross-over/last visit. See Significant Asthma Exacerbation and FEV_1 Re-assessment discussions in this section for further details.

See the discussions of Treatment Failure and Significant Asthma Exacerbation in this section for additional information.

Medication Supply
Participants receiving treatment for treatment failure may need additional medication to last the 3-week washout required prior to Visits 3, 5, 7 and 9. Whether a participant returns to the clinic for study medication will depend on the amount of time between participant's last visit and 3-week washout date.See Extra Visit due to Washout and Study Medications discussion in this section for further details.

Visit 5, 7, 9
Complete Washout form (P6_WASHOUT)

At Visit 3, the SIENA Eligibility Checklist (P6_ELIG5) documents that that the required washout has been met. At the cross-over visits (5, 7) and final visit (9), the SIENA Washout Form (P6_WASHOUT) documents that the required washout has been met.

2.66 Wisconsin Upper Respiratory Symptom Survey – 21

The Wisconsin Upper Respiratory Symptom Survey (WURSS)[11] is an instrument designed to measure the severity and functional impact of the common cold. This survey, developed at the University of Wisconsin, provides a comprehensive set of questions covering cold symptoms and related quality-of-life outcomes experienced by cold sufferers. The original version has 44 questions (WURSS-44), and an abbreviated, short version has 21 questions (WURSS-21). The SIENA trial will employ the WURSS-21 (form name WURSS_21). Data will be collected at the time of a significant asthma exacerbation.

Additional information on the development of the WURSS can be found at the following website: http://www.fammed.wisc.edu/research/external-funded/wurss.

AsthmaNet signed a licensing agreement with the Wisconsin Alumni Research Foundation (WARF) for the use of the WURSS-21 questionnaire in the SIENA study. No alterations can be made to the original form provided through the University of Wisconsin's Department of Family Medicine website. For information on data entry of this form in the AsthmaNet application, see Section 10 of the AsthmaNet General Manual of Operations.

Visit 3
Distribute Asthma Exacerbation kit and review instructions (AAAQ, WPAI_ASTHMA, WURSS-21, P6_ASTHMA_EXAC)

At Visit 3, the participant will be given 21 copies of the WURSS-21 as part of the asthma exacerbation kit. The study coordinator should review instructions for the WURSS-21 as specified on the "SIENA Asthma Exacerbation Kit Instructions" handout (P6_ASTHMA_EXAC) with the participant at this visit. The participant should be instructed to complete one survey per day, starting the first day the participant takes prednisone for treatment of an asthma exacerbation. He/she should continue to complete one survey per day until the first question on the survey ('How sick do you feel today?') is answered 'Not sick' for two days in a row. Completed surveys should be returned to the study coordinator at the participant's next regular SIENA study visit (V4-V9).

Visit 90-92
Complete Wisconsin Upper Respiratory Symptom Survey – 21 (WURSS_21)

The participant should complete one survey per day, starting the first day the participant takes prednisone for treatment of a significant asthma exacerbation, and should continue to complete one survey per day until the first question on the survey ('How sick

[11] Barrett B, Brown RL, Mundt MP, Thomas GR, Barlow SK, Highstrom AD, Bahrainian M. Validation of a short form Wisconsin Upper Respiratory Symptom Survey (WURSS-21). Health and Quality of Life Outcomes 2009, 7:76.

do you feel today?') is answered 'Not sick' for two days in a row. Completed surveys should be returned to the study coordinator at the participant's next regular SIENA study visit (V4-V9).

Visit 4-9
If the participant has experienced a significant asthma exacerbation since the last regular visit:
Collect completed Asthma Exacerbation forms (AAAQ, WPAI_ASTHMA, WURSS_21)
Distribute the number of WURSS_21 forms required to replenish participant's supply

If a participant experiences a significant asthma exacerbation, he/she should bring completed WURSS-21 forms to the next visit. If the initial forms are returned at Visit 90A-92A, and the participant is still experiencing symptoms, store the forms the participant is returning in his/her SIENA study folder until the balance of the WURSS-21 forms for the same event have been returned. Review the forms to be sure dates have been completed at the top of every form. Also ensure that the participant's SIENA ID number is on each form. Enter the forms with the appropriate 90D-92D visit ID.

At the time of the next regular visit, give the participant the number of WURSS-21 forms to replenish his/her 21-day supply. Ensure that the participant has an adequate supply at all times.

See the Asthma Exacerbation Kit discussion in this section for further details.

2.67 Withdrawals

Early Study Withdrawal
Complete SIENA Termination of Study Participation form (P6_TERM)

Participants have the right to withdraw consent for study participation at any time and for any reason. In the case of a serious adverse event, either due to an asthma exacerbation or another medical condition, the study investigator may determine that it is in the best interest of the participant to discontinue participation in the trial.

When a participant is withdrawn from the study or withdraws consent after completing Visit 1 successfully (or Visit 0A for Supervised Washout participants), a SIENA Termination of Study Participation (P6_TERM) form should be completed, entered into the database, and submitted to the DCC as soon as possible. Note that any AsthmaNet investigator at the performance site may approve and sign off on the P6_TERM form.

In addition to the P6_TERM form, participants who are withdrawing or have been withdrawn from SIENA should be asked to complete an AsthmaNet Satisfaction Questionnaire (SATQX). This questionnaire is optional and anonymous in that no participant ID number or other identifying information is recorded on the form. The participant should be given a pre-addressed, postage-paid envelope in which to return the questionnaire directly to the DCC. The Satisfaction Questionnaire is posted on the secure AsthmaNet website appended to the single P6_TERM form and as part of the Visit 9 packet. See the Satisfaction Questionnaire discussion in this section for instructions on the administration of the Satisfaction Questionnaire (SATQX).

The specific termination procedures that should be followed are dependent on when in the trial the participant terminates his/her participation. See below for additional details.

Withdrawals during the Supervised Washout (Visits 0A-1)
The primary purpose of the Supervised Washout (Visit 0A-1) is to washout well-controlled asthmatic participants from their asthma controller medication, evaluate their level of control and determine eligibility for the run-in. This phase also gives clinic personnel an opportunity to review eligibility criteria and adherence to study procedures for each participant before he/she is enrolled in the run-in. Participants who cannot accommodate the date/time of the visits, who take exclusionary medications, or who fail to complete e-diaries and peak flows in their spirotel® devices are non-compliant. These participants should not be enrolled in the SIENA run-in, as their lack of adherence will affect their eligibility for randomization.

When a participant is withdrawn from the Supervised Washout or withdraws consent prior to Visit 1 after successfully completing Visit 0A, a SIENA Termination of Study Participation (P6_TERM) form should be submitted to the DCC along with any study data that have been collected. If a participant withdraws between visits, the P6_TERM form should be submitted with the visit number of the last completed visit.

In addition to the P6_TERM form, participants who are withdrawn after successfully completing Visit 0A and prior to Visit 1 should also be asked to complete an AsthmaNet Satisfaction Questionnaire (SATQX). The participant's status at the time of termination should be completed by the coordinator at the top of the form as 'Run-in termination.'

Any spirotel® data collected between visits should be downloaded and transmitted to MedGraphics for inclusion in the SIENA dataset. Spirotel® reports should be submitted to the DCC.

Minimum data requirements for individuals terminated at Visit 0B include:

- Pulmonary Procedure Checklist (P6_PULMONARYCHK)
- Eligibility Checklist 0B (P6_ELIG0B)
- Compliance Checklist (P6_COMPLY)
- Spirotel® Quality Control (SPIROTELQC)
- Spirotel® Reports
- Termination of Study Participation form (P6_TERM)

Visit 1 Screen Failures

At any point during Visit 1, a participant may be deemed ineligible or withdraw consent. Information on such participants should be maintained at the performance site in the participant's study folder. Only those participants who pass all of the eligibility criteria at Visit 1 should have data entered into the study database and forms forwarded to the DCC. An exception to this is if a participant completed the Supervised Washout, Visit 1 data should be entered and forwarded to the DCC regardless of whether he/she passes all eligibility criteria.

If a participant is ineligible for a reason that may change soon, such as a recent respiratory tract infection, he/she may be able to meet eligibility criteria in the near future. If the participant rejoins the study, he/she must be assigned a new study ID number (through the Protocol Enrollment module of the AsthmaNet database application) and repeat Visit 1. See the Re-Enrollment discussion in this section for further details.

Minimum data packet requirements for Supervised Washout participants terminated at Visit 1 include:

- Eligibility Checklist 1 (P6_ELIG1)
- Compliance Checklist (P6_COMPLY)
- Spirotel® Quality Control (SPIROTELQC)
- Spirotel® Reports
- Termination of Study Participation (P6_TERM)

Withdrawals during the Run-in Phase (Visits 1-3)

The primary purpose of the run-in phase (Visit 1-3) is to identify an appropriate group of asthmatic participants for randomization in the SIENA trial. This phase gives clinic personnel an opportunity to review eligibility criteria and adherence to study procedures

for each participant before he/she is randomized. For the SIENA study, it is extremely important to gauge the participant's ability to maintain high levels of compliance. Participants who cannot accommodate the date/time of the visits, who take exclusionary medications, who fail to take study medications correctly and on schedule, or who fail to complete e-diaries and peak flows in their spirotel® devices are non-compliant. These participants should not be randomized at Visit 3, as their lack of adherence can affect the results of the study adversely and may jeopardize their safety if they cannot recognize asthma exacerbation conditions appropriately. The run-in phase is the optimal time to identify and withdraw non-compliant participants.

When a participant is withdrawn from the run-in or withdraws consent prior to randomization at Visit 3, a SIENA Termination of Study Participation (P6_TERM) form should be submitted to the DCC along with any study data that have been collected.

In addition to the P6_TERM form, participants who are withdrawn after successfully completing Visit 1 and prior to Visit 3 should also be asked to complete an AsthmaNet Satisfaction Questionnaire (SATQX). The participant's status at the time of termination should be completed by the coordinator at the top of the form as 'Run-in termination.'

Any spirotel® data collected between visits should be downloaded and transmitted to MedGraphics for inclusion in the SIENA dataset.

Minimum data packet requirements for individuals terminated at Visit 2 or 2A include:

- Eligibility Checklist 4 (P6_ELIG4)
- Treatment Failure Checklist (P6_TXFAIL_CHK)
- Compliance Checklist (P6_COMPLY)
- Spirotel® Quality Control (SPIROTELQC)
- Spirotel® Reports
- Termination of Study Participation (P6_TERM)

Minimum data packet requirements for individuals terminated at Visit 3 include:

- Eligibility Checklist 5 (P6_ELIG5)
- Treatment Failure Checklist (P6_TXFAIL_CHK)
- Compliance Checklist (P6_COMPLY)
- Spirotel® Quality Control (SPIROTELQC)
- Spirotel® Reports
- Termination of Study Participation (P6_TERM)

Early Withdrawals after Randomization

The intention-to-treat principle applies to the SIENA study. Once a participant has been randomized, all efforts must be made to follow the participant and to collect data on his/her progress for the duration of the study. This principle applies even for participants who are discovered to be ineligible (unless the reason for ineligibility presents a safety concern) or who fail to comply with study procedures following randomization. Once a participant leaves the performance site with his/her randomly assigned Respimat® and

Twisthaler®/MDI inhalers at Visit 3, he/she *must* be followed. Any losses in participant follow-up can lead to bias in the study results. Participant withdrawal during the post-randomization period is permissible only in the following situations:

- Withdrawn Consent (i.e., participant refusal to continue)
- Pregnancy
- Serious Adverse Event or Severe Asthma Exacerbation

  A serious adverse event, either unrelated to asthma or due to a significant asthma exacerbation, may prompt the study investigator to terminate the participant from further study participation because it is in the participant's best interest for safety reasons.
- Loss to Follow-up

  Participants who cannot be contacted for an extended period of time qualify as lost to follow-up. Clinic staff should continue to attempt to contact the participant until the time he/she would have completed the trial. At this point, a SIENA Termination of Study Participation (P6_TERM) form should be completed, entered into the database, and sent to the DCC.

Once randomized, participants cannot be terminated from the study solely for non-compliance with attendance at study visits, e-diary and peak flow completion, dosing with study medications, or any other form of non-compliance. Non-compliance may be stated as a secondary reason for participant termination on the P6_TERM form; it may not be used as the primary reason for termination.

Withdrawal at a regular post-randomization visit (4 – 9)
If a randomized participant withdraws consent during a post-randomization visit, any data already collected at that visit should be reported on the data collection forms, entered into the database and forwarded to the DCC. A SIENA Termination of Study Participation (P6_TERM) form should be submitted, including but not limited to:

- Compliance Checklist (P6_COMPLY)
- Treatment Failure Checklist (P6_TXFAIL_CHK)
- Spirotel® Quality Control (SPIROTELQC)
- Spirotel® Reports
- Termination of Study Participation (P6_TERM)

The participant should be asked to complete the SIENA Participant Study Treatment Questionnaire (P6_PARTTXQX/P6_PARTTXQX_2) and the coordinator should complete the SIENA Coordinator Study Treatment Questionnaire (P6_CTXQX). If termination is occurring at visits other than Visits 5, 7 and 9, these forms should be submitted as single forms with the current visit number on them. The participant should be given an AsthmaNet Satisfaction Questionnaire (SATQX) with pre-addressed, postage-paid envelope to complete and return at his/her leisure.

Data on the spirotel® should be downloaded following normal procedures.

Withdrawal between regular post-randomization visits
If a randomized participant withdraws consent by contacting performance site personnel between visits, he/she should be asked to return to the clinic for a brief termination visit, if possible. The purpose of the visit is to collect study materials and to ensure that the participant has plans for his/her asthma care. At a minimum, the SIENA Termination of Study Participation form (P6_TERM) must be completed and should specify the number of the last regular visit the participant completed as the visit number. In addition, a SIENA Coordinator Study Treatment Questionnaire (P6_CTXQX) should be completed using the visit number of the last visit completed.

If the participant refuses to return to the performance site for even an abbreviated visit, arrangements must be made to have the participant ship his/her spirotel® device and study medications back to the site. Data on the participant's spirotel® device should be downloaded as soon as the device is returned. Compliance should be estimated as best possible from the returned Respimat® and Twisthaler®/MDI inhalers and recorded on the SIENA Spirotel® Participant Compliance Report (P6_COMPLY). This form should be entered as a single form using the number of the last visit the participant completed. The participant should be mailed an AsthmaNet Satisfaction Questionnaire (SATQX) with return envelope and instructions for completion.

For participants who are unwilling to come to the performance site for an exit visit, the study coordinator may administer the SIENA Participant Study Treatment Questionnaire (P6_PARTTXQX/P6_PARTTXQX_2) over the phone, if the participant is agreeable. No source documentation will be available on the form in this case. This form would be entered as a single form with the number of the last visit completed under these circumstances.

Withdrawal Due to Exacerbation
Participants who have a significant asthma exacerbation during the run-in phase (pre-randomization) will be terminated from study enrollment and managed as clinically-indicated, with treatment based on clinical standard and initiated by/in accordance with the participant's usual asthma care provider. The participant may be re-screened at Visit 1 for entry into the study at the discretion of the local investigator. Eligibility criteria, such as no asthma exacerbation requiring systemic corticosteroid treatment in past 6 weeks, will need to be met at re-enrollment. See the Re-Enrollment discussion in this section for further details.

Once randomization has occurred at Visit 3, intention-to-treat principles apply. Should a participant receive systemic corticosteroid treatment for an asthma exacerbation after randomization at Visit 3, the participant will cross over to the next treatment (or have their final visit if period 3) 3-7 days after initiation of prednisone. Should asthma exacerbations become too severe following randomization, the principal investigator or site director of the participant's performance site may at any time elect to drop him/her

from further study participation for the participant's safety. Study termination procedures will be completed. Any complication resulting from an asthma exacerbation (pneumothorax, pneumomediastinum, etc.) will be recorded as an adverse event in addition to the significant asthma exacerbation event itself.

See the Significant Asthma Exacerbation discussion in this section for details on forms completion and rescue algorithm.

General Note:
After a participant has been terminated from the SIENA trial, no additional data and/or specimens may be collected from the participant with the exception of the AsthmaNet Satisfaction Questionnaire (SATQX) referenced above. If any procedures are performed and/or specimens are collected after the participant's termination date, a protocol violation will be assigned.

It should be noted that the above rule applies only to procedure-related data and specimen collection. For example, when induced sputum is collected, the results of slide reading are not known immediately. The SPUTLAB form may be completed after the participant's termination date, but the sputum induction procedure itself may not be completed after the termination date (i.e., the SPUTUM and SPUTUM_ADD_TRT forms may not be dated after the termination date). Likewise, if a participant forgets to bring his/her spirotel® device to the termination visit and he/she mails it back to the clinic at a later date, spirotel® quality control (SPIROTELQC) may take place after the termination date without penalty.

If a participant is deemed to have had a significant asthma exacerbation during period 3, he/she should be followed until he/she has finished Asthma Exacerbation follow-up. Under these circumstances, the P6_TERM form should not be completed and submitted to the DCC until Visit 90D-92D is documented. See the Significant Asthma Exacerbation discussion in this section for further details.

2.68 Work Productivity and Activity Impairment Questionnaire

The Work Productivity and Activity Impairment Questionnaire (WPAI) assesses health-related activity and work impairment, taking into account both time lost from work (absenteeism), as well as loss of productivity while at work (presenteeism). The questionnaire uses a 7-day recall period. Generic and disease-specific versions of the WPAI have been validated for use in different populations. An allergy-specific version (WPAI:AS) was developed and tested in patients with moderate-to-severe allergic rhinitis. This version incorporated classroom impairment, as well as work and activity impairment. An asthma-specific version of this adapted questionnaire (WPAI:Asthma) was validated in a sample of patients with severe or difficult-to-treat asthma[12]. The WPAI:Asthma is being used for the SIENA study. It has been validated for and is applicable to participants ages 12 and older.

For more details on the WPAI, see http://www.reillyassociates.net.

Visit 3, 5, 7, 9, 90-92, 90B-92B, 90C-92C 90D-92D
Administer Asthma-Specific Work Productivity and Activities Impairment Questionnaire (WPAI_ASTHMA)

To introduce the WPAI_ASTHMA questionnaire and to establish a baseline, this questionnaire will be administered at the randomization visit. The administration of this questionnaire is one of the early procedures performed at Visit 3, in conjunction with the administration of the other asthma outcome questionnaires such as the ACT. Study coordinators should observe the order of procedures as they are laid out on the visit procedure checklists.

If the participant experiences an asthma exacerbation between study visits, then he/she should complete the copy of the WPAI_ASTHMA questionnaire that resides in the Asthma Exacerbation kit that he/she has at home (see the discussion of the Asthma Exacerbation Kit in this section for further details) on the day he/she starts prednisone. This form should be returned to the performance site at the participant's Asthma Exacerbation visit, and the visit ID should correspond to the appropriate Asthma Exacerbation visit ID. A participant's first Asthma Exacerbation will have visit ID 90, second 91, third 92, etc. The visit date should match the date the participant supplied in the source documentation box at the time of completion.

If an asthma exacerbation is identified at the time of a regular study visit and prednisone is prescribed and will be started the same day, then the participant should complete the WPAI_ASTHMA questionnaire at the time of the visit (rather than waiting to complete it at home). The visit ID on this form should correspond to the appropriate Asthma Exacerbation visit ID.

[12] Chen H, Blanc PD, Hayden, ML, Bleecker RE, Chawla A, Lee JH. Assessing productivity loss and activity impairment in severe or difficult-to-treat asthma. Value in Health 2008;11:231-9.

The WPAI_ASTHMA will also be completed at Asthma Exacerbation phone contacts 10, 14, and 21 days following start of prednisone. The visit IDs on this form at Day 10, 14 and 21 should correspond to the Asthma Exacerbation visit ID followed by "B", "C" and "D", respectively.

See Section 4 of this MOP for data management instructions for handling WPAI_ASTHMA questionnaires completed at various times during the trial.

Administration Instructions
The WPAI_ASTHMA is completed by the participant. When administering the questionnaire, request that the participant complete the entire form and provide answers as completely and as accurately as possible. No stated or implied time limit should be set. If the participant requests help with or clarification of any question, the study coordinator may provide the following information:

Q1/Q1000: Current employment status:

The participant should answer this question 'yes' if he/she works part-time or full-time, is self-employed, works in a family business, is on vacation from paid employment (e.g., school teachers on leave for the summer). The participant should answer this question 'no' if he/she does not work for pay, only does volunteer work, usually works but has been laid-off or unemployed during the past seven days, or is a seasonal worker not currently working.

Q3/Q1020 and Q7/Q1060: Work/class time missed due to asthma:

Include: any time taken off from work/class due to asthma itself, doctor visits for asthma, trips to pharmacy for asthma medication, side effects of asthma medications, and time taken off partly due to asthma and partly due to something else.

Exclude: time taken off from work/class the day of the clinic visit and time taken off work/class that the participant is not sure was at least partially related to asthma.

Participants should use a black or blue pen to complete the questionnaire. If the participant wishes to change a response, the original response should be crossed out with a single line and then dated and initialed by the participant. The final response should be circled for clarification. No changes to the participant-completed form may be made by study personnel; changes may only be made by the participant.

When the participant is finished with the questionnaire, collect it and review it for completeness before proceeding with the visit. If a question has been left blank, ask the participant to do his/her best to answer it. The answers to all of the questions are necessary to score the instrument. Check that the participant's responses are clearly marked. Complete Q1030, 1070 and 1080 with the numeric value the participant circled for each question. If the participant's intended answer is unclear, ask him/her to clarify and to make the appropriate data correction.

The participant should provide source documentation on the WPAI_ASTHMA form by providing his/her initials and the date/time in the source documentation box. Review the source documentation provided by the participant to ensure that the date and time are accurate before collecting the form.