## 2.1 Adherence Issues

Participants enrolled in the VIDA protocol are involved in study activities every day 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 VIDA 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 (P1_DAILYACT2, P1_DAILYACT3, P1_DAILYACT4, P1_DAILYACT6, P1_DAILYACT8).

- 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 VIDA 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.

For VIDA there are no defined time intervals for the screening phase visits, other than the constraint that Visit 2 must occur no later than 8 weeks following Visit 0. Therefore, no visit scheduler reports are in place for this portion of the study. Starting with Visit 2, a visit scheduler report will generate the ideal date and lower and upper regular and extended windows for future visits as follows:

- At Visit 2 a scheduler will provide the acceptable dates for scheduling Visit 3.
- At Visit 3 a scheduler will provide the acceptable dates for scheduling Visit 4.
- At Visits 4, 6 and 8, a visit scheduler will show acceptable dates for all remaining study visits.

When scheduling Visit 2 within the 8-week time limit of Visit 0, a complete listing of visit dates should be generated with the participant's daily schedule in mind. At that point in the study, multiple potential schedules may be generated for each participant by entering several start dates into the schedulers for Visit 2, Visit 3 and Visit 4. Start dates entered into the Visit 3 and 4 schedulers must be consistent with those allowed by

the previous schedulers so that a given set of reports covers the entire study and keeps the participant's visits within the visit windows. Generating several complete lists of visit dates allows the participant to choose the most convenient schedule for him/her. See the Visit Schedule 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 2 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 brief description of each of the VIDA handouts follows:

Daily Activities Handouts

VIDA Daily Activities: Visit 2 (P1_DAILYACT2)
VIDA Daily Activities: Visit 3 (P1_DAILYACT3)
VIDA Daily Activities: Visit 4 (P1_DAILYACT4)
VIDA Daily Activities: Visit 6 (P1_DAILYACT6)
VIDA Daily Activities: Visit 8 (P1_DAILYACT8)

These handouts contain simple summaries of the study activities that must be carried out each day, including dosing with open-label Alvesco® inhaled corticosteroid and scheduled daily capsules, as well as twice daily peak flow monitoring and diary question completion using the spirotel® device. These handouts also provide the participant a quick reference for his/her peak flow and rescue use values for determination of treatment failure conditions. See the Daily Activities Handout discussion in this section for further details.

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 2 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 2 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 study inhalers.

Participants must demonstrate proper metered-dose inhaler (MDI) inhalation technique as assessed through the MDI Inhalation Technique Checklist (No Spacer) (TECH_MDI_NOSP) before leaving Visit 2. Proper inhalation technique is an eligibility criterion assessed at Visit 2. Completed TECH_MDI_NOSP form(s) should be filed in the participant's study folder at the performance site. See the Inhalation Technique Assessment discussion in this section for further details.

VIDA DOSER™ Instructions (P1_DOSERINST)

This handout instructs participants on proper use of the DOSER™ device with their study Alvesco® inhalers. The DOSER™ device improves adherence with dosing from the Alvesco® inhaler by monitoring the participant's daily dose in an objective fashion. See the DOSER ™ discussion in this section for further details.

VIDA How to Use Your MEMS®6 Cap

This handout instructs participants on proper use of the MEMS®6 event monitoring cap that is placed on their study capsule vials. The MEMS®6 device improves adherence with dosing with daily capsules by monitoring each time the cap is removed from the capsule vial. See the MEMS®6 Cap discussion in this section and the MEMS®6 Manual in Appendix 5 of the AsthmaNet General Manual of Operations for further details.

VIDA Participant Identification Card (P1_ID)

The VIDA Participant Identification Card (P1_ID) facilitates the identification, treatment, and handling of worsening asthma symptoms by the participant and by healthcare providers. Baseline peak flow and high rescue use values are completed/updated on the ID card at Visits 2 and 3. See the Participant Identification Card discussion in this section for further details.

If Your Asthma Gets Worse (P1_ASWORSE)

This handout contains instructions for recognizing and treating asthma attacks and treatment failure conditions. It outlines proper use of the Xopenex® 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 2 and reviewed at subsequent visits. For further information regarding treatment of asthma exacerbations and treatment failure conditions, see the Significant

Asthma Exacerbation, Treatment Failure, and Study Medications discussions in this section.

VIDA Wisconsin Upper Respiratory Symptom Survey – 21 (WURSS-21) Instructions

This handout instructs the participant on how and when to complete the WURSS-21 survey during the study. It improves compliance with the collection of cold data.

VIDA Visit Preparation Checklist (P1_VISPRP)

This handout is a tool for improving adherence with respect to the participant's preparation for each visit. The P1_VISPRP handout contains a checklist to help the participant remember to bring all necessary devices, 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.

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 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. Data from the Participant Compliance Report will be recorded on the VIDA Compliance Checklist (P1_COMPLY) form.

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 VIDA 'alerts' have been programmed into the spirotel® device. These alerts will prompt participants when they have met treatment failure conditions based on their

peak flows or their daily rescue puffs. They will also remind the participant to complete the WURSS-21 survey when they answer 'yes' to the diary cold question. 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 treatment failure 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 2 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 2 to document that each participant has achieved an understanding of how to use the spirotel® device correctly.

See the Spirotel® Manual of Operations in Appendix 6 of the AsthmaNet General Manual of Operations for further details.

Inhalation Technique Assessment (TECH_MDI_NOSP): Proper inhalation technique using a metered-dose inhaler (MDI) (e.g., study Alvesco®) 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) (TECH_MDI_NOSP) is used to document that each participant has achieved proper MDI inhalation technique at Visit 2. 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.

DOSER™: The electronic DOSER™ device is used to monitor each participant's compliance with taking scheduled doses of study Alvesco® throughout the study. The DOSER™ records the number of puffs the participant takes each day. Its memory will be reviewed at each visit to determine how well the participant followed protocol dosing

between visits. A VIDA Alvesco® Dosing Compliance Worksheet (P1_COMPLY_WKS) and related VIDA Compliance Checklist (P1_COMPLY) form will be completed at each visit to document the participant's compliance on the basis of the DOSER™ information. Participants will be counseled if they are less than 75% compliant with overall dosing and/or less than 75% compliant with taking correct daily study doses. See the DOSER™ and Dosing Compliance discussions in this section for further details.

MEMS®6: The electronic Medication Event Monitoring system (MEMS®6) is a specialized cap that is used with capsule vials to monitor each time the vial is opened. The openings of the vial are assumed to correlate with when a participant takes his/her study medications. The MEMS®6 cap will be used on the participants' regular dose capsule vials throughout the study to monitor compliance with taking the blinded vitamin D/placebo capsules. Data collected by the MEMS®6 cap will be downloaded to a report at each study visit, starting with Visit 3, to review the participant's compliance. Data from the MEMS®6 report will be recorded on the VIDA Compliance Checklist (P1_COMPLY) form. Participants who are less than 75% compliance with taking their study capsules will be counseled.

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 the information that is collected at home with the spirotel® device to the success of the trial. 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 using your spirotel® regularly. Is there anything we can do to help you? Are you having trouble operating the device at home? Are you re-evaluating your ability to participate in the study?"

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.

## 2.2 Adverse Events

### Definition and Reporting

Adverse events include the following:

- Clinical Adverse Events:

  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.

- Laboratory Adverse Events:

  Occurrences of abnormal laboratory tests or other test (e.g., ECG) results. These events are documented on the Clinical Adverse Events (AECLIN) form.

- Treatment Failure and/or Significant Asthma Exacerbation:

  See the discussions of Treatment Failure and Significant Asthma Exacerbations in this section for the protocol criteria. These events are documented on the Clinical Adverse Events (AECLIN) form as well as on protocol-specific forms.

- 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.

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

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 VIDA study include:

- 000.00: Protocol-defined treatment failure event
- 275.42: Hypercalcemia (elevated urine Ca:Cr ratio or serum calcium value)
- 278.4: Hypervitaminosis D (elevated serum vitamin D measurement)
- 493.92: Significant asthma exacerbation

**Visit 0**
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 signed the informed consent form (original signature date) and the date of Visit 0, record the events on the Visit 0 AECLIN form. If no adverse events are recorded for the participant at Visit 0, check the 'None' box.

A brief medical history is taken during Visit 0 to establish the participant's study eligibility. Pre-existing conditions should be documented in the participant's clinic notes and stored in his/her study folder for future reference; they should not be recorded on the AECLIN form.

**Visit 1**
Follow up clinical and laboratory adverse events from previous visit and record any new events (AECLIN)

A comprehensive medical history is taken during Visit 1. 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 VIDA 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 2-10, 88, 90-92**
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 10, 88 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.

### General Information

If an adverse event is deemed serious by the above definition, a Serious Adverse Event Reporting Form (SERIOUS) should be completed and faxed to 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.

The term 'study drug' on the AECLIN form should be interpreted to mean any drug dispensed as part of the study, including open-label Alvesco®, blinded vitamin D/placebo capsules, and oral corticosteroid response prednisone. If an adverse event is thought to be related to at least 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 dose of Alvesco® or study capsules occurred because of an adverse event, then a VIDA Change in Study Medications (P1_CHANGE_MEDS) form also should be completed.

In general, if an adverse event during the run-in or oral corticosteroid response phase requires alteration of the Alvesco® dose, then the participant will need to be terminated from study participation. He/she may re-enroll when the adverse event has resolved fully at the discretion of the performance site investigators.

Treatment failures that occur during the VIDA trial must be recorded on the Treatment Failure Checklist (P1_TXFAIL_CHK). Significant asthma exacerbations should be recorded on the Significant Asthma Exacerbation (P1_SIGEX) form as well as on the P1_TXFAIL_CHK form at the visit when they are reported. In addition, significant

asthma exacerbations should be recorded on the AECLIN form using ICD-9 code 493.92, and treatment failures should be recorded on the AECLIN form using ICD-9 code 000.00. If a participant experiences a treatment failure or significant asthma exacerbation during the run-in period or oral corticosteroid response period, he/she is ineligible for randomization and should be terminated. See the discussions of Treatment Failures and Significant Asthma Exacerbations in this section for further details.

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

## 2.3 Appointments: Confirming and Scheduling

**Visits 0, 1**
Schedule Visit 1
Schedule Visit 2

No formal visit windows have been established for scheduling Visit 1 or Visit 2. However, the protocol states that the window between Visit 0 and Visit 2 may be no longer than 8 weeks. Study coordinators must keep this in mind when scheduling Visits 1 and 2. If more than 8 weeks elapse before Visit 2 is completed, the participant will be considered ineligible and will need to re-enroll in the trial if he/she wishes to continue.

**Visits 2-9, 90-92**
Confirm/Schedule upcoming appointment(s)
Review Visit Preparation handout (P1_VISPRP)

At each visit, review the VIDA Visit Scheduler Report and confirm the date of the next regular appointment. 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. If convenient, set up future appointments at the same time.

Review the VIDA Visit Preparation (P1_VISPRP) handout 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, VIDA Asthma Monitoring Log (P1_ASTHMA_LOG), devices, vitamins/supplements, 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 (+/-3 hours) 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 VIDA scientific coordinator at the DCC should be contacted to obtain an exception. If a participant is being seen for treatment failure conditions, the 3-hour window does not apply; the participant should be seen as soon as possible.

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

## 2.4 Asthma Bother Profile

**Visits 1, 3, 10**
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 VIDA 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

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

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 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.

## 2.5 Asthma Control Test

**Visits 1, 3, 5-10, 88, 90-92**
Administer Asthma Control Test (ACT)

Asthma control is an important secondary outcome in the VIDA trial. It will be assessed by asthma control days recorded in the participant's e-diary device (i.e., days with no symptoms or rescue Xopenex® use) and by the Asthma Control Test (ACT). The ACT is administered at almost every VIDA visit.

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 VIDA 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.

Two versions of the ACT exist: a version validated for ages 12 and up (ACT), and a pediatric version for ages 4-11 (C-ACT). The VIDA study will be using the 'adult' ACT version of the questionnaire. 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.

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 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.

When administering the questionnaire, request that the participant complete the entire 5-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.

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

- Provide the participant a quiet place to complete the questionnaire.
- Participants should be alone when they complete the questionnaire. Friends and relatives should wait in a separate room.
- Before the participant completes the ACT, the study coordinator should do the following:
    - Tell the participant that all questions should be answered.
    - Tell the participant that only one response may be given for each question.
    - Remind the participant that he/she is scoring problems experienced due to asthma and not because of any other problems.
    - Remind the participant that the ACT is collecting data about their asthma over the past 4 weeks.

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.

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

## 2.6 Asthma Symptom Utility Index

**Visits 1, 3, 5-10**
Administer Asthma Symptom Utility Index (ASUI)

An important pharmacoeconomic outcome of the VIDA trial is "asthma control" days calculated from symptom and rescue use information provided in the participant's e-diary. The Asthma Symptom Utility Index (ASUI), an eleven-item questionnaire developed by Dennis Revicki et al[2], also will be used to assess the participant's symptoms during the 2-week period leading up to most visits. The ASUI will be analyzed in conjunction with the Asthma Control Test (ACT).

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

[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.

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.

## 2.7 Baseline Peak Flow and Rescue Use Values

Baseline peak flow (PEF) and rescue medication use values are determined at Visit 2 and updated at Visit 3. Values are recorded on the VIDA Baseline PEF and Rescue Use Values (P1_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.

**Visit 2**
Complete Baseline Peak Flow and Rescue Use Values form (P1_BASELINE)

At Visit 2 the participant is just starting the VIDA run-in 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 2 as follows:

Baseline Peak Flow (PEF)

If the participant completes baseline spirometry and methacholine challenge at Visit 2 in order to meet eligibility criteria, then the baseline PEF is the spirometry peak flow value corresponding to the best effort during baseline spirometry at Visit 2 (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 does not complete baseline spirometry at Visit 2 because he/she met the reversal criterion at Visit 1, then the baseline PEF is the peak flow value corresponding to the best effort during baseline (pre-bronchodilator) spirometry at Visit 1 (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.

The baseline PEF value is recorded in Q1000 on the P1_BASELINE form. It is also recorded on the Participant Identification Card (P1_ID) and is used for calculating reference values for treatment failure which are recorded on several of the participant handouts.

Baseline Rescue Use Value

At Visit 2 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 during the run-in. 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 Xopenex® used, which will be input into the participant's spirotel® e-diary each day. Note that one use of nebulized albuterol should be counted as two puffs.

The baseline rescue use value is recorded in Q1010 on the P1_BASELINE form. The participant's High Rescue Inhaler Use value is calculated by adding 8 to the baseline rescue use value. The High Rescue Inhaler Use value is used to determine when a participant meets certain treatment failure criteria. If the participant uses at least the number of puffs per day denoted by the High Rescue Inhaler Use value, for a two day period, then he/she meets treatment failure conditions. The High Rescue Inhaler Use value is recorded on the Participant Identification Card (P1_ID), as well as on several of the participant handouts.

**Visit 3**

Complete Baseline Peak Flow and Rescue Use Values form (P1_BASELINE)

At Visit 3 the participant is completing the VIDA run-in period and now 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 3 on the basis of the spirotel® data. These references will be used for the remainder of the study to determine when the participant meets certain treatment failure criteria. The baseline peak flow and rescue use values are defined at Visit 3 as follows:

Baseline Peak Flow (PEF)

At Visit 3 the baseline PEF is defined as the average pre-bronchodilator AM PEF value recorded during the last two weeks of the run-in period. This is further defined as the average of the pre-bronchodilator AM PEF values recorded the 14 days prior to Visit 3, including the AM PEF value from the morning of Visit 3, rounded to the nearest liter/minute. If a participant used his/her Xopenex® 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® VIDA Eligibility and Baseline Report generated at Visit 3 after uploading data from the participant's device summarizes the participant's baseline PEF and rescue use values. The 'Baseline PEF' value from the report should be recorded in Q1000 on the P1_BASELINE form at this visit. This value will also be programmed into the spirotel® device at Visit 3 and updated on the Participant Identification Card (P1_ID) and several participant handouts.

Once established at Visit 3, the participant's baseline PEF value will not change for the remainder of the trial.

Baseline Rescue Use Value

At Visit 3 the baseline rescue use value is defined as the average daily use of levalbuterol (Xopenex® RESCUE inhaler) during the last 2 weeks of the run-in. This is further defined as the average daily RESCUE inhaler puffs used during the 14 days prior to Visit 3, 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 Spirotel® VIDA Eligibility and Baseline Report generated at Visit 3 after uploading data from the participant's device summarizes the participant's baseline PEF and rescue use values. The 'Baseline Rescue Use' value from the report should be recorded in Q1010 on the P1_BASELINE form at this visit. This value will also be programmed into the spirotel® device at Visit 3.

The participant's High Rescue Inhaler Use value is calculated by adding 8 to the baseline rescue use value. The High Rescue Inhaler Use value is used to determine when a participant meets certain treatment failure criteria. If the participant uses at least the number of puffs per day denoted by the High Rescue Inhaler Use value, for a two day period, then he/she meets treatment failure conditions. The High Rescue Inhaler Use value is recorded on the Participant Identification Card (P1_ID), as well as on several of the participant handouts.

Once established at Visit 3, the participant's baseline rescue use value will not change for the remainder of the trial.

## 2.8 Certification

### Study Coordinators and Technicians

Coordinators who carry out VIDA study visits must be certified to do so. That is, personnel who complete pregnancy tests (PREG_TEST form) or any of the protocol-specific VIDA forms (designated by a P1 prefix in the form name) must possess VIDA protocol certification. *Note that this includes completion of the VIDA Pulmonary Procedure Checklist (P1_PULMONARYCHK).*

To obtain VIDA coordinator certification, clinical personnel must complete the following steps:

- Thoroughly read the VIDA protocol and this Manual of Operations.
- Pass the VIDA coordinator certification exam. This exam can be found on the AsthmaNet secure website in the Certification:VIDA folder. Exams should be completed, scanned into a pdf file, and e-mailed to the AsthmaNet-Certification alias. Include 'VIDA 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, MEMS®6 cap procedures, spirometry, skin testing, sputum induction or methacholine challenge as part of a VIDA 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 VIDA study certification. It is acceptable for these procedures to be performed during the VIDA study by technicians who possess only individual procedure certification and not VIDA 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 VIDA protocol, a VIDA-certified coordinator must complete the VIDA Pulmonary Procedure Checklist (P1_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 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.

### Licensed Medical Practitioners (LMPs)

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

Non-physician LMPs, such as nurse practitioners and physician's assistants, may perform physical exams for the VIDA study (see the Physical Exams discussion in this section for details). These individuals are not required to take either version of the VIDA exam. 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 VIDA 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.

## 2.9 Cold History

Respiratory tract infections (i.e., “colds”) are known to be associated with worsening asthma symptoms and asthma exacerbations. One of the secondary aims of the VIDA trial is to determine whether or not vitamin D alters the frequency or severity of cold events and related effects on the participants’ asthma.

At the randomization visit (Visit 4) participants are introduced to the Wisconsin Upper Respiratory Symptom Survey (WURSS), a tool to monitor the severity of cold symptoms when infections occur during the study. At this visit a short cold history is also taken.

**Visit 4**
Administer Cold History (COLD_HX)

The Cold History (COLD_HX) form was created by AsthmaNet researchers. This form collects baseline information on the frequency, severity, and effects on asthma of colds the participant experienced in the past year.

The cold history is 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.

See Section 10 of the AsthmaNet General Manual of Operations for further details regarding the completion of the COLD_HX form.

## 2.10 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 or treatment failure event.

The VIDA 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. It is especially important for the VIDA trial that all vitamins and supplements be recorded accurately for future reference. This information will be used to complete the VIDA Vitamin D Intake Questionnaire (P1_VITD_INTAKE) at future visits. Ideally the participant will bring his/her supplement bottles to all visits so that his/her vitamin D and calcium intake can be monitored closely during the trial.

Study medications, including open-label Alvesco® and Xopenex® rescue medication and blinded study capsules, should not be regarded as concomitant medications and should not be recorded on CMED or CMED_NON. Prednisone taken to determine the participant's oral corticosteroid response at Visit 4 is considered a study medication and also should not be recorded as concomitant medication; however, 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 inhaled corticosteroids (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). Alterations in the dose of Alvesco® that occur during the trial due to treatment of a treatment failure or exacerbation event or due to a protocol-specified dose taper should be documented on the VIDA Change in Study Medications (P1_CHANGE_MEDS) form; these dose changes should not be recorded on the CMED form. See the discussions of Treatment Failure and Inhaled Corticosteroid Dose Taper in this section for further details.

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)

**Visit 0**

Record concomitant medications the participant has taken since signing the informed consent 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. Remind the participant to bring his/her bottles of vitamins and supplements to each visit.

- 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 signed the informed consent (original signature date), record them on the Concomitant Medications for Asthma/Allergy and Adverse Events (CMED) form. Record medications taken on the day of Visit 0, 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: VIDA requires participants to be on a controller medication (either inhaled corticosteroid or leukotriene modifier) during the screen phases of the study. These medications must be recorded on the CMED form. VIDA also requires that participants who will need an intranasal steroid during the study begin using one on or before Visit 2. 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 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 0 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 VIDA Exclusionary Medical Conditions (P1_EXCLMED) reference card. If the applicable condition is not listed specifically, contact the DCC for guidance.

When scheduling Visit 0, 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 high doses of vitamin D (>1,000 IU/day) and calcium supplementation (>2,500 mg/day) for 6 weeks prior to Visit 0. These washouts are listed on the VIDA Exclusionary Drugs (P1_EXCLDRUG) reference card. Be sure to discuss these study requirements with the participant prior to Visit 0. 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 1-10, 88, 90-92**

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 at Visit 0 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.

**Visits 10, 88 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.' 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.

## 2.11 Contact Information

**Visit 0**
Administer Adult Participant Contact Information (CONTACT_ADULT) form

The Adult Participant Contact Information (CONTACT_ADULT) form is completed by the participant. Its 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.

- This form serves as source documentation proving the existence of the participant. It **must** be completed.

- It is important to obtain complete and accurate phone number information for the participant during Visit 0. Participants will need to be contacted to be told their eligibility status on the basis of their Visit 0 serum vitamin D measurement. They will also need to be contacted via phone if they miss a visit or for regular phone contacts as part of the VIDA trial.

Store the CONTACT_ADULT 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, Channing Lab, etc.).

**Visit 0**
Review and distribute Clinic Contact Information handout (P1_CLINFO)

The VIDA Clinic Contact Information (P1_CLINFO) handout is completed by the study coordinator who is in charge of the VIDA study at the performance site. This document provides participants relevant information so that they can easily contact their study coordinator via phone, pager, or e-mail during the time between Visit 0 when vitamin D blood samples are drawn and the time when results are available and their study eligibility is known.

Because it will take approximately one week for each participant's screen data and vitamin D blood sample to be processed and for his/her eligibility for continuation in the screening process to be verified, it is possible that a participant's situation may change during that time. If an individual changes his/her mind and no longer wishes to be

considered for participation in the VIDA study, he/she should be instructed to contact the study coordinator as soon as possible to withdraw consent. Expedited contact allows for a VIDA Termination of Study Participation (P1_TERM) form to be completed and data entered, and for the participant's status to be updated in the VIDA database. For further information regarding termination procedures, see the Withdrawal discussion in this section. For further details on completion of the P1_TERM form, see section 4 of this manual.

The P1_CLINFO handout and its purpose should be reviewed with the participant near the end of Visit 0. As this form is the only study-related item the participant has in his/her possession at the end of the screening visit, he/she should be instructed to keep it in a safe place where it can easily be located for later reference.

## 2.12 Daily Activities Handout

**Visit 2**
Complete and distribute Daily Activities handout (P1_DAILYACT2)

Near the end of Visit 2, review the summary handout "VIDA Daily Activities (Visit 2)" (P1_DAILYACT2). This handout summarizes the procedures that study participants must carry out each day of the run-in period until Visit 3. The following values, which help participants identify the onset of treatment failure, should be completed on side 2 of the handout in the blank spaces provided as follow:

2. Enter the 65% Baseline PEF value from the Participant ID Card (P1_ID)
3. Enter the 65% Baseline PEF value from the Participant ID Card (P1_ID)
4. Enter the High Rescue Inhaler Use value from the Participant ID Card (P1_ID)

**Visit 3**
Complete, distribute, and review Daily Activities handout (P1_DAILYACT3)

Remove the "VIDA Daily Activities (Visit 2)" handout (P1_DAILYACT2) from the participant's folder and discard it. Obtain a copy of the "VIDA Daily Activities (Visit 3)" (P1_DAILYACT3) handout. This reference lists the procedures the participant must carry out each day of the oral corticosteroid response period until Visit 4. The following values, which help participants identify the onset of treatment failure, should be completed on side 2 of the handout in the blank spaces provided as follow:

2. Enter the updated 65% Baseline PEF value from the Participant ID Card (P1_ID)
3. Enter the updated 65% Baseline PEF value from the Participant ID Card (P1_ID)
4. Enter the updated High Rescue Inhaler Use value from the Participant ID Card (P1_ID)

Note that the above values are updated on the Participant ID Card at Visit 3. The updated values should be transcribed on the P1_DAILYACT3 handout. Review the peak flow and high rescue use values on the handout and confirm that the participant understands how to monitor his/her asthma.

**Visit 4**
Complete, distribute, and review Daily Activities handout (P1_DAILYACT4)

Remove the "VIDA Daily Activities (Visit 3)" (P1_DAILYACT3) handout from the participant's folder and discard it. Obtain a copy of the "VIDA Daily Activities (Visit 4)" (P1_DAILYACT4) handout. This reference lists the procedures the participant must carry out each day of the post-randomization period until Visit 6.

In the morning activities section at the top of side 1 of the handout, dates should be completed in step 3. In the first bullet, complete tomorrow's date. The participant should take his/her loading dose capsules (only) the morning after Visit 4. In the second bullet, complete the date corresponding to the day after tomorrow. The participant should begin taking his/her regular dose capsules that morning. Ensure that the participant understands that he/she should take both of the loading dose capsules the following morning and no regular dose capsules. Ensure that the participant understands that he/she should begin taking one regular dose capsule each morning starting the day after tomorrow.

The following values, which help participants identify the onset of treatment failure, should be completed on side 2 of the handout in the blank spaces provided as follow:

2. Enter the 65% Baseline PEF value from the Participant ID Card (P1_ID)
3. Enter the 65% Baseline PEF value from the Participant ID Card (P1_ID)
4. Enter the High Rescue Inhaler Use value from the Participant ID Card (P1_ID)

Review the peak flow and high rescue use values on the handout and confirm that the participant understands how to monitor his/her asthma.

**Visit 6**
Complete, distribute, and review Daily Activities handout (P1_DAILYACT6)

Remove the "VIDA Daily Activities (Visit 4)" (P1_DAILYACT4) handout from the participant's folder and discard it. Obtain a copy of the "VIDA Daily Activities (Visit 6)" (P1_DAILYACT6) handout. This reference lists the procedures the participant must carry out each day until Visit 8.

On side 1 of the handout in the morning activities section, fill in the participant's AM number of Alvesco® puffs. This value will change at visit 6 if the participant qualifies for a dose taper.

On side 1 of the handout in the nighttime activities section, fill in the participant's PM number of Alvesco® puffs. This value will change at visit 6 if the participant qualifies for a dose taper. Complete the value even if it is 0.

The following values, which help participants identify the onset of treatment failure, should be completed on side 2 of the handout in the blank spaces provided as follow:

2. Enter the 65% Baseline PEF value from the Participant ID Card (P1_ID)
3. Enter the 65% Baseline PEF value from the Participant ID Card (P1_ID)
4. Enter the High Rescue Inhaler Use value from the Participant ID Card (P1_ID)

Review the peak flow and high rescue use values on the handout and confirm that the participant understands how to monitor his/her asthma.

**Visit 8**

Complete, distribute, and review Daily Activities handout (P1_DAILYACT8)

Remove the "VIDA Daily Activities (Visit 6)" (P1_DAILYACT6) handout from the participant's folder and discard it. Obtain a copy of the "VIDA Daily Activities (Visit 8)" (P1_DAILYACT8) handout. This reference lists the procedures the participant must carry out each day through the end of the study.

On side 1 of the handout in the morning activities section, fill in the participant's AM number of Alvesco® puffs. This value will change at visit 8 if the participant qualifies for a dose taper.

On side 1 of the handout in the nighttime activities section, fill in the participant's PM number of Alvesco® puffs. This value will change at visit 8 if the participant qualifies for a dose taper. Complete the value even if it is 0.

The following values, which help participants identify the onset of treatment failure, should be completed on side 2 of the handout in the blank spaces provided as follow:

2. Enter the 65% Baseline PEF value from the Participant ID Card (P1_ID)
3. Enter the 65% Baseline PEF value from the Participant ID Card (P1_ID)
4. Enter the High Rescue Inhaler Use value from the Participant ID Card (P1_ID)

Review the peak flow and high rescue use values on the handout and confirm that the participant understands how to monitor his/her asthma.

## 2.13 DOSER™

A DOSER™ device will be used with the Alvesco® inhaled corticosteroid inhaler during the VIDA trial to monitor participant compliance with taking scheduled doses. The DOSER™ provides feedback on the number of puffs the participant takes daily. Two drawbacks of the DOSER™ are that it does not register the time of actuation and it cannot discriminate between actual inhalations of medication and "dose dumping."

The standard version of the DOSER™ will be used for VIDA. This version of the device can store up to 30 days of dosing history. All DOSERs™ that are used in the study will beep each time they register an actuation, and the participant will see the number of puffs he/she has registered on the device each day.

For instructions on setting up the DOSER™, see the package insert provided by the manufacturer (MediTrack) and the DOSER™ Setup and History Review subsection that follows. **DO NOT** give a copy of these instructions to study participants. They should be directed not to alter the DOSER™ settings.

To identify each DOSER™ used at a particular performance site, a unique ID number should be assigned to and permanently marked on each device, beginning with 0001, 0002, etc. Each time a DOSER™ is assigned to a new participant or returned from a participant, this information should be entered in the DOSER™ Tracking Log (DOSER_LOG) where supplies are monitored. When a device is "awoken" for the first time, the date should be written on the DOSER_LOG. The DOSER_LOG also provides a balance column to keep track of DOSER supplies at the performance site. One DOSER_LOG will be used per performance site across all protocols that employ this device; supplies are not protocol-specific. When a device is returned that still has a significant amount of useful lifetime left, it may be put back into the supply of available devices and eventually dispensed to another participant. If a used device re-enters the supply, increment the balance by one on the next available line of the DOSER_LOG and note the 'wake up date' in the new row. When new supplies are received from the DCC, increment the balance column by the applicable number of devices in the next available row. Each time a device is given to a participant, decrement the balance column by one.

All DOSERs™ have an approximate one-year lifetime starting from the day they are "woken up" for the first time. After approximately one year the device will display a "Replace Unit" message. This is a warning that the device has only about fifteen days of use remaining and the battery is losing power. Once the warning appears, discontinue issuing the DOSER™ to study participants, note the warning in the comments field on

the DOSER_LOG, and set aside the device for recycling through the manufacturer. See the DOSER Recycling section below.

If a DOSER™ device is defective or has a life span much shorter than one year, details should be noted in the comments field on the DOSER_LOG. If a performance site notes a significant number of defective devices, the project coordinator at the DCC should be contacted with details. The project coordinator will contact MediTrack to secure replacement devices. Set aside defective devices; do not discard or recycle them.

Any replacement devices or new supplies shipped to the performance sites should be assigned new, unique number codes to distinguish them from the older devices.

## DOSER™ Setup

Read and carry out each of the following steps when preparing a given device for a participant's use. Successful setup may take several attempts. Buttons must be pressed quickly in sequence; any delay will bring the DOSER™ back to the initial display.

1. Attach the DOSER™ to the Alvesco® inhaler the participant will be issued to use first following the visit:

    a. Place the device on top of the inhaler. Gently unroll the rubber collar around the top of the inhaler.

2. Activate the DOSER™:

    a. The DOSER™'s Clear button is recessed; use either a paper clip or a pen to depress the button.
    b. Press and release the Clear button. After a short delay the display will show 0|0, which indicates that there are zero actuations remaining and zero inhalations taken today.
    c. Note that once the DOSER™ is activated, the one-year lifespan of the device begins.

3. Set the DOSER™'s internal clock:

    a. Press and release the Set button. The device will beep. The number of remaining inhalations will flash.
    b. Press and release the History button (while the '0' is flashing). The display will show '8A', meaning 8 AM (new device only).
    c. Press and release the Set button. The Set button must be depressed while the time is flashing. The device will beep and the time will increment

one hour each time the Set button is depressed (i.e., 9 AM, 10 AM, 11 AM, etc). Depress the Set button repeatedly until the time is within 30 minutes of the actual time (e.g. if the time is 10:45 AM, set the time for 11 AM; if the time is 11:20 PM, set the time for 11 PM).

d. If the correct time has passed, continue pressing the Set button and the correct time will come around again.
e. Wait 8 seconds for the display to return to normal.

4. Set the number of inhalations to the maximum value of 990:

a. Press and release the Set button. The number of inhalations remaining will flash.
b. Press and release the Clear button (while the '0' is flashing), even if inhalations remaining are at 0, as this prepares the device for Set mode.
c. Press and release the Set button (while the '0' is flashing) repeatedly. Inhalations remaining will increment 10 at a time until the maximum value of 990 is reached.
d. Wait 8 seconds. Inhalations remaining will stop flashing.
e. Note: This value should be checked at each visit. If the value is getting low (i.e., <300), reset the value to its maximum of 990. This ensures that inhalations remaining does not decrement to 0 while the participant is using the device at home.

### DOSER™ History Review

Press and release the History button. The display will show how many inhalations the participant took each day for the past 30 days. Note that Day 1 is yesterday and Day 30 is 30 days ago. The number of actuations made the day of the study visit will be displayed on the DOSER™ prior to going into history mode on the face of the device.

### Transferring the DOSER™ to a New Inhaler for the Same Participant

1. Remove the device from the old inhaler. Grip the device between the buttons and tilt it away from the inhaler until it lifts off.

2. Put the device upside down on a flat surface and roll the rubber collar back to its original position. Be careful not to press too hard, as an actuation may inadvertently be recorded.

3. Place the device on the new inhaler as explained in above. Be careful not to actuate the inhaler.

4. The device's history remains intact; inhalations taken today remain intact.

5. Note: Participants will receive multiple Alvesco® inhalers at each visit, so they will need to be trained to transfer DOSERs™ from inhaler to inhaler between visits to the performance site. These instructions are outlined on the VIDA DOSER™ Instructions handout (P1_DOSERINST), as well.

### Transferring the DOSER™ to a New Participant

For the VIDA study, most devices will not be used for more than one participant due to the length of time each individual participates in the trial and the limited lifetime of the devices. A device may be "recycled" in cases when a participant enrolls in the run-in and terminates after only a few days or weeks of participation. In this situation, because the device has not been used very long, it may be given to a new study participant. However, careful attention should be paid to the functioning of the device, and the participant should be instructed to pay close attention to the display in case the "Replace Unit" warning appears. Similar procedures apply if a participant is given a new device late in the study and he/she uses it for only a few weeks.

1. Place the device upside down on a flat surface and roll the rubber collar back to its original position.

□□□2. Press and release the Set button. The number of inhalations remaining will flash.

3. Press and release the History button. The display will flash with the current time setting.

4. While the time is flashing, turn the device upside down and depress the Clear, Set, and History buttons at the same time, while pressing the unit against a hard surface. It may help to place the device on the bottom of a thick highlighter pen when trying to coordinate all the necessary depressions. When the device is turned back over, a blank screen will appear. The memory has been erased.

5. Follow steps 1-4 in the DOSER™ Setup section above to reset the time and inhalation parameters in the device for the new participant.

**Visit 2**
Log Alvesco® inhalers (three) and log/set DOSER™ (DOSER_LOG)
Attach DOSER™ to one of the Alvesco® inhalers; dispense three inhalers

At Visit 2 set up a DOSER™ for new participant use. If the DOSER™ was used by another participant, clear out the history as directed above and check to be sure the internal clock is set correctly. Set the number of inhalations to 990 and attach the DOSER™ to the first Alvesco® inhaler the participant will use following the visit.

Complete the DOSER™ ID number, device wake up date, participant ID number, date dispensed and dispenser's initials on the DOSER™ Tracking Log (DOSER_LOG). Decrement the current balance by one unit.

**Visit 2**
Instruct the participant on how to use the DOSER™ device (P1_DOSERINST)

Review the "VIDA DOSER™ Instructions" handout (P1_DOSERINST)

Instruct the participant to depress the canister by pushing down slowly and firmly on the center of the top of the DOSER™. Be sure the participant is able to coordinate the inhaler and DOSER™ so that he/she is pressing the center of the DOSER™. It is possible to actuate the inhaler by pressing on the side of the DOSER™; however, such actuations do not register in the DOSER™'s memory and do not result in a beep from the device.

Tell the participant to be sure to store his/her Alvesco® inhaler appropriately. It should not be thrown into a backpack or purse where the DOSER™ may inadvertently register.

Instruct the participant to record any instances of DOSER™ malfunctioning on his/her VIDA Asthma Monitoring Log (P1_ASTHMA_LOG). For example, if the DOSER™ fails to register two puffs taken during the nighttime dosing session, this information should be noted on P1_ASTHMA_LOG. The participant should be aware that his/her dosing compliance is being monitored and will impact the decision as to whether or not he/she will continue in the trial beyond Visit 3.

**Visits 3-10 and 88**
Check Alvesco® DOSER™ compliance (P1_COMPLY, P1_COMPLY_WKS)

At each regularly scheduled visit and early termination visits review the history in the participant's DOSER™ and discuss any dosing compliance problems with the participant.

During the run-in period and study phase I, the participant should be taking two puffs of Alvesco® BID on a consistent basis. If the participant experiences a treatment failure event during the post-randomization phases, his/her dose may increase for a period of time. If the participant qualifies for inhaled corticosteroid dose tapering at Visit 6 and/or Visit 8, his/her dosing schedule will change. Such changes need to be taken into account when evaluating the participant's compliance at each visit.

The participant should strive to be at least 75% compliant with the dosing schedule throughout the entire trial. If the participant does not show the ability to be at least 75% compliant during the run-in period, he/she will be ineligible to continue in the trial beyond Visit 3. See the Eligibility Criteria and Dosing Compliance discussions in this section for more information.

Compliance with Alvesco® dosing is documented on the VIDA Alvesco® Dosing Compliance Worksheet (P1_COMPLY_WKS) and also on the VIDA Compliance Checklist (P1_COMPLY) at each regular visit. A copy of the worksheet should be stored in the participant's study folder at the performance site; it should not be forwarded to the DCC. Compliance documentation and calculations are subject to audit during an AsthmaNet site visit.

For guidance on compliance calculations, see the Dosing Compliance discussion in this section.

**Visits 3-9**
Log/dispense Alvesco® inhaler(s) with DOSER™ attached to one inhaler

The participant's DOSER™ will be transferred from an Alvesco® inhaler returned at the visit to a new Alvesco® inhaler that is being dispensed at the current visit. Before the participant leaves the visit, ensure that the DOSER™ is properly attached to the inhaler. If the participant noted a problem using the device properly, retrain him/her on how to use the DOSER™ effectively (P1_DOSERINST).

**Visits 10 and 88 (and any other regular visit 5-9 when a participant terminates early)**
Collect/log DOSER™ (DOSER_LOG)

When a participant leaves the study his/her DOSER™ device must be returned to the performance site. When a device is returned, record the date returned and collector's initials on the appropriate record on the DOSER™ Tracking Log (DOSER_LOG). If the DOSER™ has not been used for an extended period of time and is able to be dispensed to another participant, increment the available balance of units by one and record the DOSER™'s ID number and wake up date on the next available line on the

log. This DOSER™ should be given to the next participant who requires a device in an effort to exploit its remaining battery life to the fullest.

### Handling Participant Travel

When a participant is traveling across time zones for an extended period of time, his/her DOSER™ device should be set to reflect local time, if at all possible. It is ideal for study personnel to change the internal time settings in the device a day or two before the participant is leaving; participants should not be shown how to alter the settings for the DOSER™ due to the potential for erasing the history accidentally. If the DOSER™'s setting cannot be updated to local time, clinical personnel can estimate the adjustment in daily number of puffs when reviewing compliance upon the participant's return home. Note that this may be difficult because puffs that were taken on a given day in the correct window local time may be counted in the next day's puffs (or previous day's puffs) due to the incorrect time setting. In this case, use the number of puffs recorded in the participant's spirotel® e-diary to estimate the participant's compliance for that period of time. If e-diary data are substituted for DOSER™ data in compliance calculations, this should be noted clearly on the Alvesco® Dosing Compliance Worksheet (P1_COMPLY_WKS).

### Recycling DOSERs

MediTrack Products has instituted a green policy whereby they will accept used devices for recycling and appropriate disposal. Expired devices should be set aside and returned to the company in bulk (i.e., whenever a given site has a 'box full' and needs to recoup the space). When preparing a shipment, complete these steps:

1. Contact MediTrack Products for a return merchandise authorization at 1-800-863-9633 or 508-238-0411.
2. Charge your shipment to the company using UPS #X420X5.
3. Ship to:
   Meditrack Products
   448 Turnpike St. Suite 1-B
   S. Easton, MA 02375

## 2.14 Dosing Compliance

During the VIDA trial compliance with medication dosing is checked and documented for all scheduled study medications at all applicable visits. This includes the open-label Alvesco® inhaled corticosteroid, blinded regular dose capsules, blinded loading dose capsules, and oral corticosteroid response prednisone. Dosing compliance is documented on the VIDA Compliance Checklist (P1_COMPLY).

**Visits 3-10, 88**
Check Alvesco® DOSER™ compliance (P1_COMPLY, P1_COMPLY_WKS)

Compliance with Alvesco® dosing is checked at all visits when a participant returns Alvesco® inhalers. Compliance assessment is based on a review of the DOSER™ history for the interval between visits (complete days only), up to the past 30 days. For visits that are more than 30 days apart, only dosing for the 30 days leading up to the visit can be assessed. The DOSER™'s memory overwrites old data once it reaches 30 days.

Calculations of Alvesco® compliance are facilitated by the VIDA Alvesco® Dosing Compliance Worksheet (P1_COMPLY_WKS). This worksheet is completed during the clinic visit and stored in the participant's folder at the performance site. Information from the worksheet is used to answer questions on the VIDA Compliance Checklist (P1_COMPLY) which is entered into the study database as part of the visit packet. Compliance calculations on the worksheets are subject to audit during an AsthmaNet site visit.

Alvesco® dosing adherence is assessed for overall compliance during the visit interval and also for daily compliance on the basis of the DOSER™ history.

Note that the number of scheduled puffs (# Scheduled puffs) will change over the course of the study if the participant experiences a treatment failure event and increases his/her dose for a period of time, or if the participant qualifies for an inhaled corticosteroid dose taper at Visit 6 or Visit 8. Changes in dosing need to be taken into account when completing P1_COMPLY_WKS. Clinical personnel need to keep accurate records of when a dose change takes place and for how long. These records are facilitated by the VIDA Change in Study Medications (P1_CHANGE_MEDS) form.

Example DOSER™ compliance calculations:
The chart on the following page shows a participant's DOSER™ history and the number of scheduled puffs he/she should have taken between visits 2 and 3 (ideal 4-week

interval). Visit 2 took place on 3/28/11and Visit 3 is taking place on 4/25/11. There are 27 complete (full) days between the visits to be used for the compliance assessment. These are days when the participant should have dosed in the AM and PM if he/she were compliant, resulting in 4 total puffs registering in the device each day. Days used in the calculations are shaded in the table below. Data for "Today" and the day of the previous visit (Visit 2) should not be included in calculations because the participant has not had an opportunity to take the PM dose on the day of Visit 3, and he/she did not have an AM dose on the day of Visit 2.

| Date | 4/25 Visit 3 | 4/24 | 4/23 | 4/22 | 4/21 | 4/20 | 4/19 | 4/18 | 4/17 | 4/16 | 4/15 | 4/14 | 4/13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DOSER™ Day | TODAY | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| Scheduled Daily Puffs | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| DOSER™ Puffs | 2 | 4 | 4 | 4 | 2 | 4 | 4 | 4 | 4 | 4 | 0 | 4 | 2 |
| Compliant ? | N/A | √ | √ | √ | | √ | √ | √ | √ | √ | | √ | |

| Date | 4/12 | 4/11 | 4/10 | 4/09 | 4/08 | 4/07 | 4/06 | 4/05 | 4/04 | 4/03 | 4/02 | 4/01 | 3/31 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DOSER™ Day | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 |
| Scheduled Daily Puffs | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| DOSER™ Puffs | 2 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 0 | 4 | 2 |
| Compliant ? | | √ | √ | √ | √ | √ | √ | √ | √ | √ | | √ | |

| Date | 3/30 | 3/29 | 3/28 Visit 2 |
|---|---|---|---|
| DOSER™ Day | 26 | 27 | 28 |
| Scheduled Daily Puffs | 4 | 4 | 2 |
| DOSER™ Puffs | 4 | 4 | 2 |
| Compliant ? | √ | √ | N/A |

Compliance assessments (follow P1_COMPLY_WKS):

Overall QVAR Compliance

1. Total number of scheduled puffs: 4 x 27 = 108 puffs
2. Total number of puffs in DOSER$^{TM}$ history:
   4 + 4 + 4 + 2 + 4 + 4 + 4 + 4 + 4 + 0 + 4 + … + 2+4+4= 92
3. Percent compliance = # puffs in history / # scheduled puffs x 100%
   = 92 / 108 x 100
   = 85.2%

Results from 1, 2, and 3 above are recorded on the VIDA Compliance Checklist (P1_COMPLY) in Q1000, Q1010, and Q1020, respectively.

∴ Because the participant's overall compliance percentage was greater than 75% at Visit 3, the participant meets the eligibility criterion as assessed in Q1060 on Eligibility Checklist 5 (P1_ELIG5).

Daily QVAR Compliance

4. Total number of full days: 27
5. Total number of compliant days (i.e., days on which participant took the correct daily dose): 21
6. Percent compliance = # compliant days / # full days x 100%
   = 21 / 27 x 100
   = 77.7%

Results from 4, 5, and 6 above are recorded on the VIDA Compliance Checklist (P1_COMPLY) in Q1030, Q1040, and Q1050, respectively.

∴ Because the participant's daily compliance percentage was greater than 75%, the participant meets the eligibility criterion as assessed in Q1070 on Eligibility Checklist 5 (P1_ELIG5).

Accounting for Special DOSER™ Circumstances

- DOSER™ misfires

  If the device misfires and records more puffs than the participant actually took, he/she should record this information on his/her Asthma Monitoring Log (P1_ASTHMA_LOG) for review at the visit. A notation of the number of misfired puffs should be made on the VIDA Alvesco® Dosing Compliance Worksheet (P1_COMPLY_WKS). Puffs due to misfirings should not be included in totals for the overall compliance assessment; these puffs also should not be considered when determining whether or not the participant was compliant with dosing on a given day.

- Late day dosing

  When a participant takes his/her Alvesco® puffs after approximately 11:30 PM on a given night, the nighttime puffs may register in the next DOSER™ day, rather than in the "Today" totals. When this occurs, DOSER™ totals for two consecutive days in the run-in or Phase I may appear as 2 (AM puffs from Day 1) followed by 6 (PM puffs from Day 1 and AM and PM puffs from Day 2, combined). The DOSER™ clock may be off from real time by as much as half an hour.

  To determine whether a participant was compliant with dosing on a given day (4 daily puffs for the run-in and phase I), the Spirotel® Participant Visit Report should be consulted to determine when his/her e-diary responses and peak flow measurements were made. If the 'time trial start' values on the report are around 11:30 or later, then it may be assumed that the participant dosed late enough in the day for the puffs to register in the next DOSER™ day (because the participant answers e-diary questions and performs peak flow blows before taking his/her study medications). If that is the case, both days may be marked as compliant days for purposes of daily compliance calculations. A notation should be made to the effect of 'late day' or 'midnight' dosing on the applicable days on the VIDA Alvesco® Dosing Compliance Worksheet (P1_COMPLY_WKS).

For additional information on the DOSER™ device, see the DOSER™ discussion in this section.

**Visits 3-10, 88**
Generate MEMS®6 Monitor report
Check MEMS®6 (regular dose capsule) compliance (P1_COMPLY)

The MEMS®6 monitor is used throughout the study on the participant's scheduled daily capsule vial. The monitor is used only on the regular dose capsule vial; compliance with the one-time loading dose of two 50,000 IU capsules will be assessed via a simple capsule count (see below).

At each visit when a regular dose capsule vial is returned to the performance site, a MEMS®6 monitor report will be generated and compliance with capsule dosing between visits will be reviewed with the participant. The report will include a summary of: total number of monitored days between visits, total number of doses taken, percentage of prescribed number of doses taken, and percentage of prescribed doses taken on schedule (in the AM). Compliance values are calculated within the device based on the settings input by clinical personnel. The capsule that should have been taken the morning of a visit day should be included in the compliance calculations. The MEMS®6 Manual of Operations describes proper setup of the monitor. It is located in appendix 5 of the AsthmaNet General Manual of Operations.

Summary values from the MEMS®6 monitor report are recorded in Q1060, Q1070, Q1080 and Q1090 on the VIDA Compliance Checklist (P1_COMPLY). Participants should maintain at least 75% compliance with doses taken on schedule during the trial. If a participant's compliance is less than 75%, council the participant appropriately and ensure that he/she understands how to use the cap and how to dose correctly.

At Visit 3 the participant must have taken at least 75% of his/her required capsule doses on schedule to remain eligible. This information is recorded in Q1080 on VIDA Eligibility Checklist 5 (P1_ELIG5).

When generating a MEMS®6 monitor report at Visit 5, the day after Visit 4 must be excluded from the phase that is defined for the compliance summary. This day must be excluded because the participant takes his/her loading dose capsules that morning and does not begin his/her regular dose capsules until the following day. See the MEMS®6 discussion in this section for further details.

**Visit 4**
Check OCS response period prednisone compliance (P1_COMPLY)

At Visit 3 the participant is given a tablet vial containing 14 prednisone tablets. He/she is instructed to take two tablets each morning for the next 5-7 days until Visit 4. When the tablet vial is returned at Visit 4, the performance site coordinator will count the number

of tablets remaining in the vial. The number of tablets taken will be inferred by subtracting this number from the original number of tablets, 14. The number of tablets taken will be divided by the number prescribed and multiplied by 100 to compute the participant's compliance percentage. Note that the number of prescribed tablets depends on the number of days elapsing between Visit 3 and Visit 4 at a dose of 2 tablets per day, starting the morning after Visit 3 and including the morning of Visit 4. This information is recorded on the VIDA Compliance Checklist (P1_COMPLY) in Q1130, Q1140, Q1150, and Q1160.

If the participant must be scheduled for Visit 4 outside the 5-7 day window, then the number of prescribed tablets should be 14.

**Visit 5**
Collect/log Loading Dose capsule vial (P1_DRG_SCH, P1_COMPLY)

At Visit 4 the participant is given a loading dose capsule vial containing two 50,000 IU vitamin D or matching placebo capsules. The participant is instructed to take both capsules the next morning. When the loading dose capsule vial is returned at Visit 5, the performance site coordinator will count the number of capsules remaining in the vial. The number of capsules taken will be inferred by subtracting this number from the original number of capsules, 2. The number of capsules taken will be divided by 2 (the number of capsules prescribed) and multiplied by 100 to compute the participant's compliance percentage. This information will be recorded in Q1170, Q1180 and Q1190 on the VIDA Compliance Checklist (P1_COMPLY).

## 2.15 Eligibility Criteria

**Visit 0**
Complete Eligibility Checklist 1 (P1_ELIG1)

Visit 0 is a relatively short, pre-screen visit. Basic eligibility criteria are checked without having to take a thorough medical history. If the participant meets all of the eligibility criteria on VIDA Eligibility Checklist 1 (P1_ELIG1), then he/she is eligible to have a blood sample drawn for vitamin D determination. Vitamin D eligibility status for each participant is communicated to the performance sites via the VIDA Participant Status Report.

If the participant is ineligible based on his/her vitamin D value, then he/she should be notified by sending him/her the standard vitamin D ineligibility letter on performance site letterhead and signed by the local investigator or site director. The template for the vitamin D ineligibility letter is located on the secure AsthmaNet website in the Forms:VIDA:Handouts:Visit 0 folder.

Participants who pass all the eligibility checks on P1_ELIG1 and give a blood sample for vitamin D determination are formally enrolled in the VIDA study. Data for these participants should be entered into the VIDA database and forwarded to the DCC.

Participants who do not meet all of the eligibility checks on P1_ELIG1 are not eligible for study enrollment. Forms that were completed at Visit 0 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 P1_ELIG1 and initial/date the source documentation box on page 3 of the form.

Note that P1_ELIG1 also captures whether or not the participant has consented to participate in the VIDA Immune Substudy (also known as the Green mechanistic study). Participation in the Immune Substudy is not a requirement for VIDA participation, and only a subset of VIDA participants will be able to participate due to budgetary constraints. Q1020 on P1_ELIG1 was included only to track the participant's Immune Substudy participation status. For further details on the substudy, see the Green Mechanistic Study discussion in this section.

**Visit 1**
Complete Eligibility Checklist 2 (P1_ELIG2)
Complete Eligibility Checklist 3 (P1_ELIG3)

Participants who make it to Visit 1 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. Eligibility criteria related to the participant's medical condition and medical history are recorded on Eligibility Checklist 2 (P1_ELIG2).

Participants should review the data recorded on P1_ELIG2 and initial/date the source documentation box on page 2 of the form.

If the participant remains eligible at Visit 1 following his/her exam and medical history assessment, he/she will perform spirometry with maximum reversibility testing. Eligibility criteria related to baseline $FEV_1$ and reversal are documented on Eligibility Checklist 3 (P1_ELIG3). Participants who remain eligible at the end of Visit 1 will provide blood and urine samples for lab testing for the assessment of additional eligibility criteria. Lab-related criteria are also documented on P1_ELIG3.

Note that individuals who do not show an improvement of at least 12% in $FEV_1$ in response to 4 puffs of levalbuterol at Visit 1 remain eligible to continue in the trial provided they perform a methacholine challenge at Visit 2. $PC_{20}$ results from the challenge will determine if these individuals are eligible to continue beyond Visit 2.

**Visit 2**
Complete Eligibility Checklist 4 (P1_ELIG4)

Eligibility criteria that are assessed at Visit 2 are recorded on Eligibility Checklist 4 (P1_ELIG4). Participants who return for Visit 2 will undergo spirometry and methacholine challenge at the visit only if they did not show at least 12% reversal in $FEV_1$ at Visit 1. P1_ELIG4 is divided into sections to allow for participants to follow multiple paths in documenting study eligibility at the visit. Section 1 assesses basic criteria that apply to all participants. Section 2 allows for documentation from a past AsthmaNet methacholine challenge to fulfill the VIDA eligibility requirements. Section 3 documents the results of spirometry and methacholine challenge done at the time of Visit 2, if the participant must undergo testing at the visit. Section 4 documents the participant's ability to use the peak flow meter/e-diary device and metered dose inhalers properly. Section 4 is completed only for participants who meet all other criteria assessed at Visit 2.

Individuals who pass all of the eligibility checks on P1_ELIG4 are enrolled in the run-in period.

**Visit 3**
Complete Eligibility Checklist 5 (P1_ELIG5)

Visit 3 marks the end of the run-in period, after the participant has been receiving a standard dose of inhaled corticosteroid for 4 weeks. Participants are assessed for asthma control, lung function and compliance with study procedures at this visit. Eligibility criteria are documented on Eligibility Checklist 5 (P1_ELIG5).

Participants who meet all other eligibility criteria at the visit will give a urine sample for lab testing. Lab-related criteria are also documented on P1_ELIG5. If a participant passes all of the eligibility criteria on P1_ELIG5, he/she is eligible to be randomized at Visit 4, assuming that he/she does not experience an exacerbation or treatment failure during the one-week oral corticosteroid response phase of the study.

Inclusion/exclusion criteria assessed at each of visits 0-3 are outlined in detail below.

**Note: Nightshift workers and others with altered schedules**

VIDA 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, dosing with scheduled capsules and inhalers during the AM hours (5 AM until 10 AM ideal timeframe) and completing the e-diary questions during the specified AM and PM scheduled sessions. Depending on the participant's schedule, his/her AM and PM symptoms and peak flows may be reversed. A notation should be made to this effect in the clinic notes and on the Spirotel® Participant Visit Report. At Visit 3, when assessing the participant's symptoms for eligibility, adjustments may need to be made to the information provided on the Spirotel® VIDA Eligibility and Baseline Report for these individuals.

**Visit 0**
Inclusion Criteria

- Ability to provide informed consent, as evidenced by the signing of a copy of the VIDA study consent form approved by the study institution's Committee on Human Subjects' Research (i.e., Institutional Review Board).

The informed consent document must be signed on or before the Visit 0 date.

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

This criterion is documented on P1_ELIG1.

- Male or female, age 18 and older (no upper limit).

  This criterion is documented on P1_ELIG1.

- Physician-diagnosed asthma for at least 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 on P1_ELIG1.

- Experienced no more than one treatment failure event in the VIDA run-in or oral corticosteroid response period on previous enrollments

  Participants who experience a treatment failure or asthma exacerbation event during the run-in period on low dose inhaled corticosteroids or during the oral corticosteroid response period are ineligible for continued participation in the study. These participants must be withdrawn from the study and a VIDA Termination of Study Participation (P1_TERM) form completed. Once the treatment failure has resolved for at least 2 weeks, or the exacerbation has resolved for at least 4 weeks, the participant can be considered for re-enrollment, starting at Visit 0. If he/she already enrolled multiple times and experienced two treatment failure or exacerbation events during the run-in or oral corticosteroid response period (one event on each of two separate enrollments), he/she is ineligible for further study participation. This is indicative of a person whose asthma cannot be controlled on the baseline study dose of inhaled corticosteroids.

  This criterion is documented on P1_ELIG1.

- Stable asthma controller therapy dose for at least 2 weeks prior to Visit 0.

  For purposes of this study, ‘controller therapy’ is defined as inhaled corticosteroids (ICS) and/or leukotriene modifiers. Potential participants can also

be on combination ICS and long-acting beta-agonists (LABA) to qualify. Use of LABAs alone does not qualify. Use of anticholinergics alone does not qualify.

This criterion is documented on P1_ELIG1.

- If currently on inhaled corticosteroids, the daily dose must not exceed the equivalent of 1000 mcgs of inhaled fluticasone (dry power inhalation (DPI) preparation).

  For purposes of evaluating eligibility for VIDA trial, the following equivalencies with 1000 mcg inhaled fluticasone (DPI) (e.g., Flovent® Diskus®, Advair® Diskus®) have been defined:

  - 800 mcg beclomethasone HFA (QVAR®)
  - 1800 mcg budesonide DPI (Pulmicort Flexhaler®)
  - 1600 mcg budesonide/formoterol MDI (Symbicort®)
  - 960 mcg ciclesonide HFA (Alvesco®)
  - 880 mcg fluticasone HFA (Flovent®)
  - 920 mcg fluticasone/salmeterol HFA MDI (Advair® MDI)
  - 880 mcg mometasone DPI (Asmanex® Twisthaler®)
  - 1000 mcg mometasone/formoterol MDI (Dulera®)

  These equivalencies are summarized on the VIDA Inhaled Corticosteroids Equivalency (P1_ICS_EQUIV) reference card.

  If a participant is taking an inhaled corticosteroid that is not included on the reference card, contact the VIDA scientific coordinator at the DCC for assistance in evaluating his/her eligibility for the trial.

  This criterion is documented on P1_ELIG1.

- 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 2.

  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 0) and the need for one is unclear. Examples include: Nasonex, Flonase, Nasacort, Rhinocort, etc. Intranasal steroids are not provided by the VIDA study.

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

This criterion is documented on P1_ELIG1.

- Serum vitamin D level <30 ng/mL.

  If the participant meets all of the other inclusion/exclusion criteria at Visit 0, then he/she is eligible to have a blood sample drawn for vitamin D determination. Samples are sent to Channing Lab in Boston for analysis and reporting of results back to the DCC. Vitamin D eligibility status for each participant is communicated to the performance sites via the VIDA Participant Status Report. See the Serum Vitamin D Laboratory Test and Participant Status Report discussions in this section for further details.

  Individuals with Visit 0 vitamin D levels less than 30 ng/mL (that is, in the insufficient or deficient range) are eligible to continue in the trial. Actual vitamin D levels will not be shown to clinical personnel; refer to the 'Vitamin D Eligible' column on the Participant Status Report to determine if a given individual meets this entry criterion.

**Visit 0**
Exclusion Criteria

- Plans to move away from the clinical site in the upcoming 9 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 VIDA 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 (10 visits) should be screened and enrolled.

  This criterion is documented on P1_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 VIDA 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 VIDA 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 VIDA trial.

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

  This criterion is documented on P1_ELIG1.

- Lifetime smoking history greater than 10 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 + .5 = 2.9 pack-years

This criterion is documented on P1_ELIG1.

Note: Pack-year history is not quantified on a data collection form until the Adult Asthma and Allergy History (ASTHMA_HX_ADULT) form is completed at Visit 1. Coordinators should keep a record of the calculation made at Visit 0 to ensure that the value recorded at Visit 1 is consistent and accurate.

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

  This criterion is documented on P1_ELIG1.

  Note: Participants may use smokeless tobacco products (e.g., chew, snuff etc.) during the study. However, use of these substances should be discouraged. Participants must refrain from using these products on the day of a study visit. This exclusion is documented on the VIDA Pulmonary Procedure Checklist (P1_PULMONARYCHK) form at each visit that includes spirometry.

- Chronic oral corticosteroid therapy.

  Any regular, daily use of oral corticosteroids (e.g., prednisone) within 6 weeks of Visit 0 is exclusionary.

  If the participant received a short burst of prednisone within the 6-week timeframe, he/she is eligible to be screened, with the proviso that all prednisone must be washed out for at least 6 weeks prior to scheduling Visit 1. The participant must also meet the criterion that follows (no exacerbation requiring systemic steroids in the past 4 weeks). Participants who receive a burst for treatment of an allergic reaction are eligible to be screened.

  Note: The participant must also meet all subsequent eligibility criteria, including no asthma exacerbations or treatment failure events prior to randomization.

  This criterion is documented on P1_ELIG1.

- Asthma exacerbation requiring treatment with systemic corticosteroids in the past 4 weeks.

Participants who have experienced a significant asthma exacerbation within 4 weeks of Visit 0 should not complete the visit at this time. These individuals should defer Visit 0 until the full 4 weeks have passed and their asthma is stable.

Also note that these treatments must be washed out for at least 6 weeks prior to scheduling the participant for Visit 1. This should be a consideration when scheduling the participant's Visit 0.

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

This criterion is documented on P1_ELIG1.

- History of life-threatening asthma requiring treatment with intubation and mechanical ventilation within the past 5 years.

  This criterion is documented on P1_ELIG1.

- History of a respiratory tract infection in the 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. The 4-week washout applies only at Visit 0. At all subsequent visits, the occurrence of a recent infection should be documented on the Clinical Adverse Events (AECLIN) form and the visit may proceed with spirometry testing and other study procedures as deemed appropriate by the study physician.

  This criterion is documented on P1_ELIG1.

- Use of supplements containing >1000 IU/day vitamin D (including cod liver oil) or >2500 mg/day calcium within past 6 weeks.

  All supplements, including multivitamins, vitamin chews, liquid cod liver oil, and cod liver oil capsules should be considered. Ideally the participant will bring his/her supplement bottles to the visit so that amounts of vitamin D and calcium can be determined and added across the various products. If calcium based antacids (e.g., TUMS) are used daily for calcium supplementation, these should be included in the participant's total daily use.

If a participant is taking more than 1000 IU/day vitamin D and/or more than 2500 mg/day calcium and is willing to reduce his/her dosage within the protocol limits, he/she may wash out from the higher doses for 6 weeks and return for a new screening visit. The participant must remain on the reduced doses for the duration of the trial.

This criterion is documented on P1_ELIG1.

- 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 VIDA trial. Participants must be on consistent immunization therapy for at least 3 consecutive months prior to Visit 0 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 VIDA trial.

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

  This criterion is documented on P1_ELIG1.

- Pregnancy or lactation at Visit 0 or plans to become pregnant in the next 9 months.

  At Visit 0 this criterion is confirmed only by participant self-report. If the participant is eligible to continue in the trial and is a woman of child-bearing potential, she will undergo a urine pregnancy test at Visit 2 if performing the methacholine challenge at that visit. All women of childbearing potential will have a urine pregnancy test done at Visit 3, prior to randomization in the trial. For additional details, see the Pregnancy Test discussion in this section.

  Note that women who are post-pregnancy and lactating but are <u>not</u> breast feeding are eligible for VIDA screening.

  This criterion is documented on P1_ELIG1.

- 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 not be used as a substitute for appropriate birth control.

This criterion is documented on P1_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.

  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. Given the use of vitamin D in this study, individuals with a history of physician-diagnosed nephrolithiasis (kidney stones) or ureterolithiasis (stones in the ureter) will also 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 VIDA scientific coordinator at the DCC for assistance.

At Visit 0 this criterion will be assessed by participant self-report. If he/she is eligible to continue beyond Visit 0, a comprehensive physical exam and medical history will be taken at Visit 1 to confirm his/her eligibility.

Exclusionary conditions include, but are not limited to:

- Addison's disease
- AIDS
- Cardiac arrhythmias (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 by any cause other than asthma
- Eating disorder (e.g., anorexia or bulimia – active disease only)
- Gastric bypass surgery (Roux-en-Y)[3]
- Hematologic disease (unstable, e.g., severe anemia)
- Hepatic disease[4]
- Hypertension (poorly controlled)
- Hyperthyroidism[5]
- Immunologic compromise[6]
- Kidney disease (chronic, e.g., glomerulonephritis, polycystic kidney disease, etc.)
- Lactation (if pregnant or breast feeding)
- Lung disease other than asthma (e.g., COPD, emphysema, chronic bronchitis, pulmonary embolism, malignancy, cystic fibrosis, among others)
- Lupus (active disease, requiring immunosuppressants)
- Any malignancy other than basal cell skin cancers
- Mental illness (uncontrolled)[7]
- Mental retardation
- Nephrolithiasis/ureterolithiasis (physician-diagnosed)

[3] Individuals who have had gastric bypass surgery are excluded due to potential malabsorptive disorders that may impact vitamin D absorption; individuals who have had laparoscopic gastric band surgery may be enrolled as long as at least 3 months have elapsed since their surgery.
[4] Nonactive hepatitis B/C is allowable; active hepatitis (including antigen positivity or disease requiring treatment) is exclusionary.
[5] Controlled hypothyroidism is allowable.
[6] Resulting in prior infections and/or susceptibility to new infections.
[7] Anxiety, depression, or bipolar disease well-controlled on allowed medications are allowable conditions for the VIDA trial.

- Neurologic disease (including epilepsy requiring treatment)
- Peptic ulcer disease (active)
- Pregnancy
- Renal insufficiency (creatinine > 1.2 mg/dl)
- Schizophrenia
- Skeletal disorders, including osteoporosis and rheumatoid arthritis[8]
- Sleep apnea (untreated)[9]
- Sleep disorder (history of)[10]
- 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 VIDA Exclusionary Medical Conditions (P1_EXCLMED) reference card.
This criterion is documented on P1_ELIG1.

- 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 Visit 2 and for the duration of the VIDA study. The VIDA Exclusionary Drugs (P1_EXCLDRUG) reference card contains a summary of this table.

  Participants only need to satisfy the stated washouts (in criteria above) from high dose vitamin D and calcium supplementation (6 weeks) and from allergen immunotherapy (4 weeks) prior to Visit 0. All other excluded drugs/substances on P1_EXCLDRUG must be washed out prior to Visit 1 and Visit 2 (if the participant resumes taking the drug after 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 0, 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 <u>any and all changes</u> in a participant's medications must be approved by a study physician and documented in the participant's clinic notes.

[8] Participants who have rheumatoid arthritis and are on excluded medications should not be screened; osteoarthritis is an allowable condition for the VIDA trial. Scoliosis, degenerative disc disease, and spinal stenosis are not exclusionary.
[9] Individuals with an OSA diagnosis who are receiving treatment with CPAP, BiPAP, or APAP are eligible.
[10] Occasional insomnia is allowable.

This criterion is documented on P1_ELIG1.

## Table 1. Drugs to be withheld throughout the study (washout periods prior to Visits 1 & 2).

| Excluded Drug | Generic Names (may not be inclusive) | Trade Names (may not be inclusive) | Washout Prior to Visits 1 & 2 |
|---|---|---|---|
| **Steroid Medications** | | | |
| Oral or intravenous steroids (for any reason), except prednisone as provided in study | | Medrol, Prednisone | 6 weeks |
| Inhaled steroids, except Alvesco® as provided in study | beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, triamcinolone acetonide | Aerobid, Asmanex, Azmacort, Flovent, Pulmicort, QVAR | None |
| **Nonsteroidal, Anti-inflammatory Medications** | | | |
| Leukotriene modifiers | montelukast, zafirlukast, zileuton | Accolate, Singular, Zyflo | None |
| 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 |
| 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 anticholinergics | atropine, ipratropium bromide, pirenzepine, scopolamine | Atrohist, Atrovent, Bellatal, Combivent, Donnatal, Scopoderm, Transderm-Scop | 6 hours |
| Long-acting anticholinergics | tiotropium | Spiriva | 72 hours |
| **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 |
| **Drugs that Alter Vitamin D Metabolism** | | | |
| Cardiac glycosides | digoxin, digitoxin, deslanoside | Cedilanid-D, Crystodigin, Lanoxin, Lanoxicaps | 1 week |
| | phenobarbital | Luminal, Solfoton | 1 week |
| | phenytoin | Di-Phen, Dilantin, Phenytek | 1 week |

## Table 1. Drugs to be withheld throughout the study (washout periods prior to Visits 1 & 2).

| Excluded Drug | Generic Names (may not be inclusive) | Trade Names (may not be inclusive) | Washout Prior to Visits 1 & 2 |
|---|---|---|---|
| **Drugs that Alter Vitamin D Absorption** | | | |
| | cholestyramine | Questran | 1 week |
| | colestipol | Cholestid | 1 week |
| Lipase inhibitors | orlistat | Alli, Xenical | 1 week |
| **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 |
| **Antibiotics** | | | |
| Macrolide antibiotics, chronic use only excluded | azithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, troleandomycin | Biaxin, Dynabac, Rulid, Surlid, TAO, Zithromax, Zitromax | 4 weeks |

## Table 1. Drugs to be withheld throughout the study (washout periods prior to Visit 0).

| Excluded Drug | Generic Names (may not be inclusive) | Trade Names (may not be inclusive) | Washout Prior to Visit 0 |
|---|---|---|---|
| **Other Excluded Drugs/Substances** | | | |
| Vitamin D supplements > 1000 IU/day | | | 6 weeks |
| Calcium supplements >2500 mg/day | | | 6 weeks |

Table 2 contains drugs and substances that are allowed during the study, but must be withheld for specified periods of time prior to visits 1-10, 88, and 90-92[11].

### Table 2. Drugs to be withheld prior to pulmonary function visits 1-10, 88, 90-92

| Drug/substance | Trade Names | Washout Prior to Visits 1-10, 88, 90-92 |
|---|---|---|
| levalbuterol (study RESCUE inhaler) | Xopenex | 6 hours |
| Oral Antihistamines (chlorpheniramine, desloratadine, diphenhydramine, fexofenadine, loratadine, and others) | Allegra, Allegra-D, Benadryl, Chlor-Trimeton, Claritin, Clarinex and others | 48 hours |
| Nasal Antihistamines (azelastine nasal, olopatadine, levocabastine) | Astelin, Astepro, Patanase, Livostin | 6 hours |
| Ophthalmic Antihistamines (azelastine ophthalmic, emedastine difumarate, epinastine ophthalmic, ketotifen fumarate, olopatadine ophthalmic) | Alaway, Elestat, Emadine, Opitvar, Pataday, Patanol, Zaditor | 6 hours |
| Oral Decongestants (pseudoephedrine and others) | Sudafed and others | 48 hours |
| Nasal Decongestants (oxymetazoline and others) | Afrin and others | 6 hours |
| Methylxanthine-containing food or beverages (caffeinated colas, coffee, tea) | Coke, Pepsi, Mountain Dew, Barq's Rootbeer, Red Bull | 6 hours |
| Methylxanthine-containing medications | Anacin, Darvon, Esgic, Excedrin, No-Doz, Norgesic, Vivarin | 6 hours |
| Alcohol-containing foods or beverages | | 6 hours |

[11] These drugs/substances are allowed between visits, but not prior to pulmonary function testing. Holds are required at Visit 2 only if spirometry and methacholine challenge are being done. Exceptions may be made for $FEV_1$ re-assessment and treatment failure visits. See Spirometry discussion.

**Visit 1**
Inclusion Criteria

- Notification that participant's Visit 0 serum vitamin D level is in the eligible range.

  Clinic personnel will be notified via the 'Vitamin D Eligible' column on the VIDA Participant Status Report if a given individual is eligible based on his/her Visit 0 vitamin D level. If the column reads 'Yes' next to the participant's ID number, then he/she is eligible to be scheduled for Visit 1. If the column reads 'No', then the participant must be terminated from further study participation by completing a VIDA Termination of Study Participation (P1_TERM) form. If the participant is vitamin D ineligible, then he/she should be sent a copy of the formal vitamin D ineligibility form letter on the performance site's letterhead and signed by the local investigator or site director. The template for the vitamin D ineligibility letter is located on the secure AsthmaNet website in the Forms:Vida:Handouts:Visit 0 folder. Terminating participants should also be sent an AsthmaNet Satisfaction Questionnaire with postage-paid envelope. Q1000 should be filled out by the coordinator as 'Run-In termination' for all participants who terminate prior to randomization.

  This criterion is documented on P1_ELIG2.

- Stable asthma controller therapy dose for at least 2 weeks prior to Visit 1.

  For purposes of this study, 'controller therapy' is defined as inhaled corticosteroids (ICS) and/or leukotriene modifiers. Potential participants can also be on combination ICS and long-acting beta-agonists (LABA) to qualify. Use of LABAs alone does not qualify. Use of anticholinergics alone does not qualify.

  In order to perform spirometry at Visit 1, participants who are taking ICS combination drugs (Advair®, Symbicort®, Dulera®) will need to hold their medication for 24 hours prior to the visit (to meet the LABA washout). Q1010 should be answered 'Yes' as long as the participant was taking his/her medication regularly the full 2 weeks prior to the visit, with the exception of the 24-hour washout period.

  This criterion is documented on P1_ELIG2.

- Beta-agonist reversibility defined as ≥12% improvement in $FEV_1$ in response to 180 mcg (4 puffs) of levalbuterol.

At Visit 1 all participants will undergo a maximum reversibility test. During this test, participants perform baseline spirometry followed by the administration of 4 puffs of levalbuterol and another spirometry session 10-15 minutes later. Additional levalbuterol is administered as the test proceeds. 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 maximum 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 Maximum Reversibility Testing (MAXREV) form). Reversal is the relative change in $FEV_1$ expressed as a percentage.

Sample reversal calculations:

- % reversal:

  To calculate the participant's % reversal with 4 puffs of levalbuterol, 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.

  Example:

  Pre-test $FEV_1$ (from Q1030 SPIRO form): 3.24 liters
  Post-test $FEV_1$ (from Q1030 MAXREV form): 3.80 liters

  Reversal % = (3.80 – 3.24) / 3.24 * 100 = 17.28%

If the participant's reversal % is ≥12% (without rounding), he/she meets the criterion. The participant in the example meets the criterion.

This eligibility criterion is recorded in Q1010 on P1_ELIG3.

Note that individuals who do not meet the reversal criterion at Visit 1 may continue in the trial, provided they meet all other eligibility criteria at Visit 1. These participants will need to undergo spirometry and a methacholine challenge at Visit 2 to attempt to meet the $PC_{20}$ eligibility criterion.

Participants who meet the reversal criterion at Visit 1 should not undergo spirometry and methacholine challenge at Visit 2.

- Baseline $FEV_1$ requirements:

  Criteria in the original VIDA protocol:

  Baseline $FEV_1$ requirements differ slightly depending on whether or not the participant meets the beta-agonist reversibility criterion at Visit 1:

  - If reversal criterion was met, then $50\% \leq FEV_1 \leq 90\%$ of predicted.
  - If reversal criterion was not met, then $50\% \leq FEV_1 \leq 85\%$ of predicted.

  Criterion in modified protocol:

  In January 2012 the AsthmaNet Data and Safety Monitoring Board (DSMB) approved requested modifications to the VIDA inclusion criteria such that participants qualify with $FEV_1 \geq 50\%$ of predicted, regardless of presence or absence of bronchodilator responsiveness.

  Use the value from Q1040 from the participant's Spirometry Testing (SPIRO) form at Visit 1 to assess this criterion.

  This criterion is documented on P1_ELIG3. See section 4 of this manual for directions on completing this form.

  A copy of the max reversibility report generated through the MedGraphics system should be submitted with the Visit 1 packet.

**Visit 1**
Exclusion Criteria

- Asthma exacerbation requiring treatment with systemic corticosteroids since Visit 0.

  Participants who have experienced a significant asthma exacerbation requiring treatment with systemic corticosteroids since Visit 0 are ineligible to continue in the trial. A VIDA Termination of Study Participation (P1_TERM) form should be completed. The participant may be considered for possible re-enrollment, starting at Visit 0, after the exacerbation resolves. When scheduling Visit 0, keep in mind that a 4-week washout from the exacerbation is required prior to scheduling Visit 0, and a 6-week washout of oral and intravenous steroids is required prior to scheduling Visit 1.

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

This criterion is documented on P1_ELIG2.

- Based on the physical exam and medical history taken at Visit 1, evidence of any of the conditions listed on the VIDA Exclusionary Medical Conditions (P1_EXCLMED) reference card.
  Exclusionary medical conditions for the VIDA trial are listed above in the Visit 0 Exclusion Criteria section, as well as on the P1_EXCLMED reference card. This reference does not include an exhaustive list of exclusionary conditions. If a participant has a condition that the local physician deems unsafe for VIDA participation, then he/she should not be allowed to continue in the study.
  If a participant has a condition listed on the P1_EXCLMED reference card, but the local physician feels that study participation would be appropriate, contact the VIDA scientific coordinator at the DCC with details. She will consult the VIDA lead investigators and will document the final decision.

  This criterion is documented on P1_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 VIDA study for a variety of reasons. If this is the case, the participant should be terminated from the study.

  This criterion is documented on P1_ELIG2.

- Use of any of the drugs listed in Table 1 (above) in the specified washout periods prior to Visit 1. The VIDA Exclusionary Drugs (P1_EXCLDRUG) reference card contains a summary of this table.

  If it is possible for the participant to go off the applicable drug and meet the defined washout period, Visit 1 may be rescheduled for a later date. Keep in mind that the interval between Visit 0 and Visit 2 may be no longer than 8 weeks.

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 on P1_ELIG2.

- Use of any prescription or over-the-counter medication other than those listed on the VIDA Allowed Medications (P1_MEDALLOW) reference card.

  Chronic use of any medications other than RESCUE beta-agonist, inhaled corticosteroids (ICS), and leukotriene modifiers except:
  - acetaminophen
  - analgesics for acute/chronic pain management (with MD discretion)
  - antianxiety agents/anxiolytics (e.g., diazepam, chlordiazepoxide, alprazolam, lorazepam, gabapentin, buspirone) at a chronic, stable dose
  - antibiotics (oral) (e.g., tetracycline, penicillin, cephalosporin, quinolones, monobactam, sulfonamides, minocycline, nitroimidazoles (Flagyl), macrolides (for intermittent use only))
  - antibiotics for acne (topical/oral) (macrolides allowed for intermittent use only)
  - anticholesterol medications (e.g., Lopid, statin medications), except cholestipol and cholestyramine
  - specific antidepressants at stable, chronic dose
    - Selective Serotonin Reuptake Inhibitors (SSRI) (e.g., alaproclate, etoperidone, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, zimelidine)
    - 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 (oral and nasal) (e.g., chlorpheniramine (Chlor-Trimeton), desloratadine (Clarinex), diphenhydramine (Benadryl), fexofenadine (Allegra, Allegra-D), loratadine (Claritin), azelastine (Astelin), and others)
  - specific antihypertensive medications- stable dose for well-controlled hypertension
    - alpha blockers (e.g., doxazonsin, 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 (over-the-counter) (e.g., dextromethorphan)
- bisphosphonates (e.g. alendronate (Fosamax), ibandronate (Boniva), zoledronic acid (Zometa))
- calcium-based antacids used PRN (e.g., TUMS) (if used for calcium supplementation, must count towards 2,500 mg/day max dose)
- calcium supplements at a stable dose throughout study (up to 2,500 mg/day)
- CNS stimulants/appetite suppressants (e.g., amphetamine preps, lisdexamfetamine, methylphenidate, hydrochloride, sibutramine)
- Cox-2 drugs (e.g., celecoxib (Celebrex), rofecoxib (Vioxx), valdecoxib (Bextra))
- decongestants (nasal) (e.g., oxymetazoline (Afrin) and others)
- decongestants (oral) (e.g., pseudoephedrine (Sudafed) 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 (over-the-counter) (e.g., guaifenesin)
- eye preparations for allergic eye symptoms (topical) (e.g., antihistamines, NSAIDS, antiallergic compounds)
- $H_2$ 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 (for treatment of stable, controlled diabetes)
- intranasal steroids (any drug) at a stable dose throughout the entire study, starting at or prior to Visit 2
- laxatives
- Librax
- lithium
- migraine analgesics/preventatives (e.g., butalbital, Midrin, tripan drugs, topiramate (Topamax))
- nasal antiallergic spray (Cromolyn/Atrovent)
- nasal saline spray

- non-steroidal anti-inflammatory medications (e.g., aspirin, ibuprofen, naproxen, ketoprofen)
- Norplant®
- oral contraceptives
- proton pump inhibitors (e.g., omeprazole (Prilosec), lansoprazole (Prevacid), esomeprazole (Nexium)) for GERD
- psyllium
- sleep aids (prescription or over-the-counter) used PRN
- stool softeners
- study medications (Alvesco®, RESCUE Xopenex®, oral corticosteroid response period prednisone, RESCUE prednisone (only for use as directed by a study physician), blinded capsules)
- thyroid replacement medication (e.g., Levothroid, Levoxyl, Synthroid)
- tretinoin for acne (Retin-A, Atralin, Renova, Avita, Altinac)
- vitamins, minerals (vitamin D supplements allowed if ≤1,000 IU/day; calcium supplements allowed if ≤2,500 mg/day; include all sources when determining participant's total daily dose of each, including TUMS for calcium)
- Xolair (omalizumab) at stable dose throughout study

- low-potency topical corticosteroids (BID) (e.g., aciometasone dipropionate, desonide, dexamethasone, dexamethasone sodium phosphate, fluocinolone acetonide, hydrocortisone, hydrocortisone acetate)

- medium-potency topical corticosteroids (BID) (e.g., betamethasone benzoate, betamethasone dipropionate, betamethasone valerate, clocortolone pivalate, desoximetasone, diflorasone 0.05%, fluocinolone acetonide, fluocinonide 0.05%, flurandrenolide, fluticasone propionate, hydrocortisone butyrate, hydrocortisone valerate, mometasone furoate, triamcinolone acetonide)

This list is summarized on the VIDA Allowed Medications (P1_MEDALLOW) reference card.

In general, a participant is ineligible if he/she chronically uses any medication other than rescue beta-agonist, study drug, and those in the preceding list. 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 VIDA Exclusionary Drugs (P1_EXCLDRUG) reference card, first consult the local investigator. If the local investigator feels the participant should be considered eligible, then contact the VIDA 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.

Note that participants are required to be on leukotriene modifiers and/or inhaled corticosteroids at a stable dose for at least 2 weeks prior to Visit 1. These drugs are considered allowed medications for this period of the study, until the participant is formally enrolled in the run-in at Visit 2 and begins taking study medications.

This criterion is documented on P1_ELIG2.

- Impaired renal function defined as an estimated glomerular filtration rate (eGFR) less than 30 ml/min.

  Results of the eGFR test are recorded on the VIDA Laboratory Results (P1_LAB) form at Visit 1. If the participant's eGFR is less than 30 ml/min, the participant is ineligible for continued study participation.

  See the Serum Calcium and Creatinine/eGFR Laboratory Tests discussion in this section for further details on this test.

  This criterion is documented on P1_ELIG3.

- Serum calcium value greater than 10.2 mg/dl on entry.

  Results of the serum calcium test are recorded on the VIDA Laboratory Results (P1_LAB) form at Visit 1. If the participant's serum calcium is greater than 10.2 mg/dl, the participant is ineligible for continued study participation.

  If the participant's serum calcium value is elevated, record this fact as an adverse event on the Clinical Adverse Events (AECLIN) form using ICD-9 code 275.42 (hypercalcemia).

  See the Serum Calcium and Creatinine/eGFR Laboratory Tests discussion in this section for further details on these tests.

This criterion is documented on P1_ELIG3.

- Urine calcium:creatinine ratio ($U_{Ca}$:$U_{Cr}$ ratio) greater than 0.37.

  Results of the $U_{Ca}$:$U_{Cr}$ ratio test are recorded on the VIDA Laboratory Results (P1_LAB) form at Visit 1. If the participant's $U_{Ca}$:$U_{Cr}$ ratio is greater than 0.37 (when both urinary calcium and creatinine are expressed in mg), the participant is technically ineligible for continued study participation. However, at the local investigator's discretion, if the participant meets all other eligibility criteria at the visit, he/she may be allowed to continue in the pre-randomization phases of the study, pending the results of follow-up $U_{Ca}$:$U_{Cr}$ testing at Visit 3. The participant should be advised to increase fluid intake in the interim. If this exception is being made, answer Q1050 on P1_ELIG3 'Yes' (gray box) and answer Q1060 'Yes.' This coding will create a data conflict that will result in an error. Mark the error unresolvable and include a comment regarding the exception. Note that local investigator approval must be obtained before proceeding with this exception. If urinary calcium and creatinine are measured in mmole rather than mg, the appropriate cutoff for eligibility assessment is 1.0. Values must be converted to mg/L before completing the P1_LAB form.

  If the participant's $U_{Ca}$:$U_{Cr}$ ratio is elevated, record this fact as an adverse event on the Clinical Adverse Events (AECLIN) form using ICD-9 code 275.42 (hypercalcemia). There is no available code for hypercalciuria.

  See the Urine Calcium:Creatinine Ratio Laboratory Test discussion in this section for further details on this test.

  This criterion is documented on P1_ELIG3.

**Visit 2**
Inclusion Criteria

- Stable asthma controller therapy dose for at least 2 weeks prior to Visit 2.

  For purposes of this study, 'controller therapy' is defined as inhaled corticosteroids (ICS) and/or leukotriene modifiers. Potential participants can also be on combination ICS and long-acting beta-agonists (LABA) to qualify. Use of LABAs alone does not qualify. Use of anticholinergics alone does not qualify.

  The subgroup of participants who need to perform spirometry and methacholine challenge at Visit 2 to confirm eligibility will need to hold their medications for 24

hours prior to the visit if they are taking ICS combination drugs (Advair®, Symbicort®, Dulera®) (to meet the LABA washout). Q1010 on Eligibility Checklist 4 (P1_ELIG4) should be answered 'Yes' as long as the participant was taking his/her medication regularly the full 2 weeks prior to the visit, with the exception of the 24-hour washout period.

This criterion is documented on P1_ELIG4 in section 1 of the form.

- Baseline $FEV_1$ requirements:

  This criterion will be assessed at Visit 2 only for the subgroup of individuals who must complete spirometry and methacholine challenge to confirm their eligibility.

  Criterion in original protocol:

  Because this subgroup of individuals did not meet the reversibility criterion for entry at Visit 1, their baseline $FEV_1$ must be between 55% and 85% of predicted, inclusive.

  Criterion in modified protocol:

  In January 2012 the AsthmaNet Data and Safety Monitoring Board (DSMB) approved requested modifications to the VIDA inclusion criteria such that participants qualify with $FEV_1 \geq 50\%$ of predicted, regardless of presence or absence of bronchodilator responsiveness.

  Use the value from Q1040 from the participant's Spirometry Testing (SPIRO) form at Visit 2 to assess this criterion.

  This criterion is documented on P1_ELIG4 in section 3 of the form.

  A copy of the spirometry or methacholine challenge report generated through the MedGraphics system should be submitted with the Visit 2 packet.

- Asthma confirmed by bronchial hyper-responsiveness.

  This criterion will be assessed at Visit 2 only for the subgroup of individuals who must complete spirometry and methacholine challenge to confirm their eligibility.

  The definition of hyper-responsiveness depends on the participant's current use of inhaled corticosteroids (ICS) as follows:

Not currently using ICS: $FEV_1$ $PC_{20} \leq 8$ mg/ml

Currently using ICS: $FEV_1$ $PC_{20} \leq 16$ mg/ml

Individuals who were taking ICS/LABA medications prior to Visit 2 and held them for 24 hours before the visit for purposes of pulmonary function testing should be considered current users of ICS when evaluating this criterion.

Individuals who did not meet the reversibility criterion at Visit 1 and who do not meet the criteria on the Adult Methacholine Challenge Testing Checklist (METHACHK_ADULT) to proceed with a challenge at Visit 2, are ineligible to continue in the study. Enter and submit any collected data for these participants and complete a VIDA Termination of Study Participation (P1_TERM) form.

**Use of source documentation to meet $PC_{20}$ eligibility requirements:** As an alternative to performing a methacholine challenge at Visit 2, source documentation from a historical challenge performed within 6 months of the Visit 2 date may be submitted. To qualify, challenges must have been carried out by an AsthmaNet-certified technician using AsthmaNet equipment and procedures; ACRN challenges may not be substituted. The challenge must also have been overread by the AsthmaNet grader (i.e., tests that have a '98' prefix in the participant ID are not overread and, therefore, do not meet study source documentation criteria). The $PC_{20}$ cutoff for eligibility (i.e., 8 mg/ml or 16 mg/ml) should be assessed based on the participant's ICS status *at the time the historical test was performed*. This status may or may not be the same as the participant's status on the day of Visit 2. Source documentation will prove useful if a participant enrolled in VIDA, was withdrawn prior to randomization, and re-enrolls at a later date. If he/she completed a methacholine challenge during the original enrollment, and it was performed within 6 months of the new Visit 2 date, it may be used to qualify the participant.

This criterion is documented on P1_ELIG4 in section 2 if the participant has source documentation or in section 3 if the participant is proceeding with a methacholine challenge at Visit 2. See section 4 of this manual for instructions on form completion for various scenarios.

A copy of the methacholine challenge report generated through the MedGraphics system should be submitted with the Visit 2 packet.

Note: Individuals whose $FEV_1$ falls ≥20% in response to the diluent will have a $PC_{20}$ of 0 recorded on the Methacholine Challenge Testing (METHA) form. For purposes of evaluating study eligibility, if these individuals have a known history of asthma and the local investigator is confident that they have asthma, they may be considered eligible to continue in the study.

- 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) along with the VIDA demo device. Train the participant on the use of the spirotel® device, 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 did not demonstrate satisfactory performance, retrain him/her and complete a new checklist until his/her understanding of the device and subsequent performance improves. 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 on P1_ELIG4 in section 4 of the form.

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

  This criterion will be evaluated objectively for all participants using the MDI Inhalation Technique Checklist (Without Spacer) (TECH_MDI_NOSP). Participants must achieve a perfect score of eleven (which evaluates two separate inhalations) to pass the performance check. Participants should dose from the placebo inhaler provided by the DCC for this assessment. The inhaler has a fluorescent label that reads 'MDI Inhalation Technique Inhaler (Contains Placebo).'

  Checklist(s) should be filed in the participant's study folder at the performance site; do not forward them to the DCC. See section 5 of this manual and the Inhalation Technique Assessment discussion in this section for further details.

  This criterion is documented on P1_ELIG4 in section 4 of the form.

**Visit 2**
Exclusion Criteria

- Asthma exacerbation requiring treatment with systemic corticosteroids since Visit 1.

  Participants who have experienced a significant asthma exacerbation requiring treatment with systemic corticosteroids since Visit 1 are ineligible to continue in the trial. A Termination of Study Participation (P1_TERM) form should be completed. The participant may be considered for possible re-enrollment, starting at Visit 0, after the exacerbation resolves. When scheduling Visit 0, keep in mind that a 4-week washout from the exacerbation is required at Visit 0 and a 6-week washout of oral and intravenous steroids is required prior to scheduling Visit 1.

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

  This criterion is documented on P1_ELIG4 in section 1 of the form.

- More than 8 weeks elapsed between Visit 0 and Visit 2.

  In order to ensure that a participant's screening vitamin D level does not 'age out' over time, the protocol imposes an 8-week limit on the duration between Visit 0 screening and entry into the run-in period at Visit 2. If the screening interval takes longer than 8 weeks, the participant is ineligible to continue in the trial. In this case, file a VIDA Termination of Study Participation (P1_TERM) form and enter any data collected at the visit. The participant may be considered for possible re-enrollment if his/her schedule can accommodate the visit schedule for the entire study.

  This criterion is documented on P1_ELIG4 in section 1 of the form.

**Visit 3**
Inclusion Criteria

- Pre-bronchodilator (baseline) $FEV_1$ requirements:

  Criteria from original protocol:

  $FEV_1$ requirements at Visit 3 (as at prior visits) differ slightly depending on whether or not the participant met the beta-agonist reversibility criterion at Visit 1:

  - If 12% reversal criterion was met, then 50% ≤ $FEV_1$ ≤ 90% of predicted.
  - If 12% reversal criterion was not met, then 50% ≤ $FEV_1$ ≤ 85% of predicted.

  Criterion in modified protocol:

  In January 2012 the AsthmaNet Data and Safety Monitoring Board (DSMB) approved requested modifications to the VIDA inclusion criteria such that participants qualify with $FEV_1$ ≥ 50% of predicted, regardless of presence or absence of bronchodilator responsiveness.

  Use the value from Q1040 from the participant's Spirometry Testing (SPIRO) form at Visit 3 to assess this criterion.

  This criterion is documented on P1_ELIG5. See section 4 of this manual for directions on completing this form.

  A copy of the spirometry or methacholine report generated through the MedGraphics system should be submitted with the Visit 3 packet.

- Requirements for compliance with inhaled corticosteroid (Alvesco® MDI) dosing during the run-in:

  These criteria are evaluated objectively through data stored in the participant's DOSER™ device. A high level of compliance is required and should be emphasized throughout the trial.

  All complete (full) days between the date of Visit 2 and the date of Visit 3 should be included in the compliance calculation. In the rare event that more than 30 days elapse between Visit 2 and Visit 3, use data from the 30 days immediately

preceding Visit 3 (current contents of the DOSER™'s memory). Do not include the days of the visits in the compliance calculation.

The VIDA Alvesco® Dosing Compliance Worksheet (P1_COMPLY_WKS) and the VIDA Compliance Checklist (P1_COMPLY) should be used to assess these criteria. Follow the instructions on the forms. See the Dosing Compliance discussion in this section for an example.

See the Dosing Compliance and DOSER™ discussions in this section for further details. These criteria are documented on P1_ELIG5.

- Ability to take at least 75% of the scheduled Alvesco® puffs between Visit 2 and Visit 3 (overall MDI compliance).

  This criterion is evaluated based on information recorded in Q1020 on the VIDA Compliance Checklist (P1_COMPLY). If the participant's overall dosing compliance with the Alvesco® MDI was less than 75% during the run-in, the participant is ineligible to continue in the VIDA trial. He/she may be re-screened starting at Visit 0 at the coordinator's discretion.

- Ability to take the correct daily dose of scheduled Alvesco® at least 75% of the days between Visit 2 and Visit 3 (daily MDI compliance).
  This criterion is evaluated based on information recorded in Q1050 on the VIDA Compliance Checklist (P1_COMPLY). If the participant's daily dosing compliance with the Alvesco® MDI was less than 75% during the run-in, the participant is ineligible to continue in the VIDA trial. He/she may be re-screened starting at Visit 0 at the coordinator's discretion.

If the DOSER™ misfires or otherwise malfunctions and the participant has documented these problems on his/her VIDA Asthma Monitoring Log (P1_ASTHMA_LOG) or elsewhere, an exception may be made to allow the participant to continue in the study even if he/she had compliance less than 75% on the basis of the DOSER™ data. However, all other compliance criteria must be met before such an exception is warranted. Exceptions must be brought to the attention of the VIDA scientific coordinator at the DCC before the participant is randomized at Visit 4.

If a participant's DOSER™ is lost or the history is completely blank or unreadable, the participant's spirotel® e-diary data may be reviewed as a substitute means of assessing dosing compliance. In this situation review the participant's Spirotel® Participant Visit Report generated at Visit 3 and complete a

P1_COMPLY_WKS form on the basis of diary questions Q2 and Q10. Note on the top of the worksheet that e-diary information was used in lieu of the DOSER™ and why. Do not complete Q1000-Q1050 on P1_COMPLY in this case. Evaluate the eligibility criteria on the basis of the e-diary information. This exception must be brought to the attention of the VIDA scientific coordinator at the DCC before the participant is randomized at Visit 4. Because the spirotel® device contains self-report information, its data should be used to assess compliance only when absolutely necessary.
Any problems noted with the DOSER™ should be clearly documented on the DOSER™ Tracking Log (DOSER_LOG) for future reference.

- Ability to take at least 75% of the scheduled capsules within the protocol time window (AM) during the interval between Visit 2 and Visit 3.

  This criterion is evaluated objectively through data stored in the participant's MEMS®6 monitor. A high level of compliance is required and should be emphasized throughout the trial. See the Dosing Compliance and MEMS®6 Cap discussions in this section for further details.

  This criterion is evaluated based on information recorded in Q1090 on the VIDA Compliance Checklist (P1_COMPLY). If the participant's dosing compliance with the scheduled capsules was less than 75% during the run-in, the participant is ineligible to continue in the VIDA trial. He/she may be re-screened starting at Visit 0 at the coordinator's discretion.

  If a participant's MEMS®6 monitor is lost or the history is completely blank or unreadable, the participant's spirotel® e-diary data may be reviewed as a substitute means of assessing dosing compliance. In this situation review the participant's Spirotel® Participant Visit Report generated at Visit 3 and determine compliance on the basis of diary question Q3. Do not complete Q1060-Q1090 on P1_COMPLY in this case. Evaluate the eligibility criterion on the basis of the e-diary information and document your calculations. This exception must be brought to the attention of the VIDA scientific coordinator at the DCC before the participant is randomized at Visit 4. Because the spirotel® device contains self-report information, its data should be used to assess compliance only when absolutely necessary.

  This criterion is documented on P1_ELIG5.

- Ability to complete at least 10 of the last 14 days of diary entries and peak flows using the spirotel® device.

This criterion is evaluated on the basis of data stored in the participant's spirotel® device for the 14 days prior to Visit 3. The participant's compliance is assessed and summarized on the Spirotel® VIDA Eligibility and Baseline Report which is generated for each participant after uploading his/her spirotel® data at Visit 3. For further details on how compliance is defined and calculated for this eligibility criterion, see the Spirotel® discussion in this section and, more specifically, the VIDA Spirotel® Reports subsection.

This criterion is documented on P1_ELIG5.

- Asthma symptoms on at least two days or one night per week, on average, over the last 2 weeks as reported on participant e-diary.

  This criterion is evaluated on the basis of data stored in the participant's spirotel® device for the 2 weeks (14 days) prior to Visit 3. The participant's average number of days and, separately, nights per week with reported symptoms (of any severity) are assessed and summarized on the Spirotel® VIDA Eligibility and Baseline Report. This report is generated for each participant after uploading his/her spirotel® data at Visit 3. For further details on how symptoms are summarized for this eligibility criterion, see the Spirotel® discussion in this section and, more specifically, the VIDA Spirotel® Reports subsection.

  Note: If a participant works nightshift and has altered sleep/wake cycles as a result, his/her AM and PM symptoms may be reversed in the e-diary. In this case, it is likely that the symptom summary on the Spirotel® VIDA Eligibility and Baseline Report also will be reversed. Carefully review the participant's e-diary information on the Spirotel® Participant Visit Report to ensure that he/she meets the eligibility criterion. Make a notation on the Eligibility and Baseline Report if alterations are necessary to the symptom summary.

  This criterion is documented on P1_ELIG5.

**Visit 3**
Exclusion Criteria

- Use of any of the excluded drugs listed in Table 1 (above) during the run-in period. This includes use of oral corticosteroids for any indication. The VIDA Exclusionary Drugs (P1_EXCLDRUG) reference card contains a summary of this table.

This criterion is documented on P1_ELIG5.

- Need for additional controller medications for asthma symptoms during the run-in.

  If the participant requires treatment with a higher dose of Alvesco® (i.e., more than 2 puffs BID, 80 mcg/puff) or with another inhaled corticosteroid (ICS) or other controller medication during the run-in period, he/she is ineligible to continue in the study. Participants must be able to tolerate the run-in (low) dose of ICS without needing additional controller medications in order to be randomized. This ensures that the study population will consist primarily of individuals who are likely to remain stable during the ICS stable dose phase (Phase I) so that most treatment failures will occur during the tapering phases (Phases IIa and IIb).

  This criterion is documented on P1_ELIG5.

- Hospitalization or urgent medical care visit for asthma during the run-in.

  If the participant was hospitalized for asthma, complete a Serious Adverse Event Reporting Form (SERIOUS).

  This criterion is documented on P1_ELIG5.

- Treatment failure during the run-in.

  At Visit 3 the participant will be evaluated for the first time using the VIDA treatment failure criteria as documented on the VIDA Treatment Failure Checklist (P1_TXFAIL_CHK). The spirometry-related criterion will not be assessed at Visit 3 due to the lack of a consistent baseline spirometry visit for all participants.

  If the participant meets any criteria for treatment failure at Visit 3, he/she is ineligible to continue in the trial. He/she may be considered for re-screening starting with Visit 0 if the local investigator believes the participant has a high probability of succeeding upon re-enrollment. Once an individual experiences two treatment failure events during the VIDA run-in and/or oral corticosteroid response phase, he/she may not undergo further re-screening.

  See the Treatment Failure discussion in this section for further details on treatment failure criteria.

This criterion is documented on P1_ELIG5.

- Urine calcium:creatinine ratio ($U_{Ca}$:$U_{Cr}$ ratio) greater than 0.37.

  Results of the $U_{Ca}$:$U_{Cr}$ ratio test are recorded on the VIDA Laboratory Results (P1_LAB) form at Visit 3. If the participant's $U_{Ca}$:$U_{Cr}$ ratio is greater than 0.37 (when both urinary calcium and creatinine are expressed in mg), the participant is ineligible for continued study participation. No exceptions can be made at Visit 3.

  If urinary calcium and creatinine are measured in mmole rather than mg, the appropriate cutoff for eligibility assessment is 1.0. Values must be converted to mg/L before completing the P1_LAB form.

  If the participant's $U_{Ca}$:$U_{Cr}$ ratio is elevated, record this fact as an adverse event on the Clinical Adverse Events (AECLIN) form using ICD-9 code 275.42 (hypercalcemia). There is no available code for hypercalciuria.

  See the Urine Calcium:Creatinine Ratio Laboratory Test discussion in this section for further details on this test.

  This criterion is documented on P1_ELIG5.

## 2.16 Extra Study Visits

### Treatment Failure Visits
### Visit 90-92

For safety reasons, participants who experience a treatment failure will be seen at the performance site as soon as possible, but at least within 1 week from the day they have been categorized as experiencing the treatment failure. This visit will provide an opportunity to examine the participant and to ensure that he/she is responding to the increased dose of inhaled corticosteroid appropriately. If additional treatment is needed, it will be initiated at the time of the visit.

If the treatment failure follow-up visit is scheduled within the visit window for a regular protocol visit, the regular visit may be performed in conjunction with the safety follow-up assessment. A study physician should be consulted to determine whether the participant is well enough to perform all study-related procedures, such as methacholine challenge and sputum induction, at applicable visits.

If the safety follow-up visit is scheduled outside the window for the participant's next regular protocol visit, the treatment failure (TF) visit checklist (Visit 90-92, P1_VISITJ) should be followed. Treatment failure visit packets (90–92) apply only after the participant is randomized in the trial, as participants who experience treatment failure during the run-in or oral corticosteroid response periods are ineligible to continue in the study and should be terminated at that time. After randomization, when a given participant reports his/her first treatment failure event between regular visits, visit number 90 should be used for the visit packet and all corresponding single forms completed at the visit. Treatment failure packets should be entered and submitted to the DCC only if the treatment failure event is confirmed on the VIDA Treatment Failure Checklist (P1_TXFAIL_CHK). Visit number 91 should be used for the same participant's second TF visit, and visit number 92 for the third TF visit. Note that participants will need no more than three TF visit packets, as they are terminated from further study participation when the third post-randomization failure event occurs.

At the beginning of the TF visit, the participant should be asked to complete the Asthma Control Test (ACT) if he/she is able. While he/she is completing the short questionnaire, clinical personnel should upload the participant's spirotel® device and print the Spirotel® Participant Visit Report. The report should be reviewed along with the participant's Asthma Monitoring Log (P1_ASTHMA_LOG) to determine if treatment failure criteria concerning increased rescue use and/or low peak flows were met and when. If any medications other than study RESCUE Xopenex® and/or Alvesco® were used to treat

the event, they should be recorded on the Concomitant Medications for Asthma/Allergy and Adverse Events (CMED) form. Any adjustments to the participant's Alvesco® dose should be recorded on the VIDA Change in Study Medications (P1_CHANGE_MEDS) form. The treatment failure event should be recorded on the Clinical Adverse Events (AECLIN) form using ICD-9 code 000.00. If the event also qualifies as a significant asthma exacerbation, it also should be recorded on AECLIN using ICD-9 code 493.92.

Spirometry should be carried out at the visit for safety and to determine if the participant meets $FEV_1$-related treatment failure criteria. Spirometry should be carried out regardless of the participant's eligibility according to the VIDA Pulmonary Procedure Checklist (P1_PULMONARYCHK) because he/she most certainly meets at least one treatment failure criterion by virtue of being present at the visit. P1_PULMONARYCHK should be completed truthfully, indicating any drug holds that were not met, and entered into the database as part of TF visit packet. If a Visit 90, 91, or 92 is being done, use these visit numbers in the MedGraphics system.

The VIDA Treatment Failure Checklist (P1_TXFAIL_CHK), Treatment Failure Information (P1_TXFAIL) form, and, if applicable, VIDA Significant Asthma Exacerbation (P1_SIGEX) form should be completed and entered with the packet.

All participants who are scheduled for a TF visit should undergo a long physical exam by a licensed medical practitioner. A study physician should be consulted, as warranted.

Before the participant leaves the visit, ensure that he/she has an adequate supply of RESCUE Xopenex® and Alvesco®. Return his/her spirotel® and ASTHMA_LOG to him/her for continued completion until the next regular visit. Note that the return visit number in the spirotel® should remain the same as it was previously programmed; do not update it at a TF visit.

### Follow-Up Visits for Confirmation of Treatment Failures: $FEV_1$ Re-assessment Visits

If a participant has a pre-bronchodilator $FEV_1 \leq 80\%$ of baseline pre-bronchodilator $FEV_1$ (from Visit 3) at a visit and <u>does not</u> meet any other treatment failure (TF) criteria at the visit, 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 levalbuterol 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 treatment failure conditions have progressed. No additional provocative procedures (e.g., methacholine challenge, sputum induction) scheduled for the day of the original visit should be performed. Be sure to return the participant's spirotel® device and VIDA Asthma Monitoring Log (P1_ASTHMA_LOG) to him/her before he/she leaves the performance site.

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 treatment failure is met. Note that although participants should be encouraged to meet all of the necessary drug and substance holds for spirometry testing, they may proceed with testing at re-assessment visits even if not all the holds on the VIDA Pulmonary Procedure Checklist (P1_PULMONARYCHK) are met. The P1_PULMONARYCHK form and the Spirometry Testing (SPIRO) form from the re-assessment visit should be entered into the VIDA database as single forms (in addition to the regular packet forms), even if the participant does not meet the $FEV_1$ criterion.

At the $FEV_1$ re-assessment visit, after spirometry testing is complete, the participant's spirotel® device should be uploaded and his/her P1_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 P1_ASTHMA_LOG should be reviewed to determine if the participant has met the rescue use and/or peak flow criteria since the original visit. In the event that a criterion has changed, the applicable question on the Treatment Failure Checklist (P1_TXFAIL_CHK) should be updated. The VIDA Compliance Checklist (P1_COMPLY) should be updated to reflect the additional spirotel® data in Q1100, Q1110, and Q1120. Dates on these forms should be updated to the re-assessment visit date to confirm that they have been reviewed and updated accordingly. Continue with the remainder of the visit procedure checklist for the original visit.

Note: When the participant returns for the $FEV_1$ re-assessment visit, the first procedure performed is spirometry. 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.

## 2.17 Genetics Blood Draw

**Visit 3 or 6**
Obtain blood sample for DNA extraction and genetic analysis (three 10ml 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

Before drawing blood for genetic analysis, verify that the participant has given consent to participate in the genetic analysis component of the VIDA 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 VIDA study. The genetic analysis participation rate for each clinical center partnership and performance site will be summarized on the VIDA Accrual Report.

The genetic analysis blood draw is scheduled for Visit 3 in the VIDA protocol; however, most participants will not provide blood for any other tests at this visit, necessitating an extra 'stick'. Individuals who have agreed to participate in the Immune Substudy (Green mechanistic study) will have blood drawn at the end of Visit 3 and may wish to contribute genetics blood at the same time. If a participant is not participating in the Immune Substudy and wishes to defer his/her genetics blood draw until Visit 6, when a serum vitamin D test is needed for the protocol, that is acceptable. 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 adults 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.

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.

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 for specific information on completing the GABLOOD form. Note that the participant 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 genetics blood sample, but the sample is not obtained at Visit 3 for whatever reason, the blood draw may be delayed to any subsequent protocol visit. Visit 6 is the ideal time to attempt to draw the genetics blood, in conjunction with the blood draw for vitamin D determination. If the genetics blood draw is deferred until Visit 6 (or any other future visit), then the Visit 3 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 6). If the blood draw is attempted at Visit 3 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 3 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 3 in the study must have a GABLOOD form present in the database.

## 2.18 Green Mechanistic Study (Immune Substudy)

An ancillary, mechanistic study called “Immune Regulation by Vitamin D in Suboptimally Controlled Asthmatics” (Immune Substudy for short) has been approved for the VIDA trial. This study is being supervised by Dr. Jonathan Green from the St. Louis clinical center partnership and Drs. Manuela Cernadas and Dale Umetsu from the Boston clinical center partnership.

The Immune Substudy aims to determine whether vitamin D deficiency in asthmatics results in a pro-inflammatory state that contributes to the lack of response to conventional asthma therapy. It is hypothesized that the pro-inflammatory state is due to dysregulation of cells of both the innate and adaptive immune systems and that repletion of vitamin D will restore immune homeostasis and responsiveness to therapy. Specifically, the researchers propose that treatment of vitamin D deficient asthmatics will 1) increase the number and function of tolerogenic dendritic cells; 2) increase the number and function of IL-10 producing Tr1 cells and FopxP3 positive induced T regulatory cells (iTregs); and 3) decrease pro-inflammatory cytokine secretion by CD4+ T cells.

To carry out this study, two peripheral blood draws of 100 ml each will be required from 100 VIDA study participants. Blood draws will occur at Visit 3 (prior to vitamin D treatment) and Visit 6 (at the end of 12 weeks of vitamin D/placebo treatment and prior to any inhaled corticosteroid dose tapering). To ensure that it is safe to draw the large volume of blood needed for this study, all Immune Substudy participants will be tested for hematocrit (hct) level at the end of Visit 2. All VIDA performance sites are invited to participate in recruitment for this ancillary study.

**Visit 0 Obtain Consent**

Consent for the Immune Substudy is sought at the time the participant is being consented for the VIDA parent study at Visit 0. The participant’s consent status is tracked on VIDA Eligibility Checklist 1 (P1_ELIG1) in Q1020. Before drawing blood from a participant for hematocrit level at Visit 2, or at Visit 3 or Visit 6, confirm that he/she consented to be part of the Immune Substudy.

**Visit 2**
Obtain blood sample for hematocrit determination (local lab)

At the end of Visit 2, if the participant has consented to participate in the Immune Study and the study is still recruiting, obtain a blood sample for hematocrit determination (follow local lab specifications for this test). Hematocrit measures the percentage of the

participant's blood that is made up of red blood cells. If the participant's result is < 25%, he/she is considered anemic and is ineligible to proceed with blood draws for the Immune Substudy.

Note that the hematocrit level is not entered into the VIDA database or submitted to the DCC. Maintain a copy of the participant's lab report in his/her VIDA study folder at the performance site.

### Lab Notification of Planned Visit 3 or 6

When the date of a Visit 3 or 6 has been confirmed with a study participant who has consented to be in the mechanistic study, this information should be e-mailed to lab personnel. Because samples are shipped the same day they are collected, it is helpful for lab staff to know when visits are occurring so that they know what days they will be analyzing the samples. Near the end of Visit 2, the Visit 3 date should be confirmed and communicated to the labs. Near the end of Visit 5, the Visit 6 date should be confirmed and communicated to the labs. Forward the participant ID number, visit number (3 or 6) and the scheduled visit date to the AsthmaNet_VIDA_mech_lab alias.

If a scheduled visit date changes or the visit is cancelled, notify the labs via the e-mail alias as soon as possible. If no usable blood tubes are collected during a scheduled visit, notify the labs so they are aware that no shipment will be forthcoming.

### Obtaining and Processing Blood Samples

**Visit 3, 6**
Obtain blood samples for Immune Substudy (1 red/grey top SST and 9 green top tubes) (P1_MECH_GREEN)
Enter sample information into Biological Sample Tracking module

For participants who have consented to participate in the Immune Substudy and whose Visit 2 hematocrit levels were normal, proceed with drawing blood for the study using the following guidelines:

- Blood samples for the Immune Substudy should only be drawn Monday-Thursday. Samples obtained on Friday will not arrive at their destination labs in time for processing and should not be collected or shipped.

  <u>For the Visit 6 blood draw only</u>: If a participant must schedule Visit 6 on a Friday, he/she may return to the performance site within 1 week after the visit for purposes of providing the blood samples for the Immune Substudy. It is

preferable to have the samples drawn on a Monday-Thursday during the regular visit; this option should only be used if absolutely necessary.

Note: If no samples are obtained at Visit 3, or if the Visit 3 samples are deemed unusable by the lab for any reason, the Visit 6 blood draw should not be performed. In these cases the participant's 'Green Mech Study' status on the VIDA Participant Status report will be blank.

- Sample collection and handling should be performed in accordance with the policies and procedures determined by each site and institution.

- Blood collection tubes used by each site should be maintained at room temperature.

- At Visit 3 and Visit 6, fill 10 vacutainers with blood from the participant using standard technique in the following order:
  1 – 10 ml BD vacutainer serum separator tube (SST) – red/grey top (BD #367985)
  9 – 10 ml BD vacutainer sodium heparin tube – green top (BD #367874)

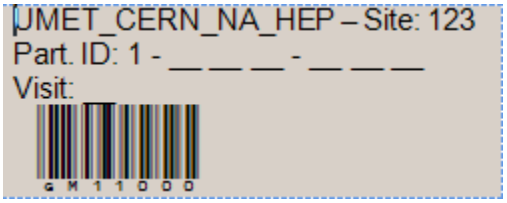
  The SST must be drawn first to avoid transfer of additives from the green top tubes to the SST. Performance sites are required to purchase and maintain a supply of these tubes for this project.

- Invert each tube gently approximately 10 times after collection.

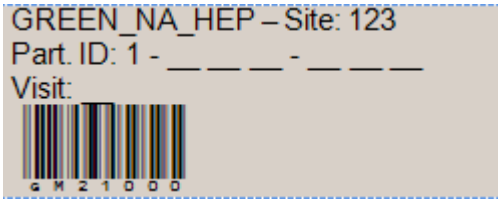
- Process the SST only (red/grey top tube) as follows:

  Allow the tube to clot for a minimum of 30 minutes in a vertical position at room temperature. After the SST has been allowed to clot, spin it down for 10 minutes in a centrifuge at full speed (between 1100 and 1300 g) for a swing-head unit or 15 minutes for a fixed angle unit. A barrier will form, separating the serum specimen from the clot.

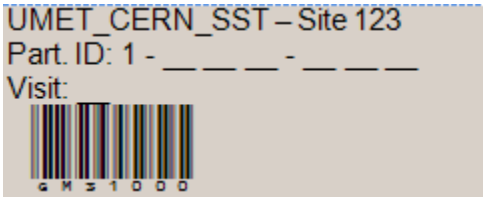
- Label each tube with a barcode label generated through the AsthmaNet Biological Sample Tracking module (Avery 5160 sheets of 30 labels). The labels must be affixed to the correct tube type. Sample labels and their associated sample type follow:



7 Green top tubes being shipped to Boston



2 Green top tubes being shipped to St. Louis



1 SST being shipped to Boston

- Scan the samples into the Biological Sample Tracking (BST) module using the procedures outlined in section 7 of the AsthmaNet General Manual of Operations. Create a shipment by scanning the barcodes for all samples available to ship a second time. Include a shipment comment that states the contents of each shipment (i.e., human blood and serum). Each shipment (from each site) will receive a unique shipment ID number when a given shipment is confirmed by a performance site. Note that shipment IDs are specific to a given sample type so that three different shipment ID numbers will be created for a given blood draw for the mechanistic study. A shipment inventory will be generated (for each shipment ID) that contains: date of shipment, shipper 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 inventories for inclusion in the shipment. Samples must be shipped via FedEx priority overnight (for 10:30 AM delivery) the same day they are collected. See complete packaging and shipping instructions below.

  Once the shipment is confirmed in the BST module, e-mails will automatically be sent to each lab that will be receiving samples the next morning. 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.

- Store the tubes at room temperature until they are ready for shipment. Hemolyzed samples should be retained for shipment. Add a site comment in the BST module if this occurs.

- Complete a VIDA Mechanistic Study Participation (Green) (P1_MECH_GREEN) form indicating the number of each tube type collected. This form must be entered into the AsthmaNet database for the performance site to receive payment for the blood draw.

### Incomplete Blood Draws

If fewer than ten tubes are collected, the actions that should be taken depend on the circumstances, as follows:

- Visit 3:

  - If 1 SST and <2 green top tubes are collected, discard all tubes. Participant will not be considered a mechanistic study subject. No blood draw should be attempted at Visit 6.

  - If 1 SST and 2 green top tubes are collected, route 2 green tops to Dr. Green's lab in St. Louis and discard SST (no samples will be shipped to the Umetsu/Cernadas lab in Boston in this case).

  - If 1 SST and ≥3 green top tubes are collected, route 2 green tops to Dr. Green's lab in St. Louis and the SST and remaining green top tubes to the Umetsu/Cernadas lab in Boston.

- Visit 6:

  - If 1 SST and 1 partial green top tube are collected, discard all tubes; no shipment should be made.

  - If 1 SST and 1 FULL or 2 green top tubes are collected, route the green top tube(s) to Dr. Green's lab in St. Louis and discard SST. No samples will be shipped to the Umetsu/Cernadas lab in Boston in this case.

- If 1 SST and ≥3 green top tubes are collected, route 2 green tops to Dr. Green's lab in St. Louis and the SST and remaining green top tubes to the Umetsu/Cernadas lab in Boston.

## Laboratory Contacts

Dr. Jonathan Green Laboratory (St. Louis)

Jonathan Green, M.D.: jgreen@wustl.edu
Jonathan Boomer, PhD.: jboomer@dom.wustl.edu
Christine Deppong, PhD: christine.deppong@gmail.com
Phone: (314) 747-3590

Dr. Dale Umetsu Laboratory (Boston)

Dale Umetsu, M.D.: dale.umetsu@childrens.harvard.edu
Azza Abdel-Gadir: azza.abdel-gadir@childrens.harvard.edu
Phone: (617) 919-2439

Dr. Manuela Cernadas Laboratory (Boston)

Manuela Cernadas (mcernadas@partners.org)
Phone: (617) 525-8136

Mechanistic Study Lab E-mail Alias: AsthmaNet_VIDA_mech_lab

## Shipment Supplies

The DCC will supply each participating performance site eight blood specimen insulated shipping kits with gel packs (SPECKIT from Cameron Packaging, Inc.) and a box of Fisher “Zipper” Seal Sample bags (5x8”) at the beginning of the VIDA trial. Performance sites will need to purchase and maintain their own supply of green top vacutainers and red/grey top SSTs (see BD catalog numbers above). Sites will also need paper towels to wrap individual tubes for shipment as outlined below.

Blood specimen shipping kits are reusable (unless there is leakage during transport). Laboratories will return empty kits (along with gel packs) to the sites from which they originated so that they can be reused. Kits will be returned using FedEx Express Saver and the DCC’s account number (#184551136) specifying the VIDA mechanistic study in the reference section. If shipping kits are not returned to a given site in a timely manner, contact Dr. Manuela Cernadas at (617) 525-8136 (mcernadas@partners.org).

Performance sites are responsible for ensuring that they have sufficient shipping materials available for their expected enrollment into the Immune Substudy.

Each shipping kit includes the following:


**A** (1) 7-3/4" x 5-7/8" x 8-1/2" Foam Cooler #TK8 with Outer Shipping Corrugated Carton

**B** Two Sarstedt Absorbent-Lined Shipping Tubes (secondary receptacles) + Caps

**C** (1) Small Vial Carton (7 x 5 x 4)

**D** (4) Gel Packs

**E** Bubble Wrap

**F** Packing Slip Envelope

## Shipment Instructions

Samples collected at Visit 3 and Visit 6 will be divided among three labs at two shipment locations as follows:

For each collection of 10 tubes:

- Ship 2 green top tubes at room temperature to Dr. Green's lab in St. Louis to the following address using FedEx Priority Overnight (use FedEx account #184551136). Please note VIDA mechanistic study in the reference section for billing purposes.

  Jonathan S. Boomer
  Washington University School of Medicine
  Pulmonary Division/9952 CSRB
  4940 Parkview Place
  St. Louis, MO 63110
  (314) 747-3590

- Ship 7 green top tubes and 1 SST (red/grey top) at room temperature to the labs of Drs.Umetsu and Cernadas in Boston to the following address using FedEx Priority Overnight (use FedEx account #184551136). Please note VIDA mechanistic study in the reference section for billing purposes.

  Dr. Manuela Cernadas
  Brigham & Women's Hospital
  Thorn Building, Room 909
  20 Shattuck Street
  Boston, MA 02115
  (617) 525-8136

The Immune Substudy labs are affiliated with the Boston and St. Louis clinical center partnerships. Therefore, samples collected at the performance sites within a given partnership will not need to be shipped (they can be transported by foot). Performance sites should follow the instructions below that are applicable to them:

Brigham & Women's Hospital (site 111)

- Contact the laboratories of Drs. Umetsu and Cernandas for direct pick up of 1 SST (red/grey top) and 7 green top tubes.

- The remaining 2 green top tubes should be shipped to Dr. Green's laboratory as outlined below.

Washington University Adult Site (site 161)

- Contact the laboratories of Dr. Green for pick up of 2 green top tubes.
- The remaining 7 green top tubes and the 1 SST (red/grey top) should be shipped to Drs. Umetsu/Cernadas as outlined below.

All Other VIDA Sites

- Ship 7 green top tubes and 1 SST (red/grey top) to the laboratories of Drs. Umetsu/Cernadas as outlined below.
- Ship 2 green top tubes to the laboratory of Dr. Green as outlined below.

See above for instructions for routing tubes in the case of an incomplete blood draw.

## Packaging Shipments to Dr. Green's Laboratory (St. Louis)

**WHEN READY TO SHIP:**

**STEP 1:**
Put the two green top specimen tubes into the absorbent-lined shipping tubes (see picture above).

If there are two sets (4 tubes) to be shipped: Use additional absorbent-lined shipping tubes or wrap each tube in a paper towel and place in a zipper sealed plastic bag as is described below.

Place 1 ROOM TEMP gel pack in the small 7 x 5 x 4 vial carton (see picture below).

**STEP 2:**
Put the absorbent-lined tubes on top of the ROOM TEMP gel pack.

**STEP 3:**
Place ROOM TEMP gel pack on top. The vials should now be sandwiched between the two ROOM TEMP gel packs.

**STEP 4:**
Place a ROOM TEMP gel pack in the bottom of the #TK8 insulated shipper.

**STEP 5:**
Put the closed small vial carton on top of the ROOM TEMP gel pack.

**STEP 6:**
Place a ROOM TEMP gel pack on top.

**STEP 7:**
Fill any remaining space inside the insulated shipper with the bubble wrap.

**STEP 8:**
Place your documentation (including the inventory list from BST) on the outside of the carton. Seal the shipper with tape.

**STEP 9:**
Fill out and attach FedEx mailing label. Check the FedEx Priority Overnight option. Use FedEx account #184551136. Note VIDA mechanistic study in the reference section.

**NOTE:**
Only ship the samples out Monday through Thursday, so the shipment arrives before the weekend.

**Dr. Jonathan Green Laboratory Ship To Address:**

Jonathan S. Boomer
Wash U School of Medicine
Pulmonary Division/9952 CSRB
4940 Parkview Place
St Louis, MO 63110
Phone: (314) 747-3590

## Packaging Shipments to the Umetsu/Cernadas Laboratory (Boston)

| | | |
|---|---|---|
| **WHEN READY TO SHIP:**<br><br>**STEP 1:**<br>Wrap each of the 8 blood sample tubes in a paper towel. Put the wrapped tubes into a plastic zipper seal bag (4 tubes/bag). Seal the bags.<br><br>**Note:** Do not throw out the two absorbent-lined shipping tubes that come with the kit. They can be used for shipments to Dr. Green's lab or to replace damaged items. | **STEP 2:**<br>Place the two plastic bags into the empty small 7 x 5 x 4 vial carton, one on top of the other. | **STEP 3:**<br>If there is excess remaining space in the box, you can place one room temperature gel pack underneath the plastic transport bags.<br><br>(In contrast to the shipment to Dr. Green's lab, you may have spare gel packs. Please store for future use.) |
| **STEPS 4-9: proceed as indicated above in steps 4-9 for shipments to Dr. Green's Laboratory in St. Louis.** | Note: Samples *must* be shipped in an insulated shipper to protect from weather conditions. | |

### Drs. Umetsu/Cernadas Labs Ship to Address:

Dr. Manuela Cernadas
Brigham and Women's Hospital
Thorn Building, Room 909
20 Shattuck Street
Boston, MA 02115
Phone: (617) 525-8136

## Tracking Immune Substudy Participation

The Immune Substudy participation status of each VIDA participant will be tracked on the VIDA Participant Status Report via the 'Green Mech Study Part' column. This column will set to 'Yes' for a given participant upon insertion of any of the three Immune Substudy sample types (see above) into the Biological Sample Tracking module at Visit 3. The column will remain blank for non-participants.

The VIDA Accrual Report will include a table that summarizes the number of Visit 3 Immune Substudy participants at each clinical center partnership and Network-wide.

## 2.19 Home Environment Questionnaire

**Visit 1**
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 participant completes this questionnaire. The coordinator should provide assistance for any questions when requested.

When the participant returns the questionnaire, the coordinator should review it thoroughly to be sure all questions have been answered to the best of the participant's ability. If he/she would rather not answer certain questions, they may be left blank. The participant should initial and date the source documentation box on the last page of the form when he/she is finished.

## 2.20 Household Socio-Economic Information Form

**Visit 1**
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. He/she can decline to answer any question he/she wishes.

## 2.21 Informed Consent

**Visit 0**
Acquire signed VIDA informed consent

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

The VIDA consent template explains the procedures and time commitment necessary to participate in the VIDA 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.

Guidelines for obtaining consent:

- At the beginning of Visit 0 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.

- Allow ample time for the potential participant 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 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 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, 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 at one of the screening visits or during the run-in for a reason that can be remedied (e.g., insufficient high dose vitamin D washout period or recent respiratory tract infection, etc.), he/she may be re-enrolled starting at Visit 0 at a later date. During the new Visit 0, the participant should be given a clean copy of the performance site's most current, IRB-approved VIDA consent document to review and sign. See the Re-Enrollment discussion in this section for further details.

If modifications are made to the VIDA 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 VIDA consent document the participant signed must be retained in his/her VIDA study folder and are subject to audit.

Local IRB rules and regulations should be followed at all times.

Note: The VIDA consent template contained language for the VIDA main study, optional genetic analysis participation, and optional Immune Substudy (i.e., Green mechanistic study) participation. Some IRBs required the language for one or both of the optional sections to be placed into its own consent document. At Visit 0, consent should be sought for all three study components, 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 VIDA study consent is recorded and tracked on VIDA Eligibility Checklist 1 (P1_ELIG1), as is his/her Immune Substudy participation status. Genetic analysis participation is tracked on the Genetic Analysis Blood Draw (GABLOOD) form which is completed at the blood draw visit.

**Visit 0**
Administer BioLINCC consent document
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 VIDA study (potentially including sputum supernatant, plasma, serum, DNA) will be transferred to BioLINCC and made available to other researchers. A participant 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 0, after a participant provides consent to be in the VIDA trial, he/she must be given the IRB-approved VIDA BioLINCC consent document to review. If he/she agrees to allow his/her leftover VIDA 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 consents to participate in BioLINCC for his/her VIDA samples, then his/her consent document must be retained with the VIDA study consent document in his/her VIDA study folder at the performance site. This consent document is also subject to audit during an AsthmaNet data quality site visit.

Every VIDA participant must have a BioLINCC Consent Tracking Form (BIOLINCC) completed at Visit 0. This form tracks whether or not the participant agreed to donate his/her leftover VIDA 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.

## 2.22 Inhalation Technique Assessment

**Visit 2**
Assess inhalation technique using the MDI Inhalation Technique Checklist (TECH_MDI_NOSP) and placebo provided. Complete as many TECH_MDI_NOSP forms as necessary and store in participant's folder.

Because proper medication dosing is crucial for the success of the VIDA study, each participant must demonstrate that he/she can accurately use a metered-dose inhaler (MDI). Proper MDI technique is an eligibility requirement that is assessed at Visit 2 on VIDA Eligibility Checklist 4 (P1_ELIG4).

To assure that each participant has met the AsthmaNet standards for MDI use, an MDI Inhalation Technique Checklist (Without Spacer) (TECH_MDI_NOSP) has been developed. Participants are considered eligible at Visit 2 only after they are able to carry out each of the eleven steps (corresponding to eleven points) listed on the technique checklist. There is no upper limit on the number of test puffs a participant may take to satisfy these requirements.

During the technique assessment, ten separate criteria are assessed by observing the participant inhale from a placebo MDI provided by the DCC. The placebo inhaler has a fluorescent label that reads 'MDI Inhalation Technique Inhaler (Contains Placebo)'. The participant is given one point for each of the following steps that is 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.

After successfully completing one puff/inhalation, the participant must repeat the sequence correctly for a second puff to earn the 11$^{th}$ point and pass the technique assessment.

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 TECH_MDI_NOSP checklist and stored in the participant's study folder; do not submit these forms to the DCC.

## 2.23 Inhaled Corticosteroid Dose Taper

**Visit 6, 8**
Evaluate participant for ICS dose taper (P1_ICS_TAPER)
Complete Change in Study Medications form (P1_CHANGE_MEDS), if applicable

The run-in, oral corticosteroid response period, and post-randomization phase I dose of inhaled corticosteroid (ICS, Alvesco®) is 2 puffs BID (80 mcg/puff). In order to test the hypothesis that the addition of vitamin D to a standard dose of ICS may allow sparing of ICS dose in individuals with stable asthma, participants will be evaluated at Visit 6 (beginning of phase IIa) and Visit 8 (beginning of phase IIb) to determine if they are eligible to reduce their ICS dose. Tapering the ICS dose over the course of the study allows us to determine if the addition of vitamin D reduces the likelihood of treatment failure (primary study outcome) when compared to placebo when the ICS dose is reduced.

Stability Criteria

At Visit 6 and again at Visit 8, participants will be evaluated to determine if their asthma has been stable enough for reduction of their ICS dose. Stability criteria include:

1. No significant asthma exacerbation during the VIDA trial.

   See the Significant Asthma Exacerbation discussion in this section for the definition of an asthma exacerbation for VIDA.

   If an exacerbation occurs during the post-randomization phases of the study, no further ICS dose tapering will be attempted.

2. No more than one treatment failure event since randomization at Visit 4.

   See the Treatment Failure discussion in this section for the definition of a treatment failure event.

   If a second treatment failure event occurs during the post-randomization phase of the study, no further ICS dose tapering will be attempted.

3. No treatment failure experienced within 2 weeks of the stability assessment visit.

See the Treatment Failure discussion in this section for the definition of a treatment failure event.
If the participant experienced only one treatment failure event that did not qualify as a significant asthma exacerbation and he/she might be eligible for a dose taper, the date of treatment failure should be obtained from Q1100 on the Treatment Failure Checklist (P1_TXFAIL_CHK). If this date is within 2 weeks of the current visit, the participant is ineligible to undergo the taper.

Each participant's stability criteria will be documented on the VIDA ICS Taper Stability Assessment (P1_ICS_TAPER) form.

ICS Dose Taper

If a participant meets all three stability criteria at Visit 6 and/or Visit 8, then his/her ICS dose will be reduced to 50% of his/her current ICS study dose. Dosing will reduced as follows:

| **Initial ICS Dose (phase I)** | **1st Taper (phase IIa)** | **2nd Taper (phase IIb)** |
|---|---|---|
| 2 puffs BID | 2 puffs AM | 1 puff AM |

Participants who do not meet all three stability criteria will be maintained on their current ICS dose (or the dose deemed appropriate to treat their current condition (e.g., increased dose needed to treatment a treatment failure or exacerbation event)).

If a participant does not qualify for the ICS dose reduction at Visit 6 (due to a recent treatment failure event), but he/she does qualify for dose reduction at Visit 8, then his/her ICS dose should be reduced to 2 puffs AM. This would be the first, and only, taper for this individual.

When a participant's ICS dose is changed for any reason, this information must be documented on a VIDA Change in Study Medications (P1_CHANGE_MEDS) form. At Visit 6 and/or Visit 8, if the ICS dose is tapered, a P1_CHANGE_MEDS should be completed indicating Study-defined Taper in Q1000 and documenting the change in ICS dose in Q1020-Q1050. Stop dates for a particular change in dosing are inferred by the presence/absence of additional P1_CHANGE_MEDS forms in the database. For example, suppose a form is completed at Visit 6 indicating that the participant's ICS dose was tapered (Q1000=2), the dose of Alvesco® was changed (Q1020=1), the dose changed from 4 puffs per day (Q1030=4) to 2 puffs per day (Q1040=2) starting on 5/30/11, and no further P1_CHANGE_MEDS forms are entered for this participant over

the remainder of the trial. The absence of additional P1_CHANGE_MEDS forms in the database signals that the participant remained on 2 puffs of ICS daily until the time he/she left the trial.

Capturing accurate ICS dosing information for each participant is very important to the goals of the VIDA trial, as total steroid dose (oral and inhaled) will be calculated per participant and the distribution will be compared between the vitamin D and placebo arms.

## 2.24 Medical History

**Visit 1**
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. 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 2 years of college. Following college, he smoked a pack per day (20 cigs per day) for five 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:

   (2 x .5) + (5 x 1.0) + (.50 x .25) = 6.125 pack-years

   Sam may be eligible for VIDA, given his current non-smoker status and less than 10 pack-year history. Note that pack-year history is assessed for eligibility at Visit 0 on Eligibility Checklist 1 (P1_ELIG1), but it is not recorded on a data collection form until Visit 1. Coordinators should ensure that the information provided at Visit 0 is consistent with responses provided at Visit 1 and that the participant remains eligible for continued study participation.

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.

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 at Visit 1 and for entry into the study according to the eligibility criteria. See the Re-Enrollment discussion in this section for details pertaining to the recording of run-in and oral corticosteroid response period study medications on the PRIOR_TRT form.

The medical history is administered early in the visit so that eligibility criteria that are 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.

## 2.25 MEMS®6 Cap

The MEMS®6 Monitor is a special closure that fits on a conventional medicine bottle. The closure/cap records the time and date of each opening and closing of the container from which compliance with medication dosing is inferred. A reader transfers the dosing history data from the MEMS®6 cap to a computer at which time an AsthmaNet Compliance Report can be generated for a given participant. For the VIDA trial, the MEMS®6 cap will be used to estimate each participant's compliance with taking his/her scheduled daily capsules (regular dose capsules only). Capsules should be taken every morning between 4 AM and noon starting the morning after Visit 2.

For information on configuring the MEMS®6 cap, reading the data, and generating compliance reports, see the MEMS®6 Monitor Manual of Operations in appendix 5 of the AsthmaNet General Manual of Operations.

In general, at each visit starting with Visit 3, the number of monitored days between visits (full days between visits, not including the day of the prior or current visit), number of doses taken, % prescribed number of doses taken, and doses in time-window/prescribed doses will be calculated by the monitor based on the 'Phase and Regimen' setup in the device. Results are transcribed onto the VIDA Compliance Checklist (P1_COMPLY) in fields Q1060-1090. Although 100% compliance should be encouraged, the minimum acceptable compliance for VIDA is 75%.

**Visit 2**
Program MEMS®6 monitor

Set up the monitor for the participant by entering his/her participant ID and initials into the global information portion of the 'Patient Data' tab. Follow the directions in the MEMS®6 MOP for configuring the rest of the participant's data.

**Visit 3**
Log/dispense OCS response period capsule vial with MEMS®6 cap

The MEMS®6 cap should be attached to the OCS response period capsule vial at Visit 3. The OCS response period prednisone vial will not be monitored with a cap; a simple tablet count will be done to monitor compliance with prednisone dosing.

**Visits 2-10, 88**
Perform MEMS®6 Quality Control (MEMSQC)

Quality control (QC) is required at each regular VIDA study visit to ensure that the participant's cap has enough memory and battery power to last until his/her next scheduled visit. The QC process also confirms that the device will not expire prior to the next scheduled visit. If a participant's cap fails the QC process, issue a new cap and complete a new MEMSQC form. Enter both forms with the visit packet.

**Visit 2**
Log/dispense MEMS®6 Monitor (MEMS_LOG)
**Visit 10, 88 or other early termination visit**
Collect/log MEMS®6 Monitor (MEMS_LOG)

Any time a MEMS®6 cap is given to a participant or collected from a participant, this information needs to be recorded on the MEMS®6 Monitor Log (MEMS_LOG). One general log is used to track the supply of MEMS®6 caps across all AsthmaNet studies for a given performance site. Each time a cap is dispensed, decrement the available balance of caps by 1 and record the device serial number, validity date (from the MEMS®6 Read monitor info screen in format mm/yyyy), participant ID number, date dispensed, and the dispenser's initials. Each time a cap is returned, record the date returned, collector's initials, QC status of the cap and any related comments. If the cap is viable for use with another participant, increment the balance of caps by 1 and record the serial number and validity date on the next available row. This cap should be cleaned, prepared, and dispensed the next time a cap needs to be assigned to a participant to maximize its use before it expires.

**Visit 2**
Instruct participant on use of MEMS®6 Monitor (P1_MEMSINST)

Near the end of Visit 2, introduce the participant to the MEMS®6 cap. Ensure that the participant knows that the cap is child resistant and confirm that he/she can remove the cap without a problem. Review appropriate dosing of the run-in capsules and explain that his/her compliance with dosing will be reviewed at Visit 3 and could affect his/her eligibility to continue in the trial. The participant should take his/her first capsule from the vial the morning after the visit.

**Visit 4-9**
Attach MEMS®6 cap to Regular Dose capsule vial

The MEMS®6 cap will be used with the regular dose capsule vials throughout the post-randomization phase of the trial. No MEMS®6 cap will be used with the loading dose

capsule vial dispensed at Visit 4, as this vial is accessed only once, the morning following Visit 4. Compliance with taking the loading dose will be assessed by capsule count only.

**Visit 3-10, 88**
Generate MEMS®6 Monitor Report

At each regular visit starting with Visit 3, the MEMS®6 monitor will be read to create an AsthmaNet Compliance Report. To generate a report covering the full days between the prior visit and the current visit, the study coordinator must provide parameters in the 'Phase and Regimen' tab in the device, as explained in the MEMS®6 Manual of Operations. Specifically:

- Phase begin: Enter the date corresponding to the day after the last visit and 03:00 AM in the 'Phase begin' box.
- Phase end: Enter today's date (the current visit date) and 02:59 AM in the 'Phase end' box. This morning's dose will not be included in the report summary.
- 'Drug Name' should be VIDA.
- Under 'Regimen information' choose 'at fixed time'.
    - ✓ Enter 8:00 AM as the time with a 'low limit' of 4:00 AM and an 'up limit' of 12:00 PM (noon).
    - ✓ Enter 1.0 as quantity per dose.
    - ✓ Choose capsule from dropdown menu.

The above specifications will generate a compliance report that examines the participant's dosing history for all the days between visits, recognizing cap openings between 4:00 AM and 12:00 noon as 'doses taken on schedule.'

<u>At Visit 5 Only:</u>

At Visit 5 the participant will return two capsule vials: the loading dose vial and the regular dose vial. The MEMS®6 cap is only used on the regular dose vial. Because the participant takes only the loading dose capsules the morning following Visit 4, he/she does not begin dosing from the regular dose capsule vial, by protocol, until the next morning – two days following Visit 4. When entering the 'Phase begin' date for the compliance report generated at Visit 5, ensure that the date corresponds to two days after Visit 4. For example, if Visit 4 takes place on 9/12/11, the 'Phase begin' date should be 9/14/11.

## 2.26 Methacholine Challenge

Methacholine challenges are used in the VIDA trial to establish a participant's study eligibility (through the $PC_{20}$ criterion evaluated at Visit 2 for some participants) and to collect an important secondary outcome variable, $PC_{20}$.

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 VIDA Pulmonary Procedure Checklist (P1_PULMONARYCHK) and the Adult Methacholine Challenge Testing Checklist (METHACHK_ADULT) before proceeding with the challenge. Note that METHACHK_ADULT Q1050 excludes 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 less systemic steroid was used, or it 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 levalbuterol. 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 levalbuterol if no sputum induction will follow at the visit. If the participant will be proceeding with sputum induction at Visit 3 and Visit 6, then he/she should be reversed with four puffs of levalbuterol. Results of standard reversal are recorded on the Methacholine Challenge Testing (METHA) form.

Puffs of levalbuterol given to reverse the participant from a methacholine challenge should not be counted in the RESCUE Xopenex® puffs the participant enters into his/her spirotel® device 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.

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

**Visit 2**
Complete Adult Methacholine Challenge Testing Checklist (METHACHK_ADULT)
Perform Methacholine Challenge Testing (METHA)
Complete Additional Treatment Post Methacholine Challenge (METHA_ADD_TRT) form, if needed

Spirometry and methacholine challenge testing are required at Visit 2 only for participants who did not reverse at least 12% following 4 puffs of levalbuterol at Visit 1. These procedures should not be done for individuals who met the reversal criterion.

Participants must pass all of the checks on the VIDA Pulmonary Procedure Checklist (P1_PULMONARYCHK) and the Adult Methacholine Challenge Testing Checklist (METHACHK_ADULT) before proceeding with the challenge. Results of the challenge are recorded on the Methacholine Challenge Testing (METHA) form and are referenced on VIDA Eligibility Checklist 4 (P1_ELIG4). 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 2, he/she cannot proceed with the challenge at the visit. In this case, the visit should be rescheduled if there is a chance the participant will meet the criteria in the near future. If the visit cannot be rescheduled in the 8-week window between Visit 0 and Visit 2, or if the participant is not likely to meet the criteria in that timeframe, then he/she is ineligible to continue participation in VIDA. A VIDA Termination of Study Participation (P1_TERM) form should be completed.

Participants who qualify for the methacholine challenge but do not meet the $PC_{20}$ criterion for eligibility are ineligible to continue in the VIDA study. A P1_TERM form should be completed and study termination procedures followed. See the discussion of Withdrawals in this section for further details.

**Visit 3, 6**
Complete Adult Methacholine Challenge Testing Checklist (METHACHK_ADULT)
Perform Methacholine Challenge Testing (METHA)

Complete Additional Treatment Post Methacholine Challenge (METHA_ADD_TRT) form, if needed

Participants must pass all of the checks on the VIDA Pulmonary Procedure Checklist (P1_PULMONARYCHK) and the Adult Methacholine Challenge Testing Checklist (METHACHK_ADULT) before proceeding with the challenge. Results of the challenge are recorded on the Methacholine Challenge Testing (METHA) form. 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 METHACHK_ADULT form, he/she cannot proceed with the challenge at the visit. Complete the METHACHK_ADULT form indicating the participant's ineligibility and proceed to the next procedure on the Visit Procedure Checklist. Challenge data will be missing for this participant. If the participant fails to qualify for the Visit 3 methacholine challenge, but he/she qualifies for the Visit 6 challenge, the Visit 6 challenge should be performed.

Participants who meet criteria for a significant asthma exacerbation at Visit 6 should not proceed with methacholine challenge testing at the visit. If a participant meets treatment failure criteria but does not meet exacerbation criteria, he/she may proceed with the methacholine challenge at the visit as long as all criteria on METHACHK_ADULT are met and as long as the study physician has cleared the participant for the procedure.

Standard reversal is two puffs of levalbuterol if no sputum induction will follow the methacholine challenge at the visit. If the participant will be proceeding with qualification for sputum induction at Visit 3 or Visit 6, then he/she should be reversed with four puffs of levalbuterol. Results of standard reversal are recorded on the METHA form.

## 2.27 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, methacholine challenge, and/or sputum procedures are attempted during a visit, the visit is not considered missed, even if not all procedures are completed. Spirometry is important to the VIDA study because it is necessary for a full assessment of treatment failure criteria. Visits for which only administrative procedures, such as drug collection/dispensation, spirotel® upload and quality control, and compliance assessments are carried out are considered missed visits.

Ideally all visits for a participant should occur at the same time of day (+/- 3 hours) as measured by the time that baseline spirometry takes place during a visit. 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 VIDA 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 VIDA 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 to provide him/her a new spirotel® device and Asthma Monitoring Log (P1_ASTHMA_LOG). If at all possible the participant's spirotel® device should be returned to the performance site for uploading and quality control.

### Visits 0-4, 6, 8, 10

These visits are mandatory; they cannot be missed due to the procedures that take place at the visits which could compromise the study if not carried out completely. More specifically, eligibility assessments take place at visits 0, 1, 2, and 3, randomization takes place at visit 4, inhaled corticosteroid tapers are initiated at visits 6 and 8, and termination procedures take place at visit 10.

Contact the VIDA Scientific Coordinator at the DCC if scheduling issues arise for these visits.

### Visit 5, 7, 9

These visits occur in the middle of phases I, IIa and IIb, respectively. While it is not ideal for these visits to be missed because treatment failure assessment is critical to the success of the trial, these visits may be skipped if absolutely necessary. Contact the VIDA Scientific Coordinator at the DCC to discuss possible options to prevent missed data for these visits.

If one of these visits must be missed, the participant should be asked to return his/her spirotel® device to the performance site for upload and quality control around the time of the ideal visit date for the applicable 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 capsules and/or Alvesco®. A new capsule vial number should be generated through the VIDA Randomization Module using the number of the missed visit, and a VIDA Scheduled Capsules (P1_MED) form should be completed and data entered.

## 2.28 Participant Assignment Log and Protocol Enrollment

**Visit 0**
Assign participant ID number (P1_LOG)

A Participant Assignment Log (P1_LOG) has been developed for VIDA for each performance site. This log includes columns for unique participant ID numbers, participant initials, participant's name, and assigned capsule vial numbers.

Participant ID numbers are preprinted on P1_LOG and are comprised of 7 digits:

- The first digit is the number of the AsthmaNet protocol. For the VIDA protocol the first digit is 1.

- The next 3 digits are the AsthmaNet performance site identifier (111=Brigham & Women's Hospital, 121=Northwestern, 123=University of Chicago-Adult, 125=Stroger Hospital/Rush Univ., 126=University of Illinois at Chicago, 131=National Jewish – Adult, 142=University of Wisconsin – Adult, 143=Milwaukee, 151=University of Pittsburgh - Adult, 153=Case Western, 154=Allegheny General Hospital, 161=Washington University-Adult, 171=University of California (SF)-Adult, 182=Duke, 191=Wake Forest, 192=University of Virginia, 193=NC Clinical Research-Raleigh, 194=Emory University)

- 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 VIDA protocol at Visit 0 at a given site.

To assign an individual a participant ID number, select the next available blank entry on the VIDA Participant Assignment Log. This number will be the primary participant identifier used during the VIDA study; it should be used in all communications with the DCC. The participant ID number also should be used to label the participant's VIDA 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 at Visit 0, 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 (P1_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 0**
Assign participant ID number (P1_LOG)

Immediately following assignment of the participant's ID number on the VIDA Participant Assignment Log (P1_LOG), the protocol enrollment module should be accessed to enroll the participant formally in the VIDA 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 4**
Log assigned Loading Dose and Regular Dose capsule vial numbers (P1_LOG)
**Visits 5-9**
Log assigned Regular Dose capsule vial number (P1_LOG)

After accessing the randomization module at each visit to obtain new capsule vial numbers for the participant, the vial numbers must be logged on P1_LOG. This log provides a single reference for all of an individual's capsule vials over the life of the study. If a backup vial is assigned for a participant, it should be listed under the original vial for the appropriate visit on the log.

## 2.29 Participant Identification Card

The VIDA Participant Identification (ID) Card (P1_ID) provides a quick reference for the participant to use to monitor his/her asthma. It includes baseline peak flow and rescue use information for determining when an individual may be experiencing an asthma exacerbation and/or treatment failure conditions. The ID card also contains instructions for treatment of asthma attacks by physicians and emergency department personnel who may not be familiar with the VIDA study. The ID card should be carried by the participant at all times in a wallet or purse that is readily accessible.

**Visit 2**
Complete and distribute Participant ID Card (P1_ID)

Print a VIDA Participant Identification (ID) Card (P1_ID). Write the participant's name, VIDA protocol 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 value (in liters/minute). This value is obtained from Q1000 on the VIDA Baseline PEF and Rescue Use Values (P1_BASELINE) form at Visit 2.

Calculate 65% of the participant's Baseline PEF value (round to the nearest liter/minute). Enter the resulting value in the denoted blank fields on the back of the participant's ID card. This value aids the participant in recognizing when he/she may be having an asthma exacerbation and/or experiencing treatment failure conditions.

Fill in the participant's High Rescue Inhaler Use value in the spaces provided on the front and back of the ID card. The High Rescue Inhaler Use value is calculated by adding 8 to the value recorded in Q1010 on the P1_BASELINE form at Visit 2.

If the participant uses at least the number of puffs per day denoted by the High Rescue Inhaler Use value, for a two day period, then he/she has met treatment failure conditions. This value aids the participant in recognizing when he/she needs to be seen for additional treatment of his/her asthma.

Review the contents of the ID card with the participant and explain the use of the card. Stress to the participant that the Xopenex® (RESCUE) inhaler is the first-line treatment for asthma symptoms. 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.

**Visit 3**
Update Participant ID Card (P1_ID)

Ask the participant to present his/her VIDA Participant ID Card (P1_ID). Discard.

Print a new VIDA Participant Identification (ID) Card (P1_ID). Write the participant's name, VIDA protocol 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 value (in liters/minute). This value is obtained from Q1000 on the VIDA Baseline PEF and Rescue Use Values (P1_BASELINE) form at Visit 3.

Calculate 65% of the participant's Baseline PEF value (round to the nearest liter/minute). Enter the resulting value in the denoted blank fields on the back of the participant's ID card. This value aids the participant in recognizing when he/she may be having an asthma exacerbation and/or experiencing treatment failure conditions.

Fill in the participant's High Rescue Inhaler Use value in the spaces provided on the front and back of the ID card. The High Rescue Inhaler Use value is calculated by adding 8 to the value recorded in Q1010 on the P1_BASELINE form at Visit 3.

If the participant uses at least the number of puffs per day denoted by the High Rescue Inhaler Use value, for a two day period, then he/she has met treatment failure conditions. This value aids the participant in recognizing when he/she needs to be seen for additional treatment of his/her asthma.

## 2.30 Participant Status Report

A VIDA Participant Status Report has been developed to communicate important information from the VIDA database to the performance sites on a participant-specific basis. The report shows, in order of participant ID number, all participants enrolled in the VIDA trial at a specific performance site *for whom Visit 0 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 VIDA 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.

Pre-Rand Term: Indicator of whether or not the participant was terminated from VIDA prior to randomization at Visit 4. Sets to 'No' when P1_ELIG1 is entered; updates to 'Yes' if P1_TERM indicates that participant terminated prior to randomization.

Visit 0 Eligible: Indicator of whether or not the participant was deemed eligible on P1_ELIG1, as confirmed by the verification and validation processes at the DCC. Coded 'IP' (in progress) while data are being processed and updated to 'No' or 'Yes' pending the final, cleaned data.

Vitamin D Eligible: Indicator of whether or not the participant's Visit 0 serum vitamin D value was in the eligible range (<30 ng/ml). Actual vitamin D assay results will not be given to performance site personnel. Status will be coded 'IP' once the participant's Visit 0 vitamin D sample is logged into Biological Sample Tracking (BST). Status will be updated to 'No' or 'Yes' pending the assay values received from Channing Lab. Visit 1 should not be scheduled until the Vitamin D Eligible status is set to 'Yes.'

Note: If samples that are entered into BST do not arrive at the lab or are deemed unusable by the lab for any reason, they will be excluded from consideration. In either of these situations, the participant's status will become blank until new vitamin D samples are collected and entered into BST.

Green Mech Study Part.: Sets to 'Yes' when any of the sample types collected for the Green mechanistic study (also known as the Immune Substudy) are entered into Biological Sample Tracking for Visit 3. These include: UMET_CERN_NA_HEP, GREEN_NA_HEP, UMET_CERN_SST. Column will be blank for non-participants.

Note: If samples that are entered into BST do not arrive at the lab or are deemed unusable by the lab for any reason, they will be excluded from consideration. In either of these situations, the participant's status will become blank and he/she will be regarded as a non-participant of the mechanistic study. No Visit 6 samples should be collected for these individuals. There is no window to redraw Visit 3 samples that are compromised.

Sputum Status (V3): This column shows the status of the participant's Visit 3 sputum sample and determines whether he/she is eligible to undergo Visit 6 sputum induction. Individuals (up to a total of 200) will be eligible for the Visit 6 sputum induction only if their Visit 3 sample was adequate for processing, shipment to San Francisco, and reading and had <80% squamous cells and an eosinophil count available (from the overreader in San Francisco). Status levels include:

- Ineligible/Not Done: SPUTUMCHK form indicates that participant did not attempt sputum induction at Visit 3.
- Inadequate/Not Processed: SPUTUM form indicates that sample was inadequate for lab analysis.
- Inadequate/Not Shipped to SF: SPUTLAB form indicates that sample was inadequate for shipment to San Francisco.
- Inadequate/Read: SPUTREAD form indicates that sample had at least 80% squamous cells and/or eosinophil count is missing.
- Adequate: The Visit 3 sputum sample was deemed adequate by the overreader. Participant may proceed with the Visit 6 sputum induction, if eligible for the procedure at the visit.

Note: As the Network approaches 200 Visit 6 sputum inductions, clearance from the DCC may be required prior to scheduling a Visit 6 sputum induction for those whose Visit 3 samples were adequate. The DCC will monitor the distribution of treatment arm for those who complete the Visit 6 sputum induction to ensure that approximately equal numbers in both arms are represented Network-wide.

Randomized: Participant's randomization status. Updates to 'Yes' when the participant is randomized at Visit 4. Will set to 'No' for those who are Visit 0 Eligible and Vitamin D Eligible but terminate prior to randomization.

Visit 4 Vials: Sets to capsule vial numbers assigned to the participant at Visit 4 through the randomization module. A loading dose (L vial) and regular dose (R vial) number are listed.

Visit 5-9 Vials: Sets to regular dose capsule vial numbers assigned to a participant at each of the referenced visits (through randomization module). If a backup vial is assigned for a particular visit, its number will show under the original vial's number.

Post-Rand Term: Indicator of whether or not the participant terminated from VIDA after randomization and before completion of Visit 10. Sets to 'Yes' if participant terminates early (when P1_TERM is entered); sets to 'No' when a randomized participant completes the trial.

Completed Study: Indicator of whether or not the participant completed the VIDA trial through Visit 10. Sets to 'Yes' when a participant's P1_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 at V0 and awaiting eligibility confirmation (waiting for final Visit 0 Eligible and/or Vitamin D Eligible status)
2. Enrolled at V0 and ineligible (these individuals are awaiting entry of a P1_TERM form)
3. V0 term

4. Enrolled in screen phase (V0-V2) (individuals who were deemed eligible at Visit 0 who do not have a P1_TERM form entered and have not yet completed Visit 2)
5. Screen phase term (V1-V2)
6. Enrolled in run-in (V2-V3) (individuals who have Visit 2 data entered, no P1_TERM form, and have not yet completed Visit 3)
7. Run-In term (V2-V3)
8. Enrolled in OCS response period (V3-V4) (individuals who have Visit 3 data entered and no P1_TERM form and are not yet randomized)
9. OCS response period term (V3-V4)
10. Randomized and currently active
11. Post-randomization dropout
12. Completed VIDA

The bottom of the Participant Status Report gives a frequency table for the ‘current status’ variable.

## 2.31 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[12] (PSS-10) will be used in the VIDA study. The 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 2, 10**
Administer Perceived Stress Scale (PSS_10)

The administration of the PSS-10 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 PSS 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 on that day, a new PSS-10 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

[12] 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.

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 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 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.

## 2.32 Phone Contacts

### Visits 4 (week 8), 5 (week 14)

The VIDA protocol designates 6 weeks between Visits 4 and 5 and between Visits 5 and 6. 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, formal phone contacts should be scheduled between these visits, approximately 3 weeks following Visit 4 and Visit 5. Phone contacts afford the coordinator an opportunity to determine whether the participant has met treatment failure criteria between visits and to address the participant's concerns regarding his/her asthma control.

Phone contacts are documented on the VIDA Phone Contact Form (P1_PHONE_CONTACT). 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 4. 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 P1_PHONE_CONTACT.

## 2.33 Physical Exams

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 (LEXAM_ADULT) form and brief exams are documented on the Adult Short Physical Exam (SEXAM_ADULT) form. 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 VIDA 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.

In addition to regular physical exams, additional physical measurements including height and weight, and waist, hip and neck circumference, are taken at various points during each study. These measurements are documented on the Adult Body Measurements (BODYMEAS_ADULT) form 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 VIDA protocol.

**Visits 1, 10, 90-92 and regular visits when participant meets treatment failure criteria**
Perform long physical exam (LEXAM_ADULT)

A long physical exam is required at Visit 1 in order to ensure that it is safe and appropriate for each participant to enroll in the VIDA study. A long exam is required at Visit 10 to ensure that the participant leaves the study in good health with plans for follow-up care, as needed. Long exams are also required at treatment failure visits to document the health status of the participant at the time of treatment failure. This holds

for all visits at which a participant meets treatment failure criteria. If a short exam is normally required at a visit when the participant meets failure criteria, then the short exam should be replaced by a long exam. Follow the order of procedures on the appropriate visit procedure checklist.

For the VIDA trial, participants must have interaction with a physician at Visits 1 and10, even if the physician is not performing the long exam. Although a long physical exam is required during treatment failure visits, physician interaction at these visits is not mandatory. A physician should be consulted, as warranted.

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.

**Visits 6, 8**
Perform short physical exam (SEXAM_ADULT)

A brief physical exam is conducted at Visits 6 and 8, prior to initiating an inhaled corticosteroid dose taper if the participant qualifies.

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.

**Visits 1, 10**
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. BMI from Visit 1 is used as a stratification variable for randomization at Visit 4. See the Randomization discussion in this section for further details.

Note that height is captured on the BODYMEAS_ADULT form for everyone at Visit 1 and Visit 10. Individuals who are less than 21 years of age will have their heights updated at every visit involving a baseline spirometry session until the point when they turn 21. Updated heights are recorded on the VIDA Pulmonary Procedure Checklist (P1_PULMONARYCHK) form for these individuals.

## 2.34 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 VIDA study, she must be terminated from study participation immediately.

**Visits 2, 3, 6, 10**
Complete Urine Pregnancy Test form (PREG_TEST)
Administer urine pregnancy test, if necessary

At Visits 2 and 6, the Urine Pregnancy Test (PREG_TEST) form must be completed and a urine pregnancy test administered, if necessary, only for female participants who are proceeding with a methacholine challenge at the visit; no form or pregnancy test is required for female participants who are not eligible to proceed with the methacholine challenge at these visits.

At Visits 3 and 10, the PREG_TEST form is required for all female participants, regardless of their child-bearing potential or whether they are performing a methacholine challenge at Visit 3. 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. 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. 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.***

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 Visits 2, 3, and 6. Pregnant women should not perform methacholine challenges. In addition, pregnant or nursing participants are ineligible for the VIDA protocol.

If a woman is found to be pregnant at any time during the study, she is ineligible for continued participation. Pregnant women should be terminated from further study participation immediately. Participants who become pregnant during the study should have a VIDA Termination of Study Participation (P1_TERM) form submitted to the DCC as soon as possible. Pregnancy should not be recorded and reported as an adverse event.

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

## 2.35 Randomization

**Visit 4**
Randomize the participant
Log assigned Loading Dose and Regular Dose capsule vial numbers (P1_LOG)

VIDA is a parallel arm trial during which each participant is randomized at Visit 4 to receive one of the following regimens for the remainder of the trial:

1. Open-label Alvesco® (ciclesonide) ICS + active vitamin D (100,000 IU loading dose AM after randomization, then one 4,000 IU capsule daily)

OR

2. Open-label Alvesco® (ciclesonide) ICS + placebo (placebo loading dose AM after randomization, then one placebo capsule daily)

The goal is to randomize 400 participants Network-wide (approximately 45 per clinical center partnership). Randomization will be performed within the nine partnerships, not within a given performance site.

In addition to stratifying on partnership, the VIDA randomization also stratifies on body mass index (BMI) (≤25 versus >25) and race (African American versus other race) to assure equal distributions of treatment assignments within each combination of partnership, BMI category and race category. BMI will be calculated on the basis of the height (Q1000) and weight (Q1010) recorded on the participant's Adult Body Measurements (BODYMEAS_ADULT) form at Visit 1. The participant's race will be obtained from Q1150 (primary racial identification) on his/her AsthmaNet Registry form and on his/her Registry Report. Study personnel do not need to enter the BMI and race information into the randomization module; it will be obtained directly from the AsthmaNet database.

At the end of Visit 3, if the participant meets all of the eligibility requirements documented on VIDA Eligibility Checklist 5 (P1_ELIG5), he/she is technically eligible to be randomized a week later at Visit 4. Results of his/her urine calcium/creatinine ratio from Visit 3 must be available to confirm his/her eligibility prior to Visit 4. No formal eligibility criteria are assessed at the time of Visit 4. In the rare event that the participant experiences a treatment failure or exacerbation event between Visit 3 and Visit 4 (while on study prednisone), he/she would be considered ineligible for randomization.

At Visit 4 the study coordinator should access the VIDA Randomization Module on the secure AsthmaNet website and enter the appropriate visit number (i.e., 4), the participant's VIDA ID number, and the performance site at which the participant is being randomized to complete the randomization in the system. At this point, the system is assigning the participant to the regimen that he/she will receive for the rest of the study. Capsule vials from the designated performance site that match the person's randomized arm will be assigned. At Visit 4 the module will display an assigned loading dose vial number (L__ __ __) and an assigned regular dose capsule vial number (R __ __ __ __). These vial numbers should be recorded on the VIDA Participant Assignment Log (P1_LOG) in the V4 column. Information on the participant's assigned vial numbers at each visit will be included on the VIDA Participant Status Report.

It should be noted that participants can be randomized in the VIDA randomization module at Visit 4 only if <u>all</u> of the following criteria are met:

1) The participant's VIDA ID number is enrolled in the VIDA protocol.
2) The participant's Visit 0 packet, including Visit 0 eligibility data, has been entered at the performance site (only first entry required). The Visit 0 eligibility form (P1_ELIG1) must indicate that the participant is eligible (Q1280=1).
3) The participant's Visit 0 vitamin D value must be present in the database and confirmed to be <30 ng/mL.
4) 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 (P1_ELIG2, P1_ELIG3) must indicate that the participant is eligible (Q1070=1 and Q1060=1, respectively).
5) The participant's BODYMEAS_ADULT form from Visit 1 must be entered (only first entry required) and Q1000 and Q1010 must be present to compute BMI.
6) 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 (P1_ELIG4) must indicate that the participant is eligible (Q1030=1 and (Q1130 missing or 1) and (Q1190 missing or 1) and Q1220=1).
7) No VIDA Termination of Study Participation (P1_TERM) form has been entered for the participant.
8) At least 28 days have elapsed between Visit 2 and the day the participant is being randomized.

See Section 3 of this manual for details on accessing and interacting with the VIDA randomization module.

Note that treatment assignments in the VIDA study are double-blind. That is, neither the participant, nor performance site personnel, will be aware of the status of the participant's capsules from Visit 4 through Visit 10 (study phases I, IIa and IIb). The

majority of DCC personnel are also blinded to the treatment assignments while the study is ongoing. All parties are aware that the Alvesco® (80 mcg per puff, 2 puffs BID) is open-label (i.e., active drug) for the duration of the study.

**Visits 5-9**
Generate new Regular Dose capsule vial number via randomization module (may occur up to 5 calendar days ahead of a visit)
Log assigned Regular Dose capsule vial number (P1_LOG)

At Visits 5-9, clinical personnel must utilize the VIDA Randomization Module to generate a new regular dose capsule vial number from which the participant will take his/her daily doses until the next regularly scheduled visit. To prepare for an upcoming visit, the vial number may be generated up to five calendar days ahead of a visit. If the randomization module is accessed to produce a vial number more than five calendar days before the visit is completed, a protocol violation may be assigned, depending on the circumstances.

The study coordinator should access the VIDA Randomization Module on the secure AsthmaNet website and enter the applicable visit number from a dropdown menu, the participant's VIDA 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 regular dose capsule vial number corresponding to his/her assigned treatment arm. The resulting capsule vial number should be recorded on the VIDA Participant Assignment Log (P1_LOG) under the appropriate visit number.

Information on the participant's assigned vial numbers at each visit will be included on the VIDA Participant Status Report.

It should be noted that the following criteria must be met at Visits 5-9 before a regular dose capsule vial number will be displayed:

1) The participant must have been randomized via the VIDA Randomization Module at Visit 4.
2) The participant must not have been terminated from the study (i.e., no P1_TERM form has been entered).
3) At Visit 6: A minimal amount of time must have passed since Visit 4.
4) At Visits 7 & 8: the participant must have been assigned a regular dose capsule vial a Visit 6 (Visit 6 cannot be missed).
5) At Visit 8: A minimal amount of time must have passed since Visit 6.
6) At Visit 9: the participant must have been assigned regular dose capsule vials at Visits 6 and 8 (Visits 6 and 8 cannot be missed).

## Backup capsule vials

If a participant loses his/her capsule vial(s) between visits, then he/she will require the assignment of a new (backup) capsule vial(s). To generate a new capsule vial number, the study coordinator should access the VIDA Randomization Module on the secure AsthmaNet website and enter the applicable visit number (i.e., the same visit number for which the previous (lost) capsule vial number was generated) from a dropdown menu, the participant's VIDA 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 a capsule vial 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 generate a new capsule vial number, it will be displayed. If backup capsule vials are being requested for Visit 4, the module will ask the coordinator to specify the types of vials that need to be replaced: Loading dose capsule vial and/or regular dose capsule vial. It should be a rare occurrence for loading dose capsule vials to need to be replaced given the short window between Visit 4 and when the capsules are taken the next morning.

Backup capsule vial numbers should be recorded on the VIDA Participant Assignment Log (P1_LOG) under the appropriate visit number. A VIDA Scheduled Capsules (P1_MED) form should be completed and data entered any time a backup vial is dispensed to a study participant. See the Study Medications discussion in this section and section 4 for further details.

## Backup randomization procedures

In the rare event that the VIDA Randomization Module is unavailable during any visit when it is required (i.e., visits 4-9), clinical 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. After-hours coverage will be defined at a later date prior to the first VIDA randomization visit.

It is extremely important that capsule vials are assigned using the VIDA Randomization Module and that the correct vials are used for dispensation of study capsules at the performance site. Randomly choosing an available capsule vial at Visits 5-9 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. If study capsules are dispensed to a participant from an incorrect vial, a protocol violation will be assigned.

## 2.36 Recruitment

VIDA visits will commence on April 18, 2011. Nine clinical center partnerships composed of 16 participating performance sites will recruit for VIDA.

A recruitment period of 18 months has been established for VIDA. Each clinical center partnership should strive to maintain Visit 0 screen percentages of 50% female participants and at least 33% minority participants over the recruitment period.

The gender and minority status of individuals screened at Visit 0, individuals enrolled in the run-in period, and individuals randomized in VIDA will be summarized by clinical center partnership and, within each partnership, by performance site on the VIDA accrual report. This report will be available on the secure AsthmaNet website in the Reports: Accrual: VIDA folder shortly after screening visits begin.

Target sample sizes for each partnership are based on the number of participants who are successfully screened, entered into the run-in, and subsequently randomized in the VIDA trial. Each of the nine clinical center partnerships is expected to randomize approximately 45 participants for a Network total of 400 randomized participants. As of September 2012 the Steering Committee and Data and Safety Monitoring Board gave approval for partnerships to randomize up to a maximum of 130% of the original goal (i.e., 58 randomized participants). It is expected that as many as 1600 participants (approximately 178 per partnership) may need to be screened at Visit 0 in order to enroll 800 participants in the run-in period (approximately 89 per partnership) to yield 400 randomized participants.

Approximate VIDA Timelines (pending receipt of IRB approval notices for the March 2011 modified protocol (version 20.0) from five of the nine partnerships):

| | |
|---|---|
| April 18, 2011: | First participant screened at Visit 0 |
| June 6, 2011: | First participant randomized at Visit 4 |
| Oct. 22, 2012: | Final screening visit (Visit 0) |
| Dec. 10, 2012: | Final randomization visit (Visit 4) |
| June 24, 2013: | Final participant visit (Visit 10) |

## 2.37 Re-Enrollment

Participants who do not successfully complete the VIDA screening, run-in, and oral corticosteroid response phases for reasons that may be overcome with time or additional training (e.g., lack of compliance, use of excluded medications or high doses of vitamin D or calcium, treatment failure experienced during the run-in for reasons that may be remedied, etc.) may be suitable candidates to re-enroll in VIDA for a second attempt. Randomized participants who drop out early may not re-enroll in the trial.

**Visit 0 Pre-Screen Failures**

Participants who do not qualify for the VIDA study at Visit 0 for reasons that may be overcome with time (e.g., insufficient vitamin D or calcium washout, respiratory tract infection in past 4 weeks, etc.) may be invited to repeat Visit 0 at a later date. Data collected during the unsuccessful Visit 0 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 0 packet should be stored at the performance site in a section of folders denoted as 'VIDA Visit 0 Pre-Screen Failures.'

Participants who present at the performance site for a second attempt at screening should repeat all of the Visit 0 procedures as listed on VIDA Visit Procedure Checklist A (P1_VISITA). A new visit packet should be completed.

When re-enrollment occurs, the following procedures apply:

- The participant must be given a new participant ID number from the Participant Assignment Log (P1_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 VIDA database. For information on the protocol enrollment process, refer to section 7 of the AsthmaNet General Manual of Operations.

- The participant must read and sign new copies of the VIDA and BioLINCC informed consent documents. The documents signed at the initial enrollment should reside in the folder created for the participant's original ID number. The new 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 Participant Contact Information (CONTACT_ADULT) form should be reviewed and updated by the participant. A photocopy should be made and stored with the participant's original Visit 0 packet. The original form with updates should be stored in his/her new study folder.

- A new Visit 0 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 0 and Prior to Randomization at Visit 4**

Once a participant is deemed eligible at Visit 0, he/she is formally enrolled in the VIDA study. The data collection forms from Visit 0 should be entered into the study database and forwarded to the DCC.

If a participant withdraws consent or is deemed ineligible during subsequent screening visits or during the run-in or oral corticosteroid response phases, then he/she must be formally terminated from the study. A VIDA Termination of Study Participation (P1_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, urine, or sputum samples were collected during the visit, they should be sent to the appropriate labs according to the instructions in this manual. 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 VIDA.

Note that participants who are withdrawn from the run-in or oral corticosteroid response period of the study due to treatment failure or asthma exacerbation may be re-enrolled one time at the discretion of the local investigator. If the participant experiences a second treatment failure or exacerbation during these periods of the study, he/she is ineligible for further study participation and should not be re-enrolled a third time.

Participants who are good candidates for re-enrollment must re-enter the VIDA study starting anew at Visit 0.

The following guidelines apply when the participant is re-enrolled:

- The participant must be given a new participant ID number from the Participant Assignment Log (P1_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 VIDA database. For information on the protocol enrollment process, refer to section 7 of the AsthmaNet General Manual of Operations.

- The participant must read and sign new copies of the VIDA and BioLINCC informed consent documents. The documents signed at the initial enrollment should reside in the folder created for the participant's original ID number. The new 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 Participant Contact Information (CONTACT_ADULT) form should be reviewed and updated by the participant. A photocopy should be made and stored with the participant's original Visit 0 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 packet from the participant's original enrollment. The form with the handwritten updates should be stored in his/her new study folder.

  For participants who complete the run-in and, possibly, oral corticosteroid response period before withdrawing from the VIDA trial on their prior enrollment: The Alvesco® and prednisone study medications that were administered as part of the VIDA trial should not be considered when completing or updating the PRIOR_TRT form. The participants' usual asthma treatment off-study should be entered on the form.

- Participants who underwent skin testing at Visit 2 prior to their termination may have their previous AsthmaNet skin test data reused. It is not necessary to repeat the skin test for these participants. See the Skin Testing discussion in this section for additional details.

- If the participant completed a methacholine challenge at Visit 2 prior to his/her termination and the challenge was done within 6 months of Visit 2 during a subsequent enrollment, then the challenge may be used as source documentation in lieu of another test. See the Eligibility Criteria and Methacholine Challenge discussions in this section for further details.

- All study procedures must be carried out anew, with the exceptions noted above, beginning with Visit 0. 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 VIDA 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, urine, and sputum samples must be obtained at the applicable visits.

### Special Provisions for Participants Who Were Disqualified Due to High $FEV_1$

Under the original VIDA protocol, individuals were considered ineligible to proceed if their $FEV_1$ exceeded 90% of predicted (for those who reversed at least 12% after four puffs of levalbuterol at Visit 1) or if their $FEV_1$ exceeded 85% of predicted (for those who did not reverse 12% at Visit 1). In January 2012 the DSMB approved the Steering Committee's request to remove the upper limit on the $FEV_1$ requirements during the screening period and run-in (Visits 1, 2, and 3). The DCC implemented this change in the database on February 14, 2012. The following re-enrollment provisions pertain only to those individuals who are re-enrolling because their $FEV_1$ was too high according to the original protocol; they do not pertain to individuals who were excluded for other reasons.

It should be noted that no participants may be re-enrolled under the modified eligibility criteria until the clinical site receives written IRB approval for the modified protocol. Although no changes were made to the informed consent document as a result of the protocol changes, all participants who choose to re-enroll must be re-consented at the time of their study re-entry. It should be explained to them that they will need to repeat some of the procedures they had completed previously as part of their re-enrollment.

Requirements for re-enrollment depend on the visit at which the participant was terminated and the age of his/her Visit 0 vitamin D sample. Because the eligibility criteria require that no more than 8 weeks elapse between Visit 0 and Visit 2, most individuals will need to follow normal re-enrollment procedures, beginning anew at Visit 0 with a new participant identification (ID) number as outlined above. However,

participants who were terminated at Visit 1 or Visit 2 whose Visit 0 vitamin D values are less than 8-weeks old may qualify to be re-entered into the trial at the visit at which they were disqualified (i.e., either Visit 1 or Visit 2). If the participant can re-enter the trial and complete Visit 2 in the 8-week window, the following procedures should be completed:

- For individuals originally disqualified at Visit 1:
    - Participant must be re-consented.
    - Participant will retain his/her original participant ID number.
    - Visit 0 will not be repeated.
    - Visit 1 will be repeated. Medical history forms should be reviewed and updated as described above. Remaining visit procedures must be repeated per the visit checklist. The safety laboratory tests and long physical exam must be repeated.
    - If the participant reverses at least 12% in response to four puffs of levalbuterol at the visit, or if he/she has source documentation of a qualifying $PC_{20}$ from an AsthmaNet methacholine challenge performed in the past 6 months, then coordinators may opt to combine Visit 1 and Visit 2 such that the participant enters the run-in the same day. See Appendix 2A of the VIDA Manual of Operations for details.
    - If the participant does not meet reversal criteria and does not have a valid $PC_{20}$ from source documentation, then Visit 2 will be scheduled for another day within the 8-week window of Visit 0.

- For individuals originally disqualified at Visit 2:
    - Participant must be re-consented.
    - Participant will retain his/her original participant ID number.
    - Visit 0 will not be repeated.
    - Visit 1 will not be repeated.
    - Visit 2 will be repeated. Skin testing does not need to be repeated, as described above.
    - Participant must qualify on $PC_{20}$, either through a challenge performed at the time of Visit 2, or on the basis of valid source documentation.

After a participant has re-entered the study successfully at Visit 1 or Visit 2 the DCC should be notified of his/her participant ID and the visit at which he/she resumed the study. The DCC will verify the Visit 0 – Visit 2 time constraint. If the 8-week window is met, the DCC will remove the VIDA Termination of Study Participation (P1_TERM) form and the applicable visit packet (Visit 1 or Visit 2) from the database. Dates of form receipt and verification at the DCC will be removed for the Clinical Adverse Event (AECLIN) and Concomitant Medications for Asthma/Allergy and Adverse Events (CMED) forms corresponding to the re-entry visit. These edits will re-open those forms for data entry and corrections at the clinical site. Edits should be made to the copies of the forms retained at the site. When the participant terminates the study following this enrollment, all AECLIN and CMED forms from the re-entry visit through the end of the individual's study participation should be forwarded to the DCC for verification.

The data changes outlined above must be made by the DCC before new data can be entered for a re-enrolling participant.

Coordinators are responsible for documenting concomitant medications and adverse events for all participants from their original consent date at Visit 0 through the end of their study participation.

Note: Individuals who were disqualified due to high $FEV_1$ at Visit 1 or Visit 2 whose Visit 0 vitamin D sample is outside the 8-week window required between Visit 0 and Visit 2 may be invited to re-enroll in the study following normal re-enrollment procedures outlined above.

Note: Individuals who were disqualified due to high $FEV_1$ at Visit 3 may be invited to re-enroll in the study following normal re-enrollment procedures outlined above. These individuals must restart the study at Visit 0 with a fresh vitamin D sample.

### After Randomization in VIDA

Participants who withdraw consent after they have been randomized in the VIDA study at Visit 4 are NOT eligible to re-enroll. Each participant can contribute only one set of data for the analysis.

## 2.38 Registration

**Visit 0 or Earlier**
Register participant in AsthmaNet Registry

Before a participant can be enrolled in the VIDA 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 VIDA 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 0**
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 (P1_VISITA) in the participant's Visit 0 packet.

## 2.39 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 VIDA, it is present in the Visit 10 and Visit 88 packets. In addition, the questionnaire is also posted appended to the single VIDA Termination of Study Participation (P1_TERM) form for use with participants who terminate from the study before Visit 10 and do not have a Visit 88.

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 VIDA participants who successfully complete Visit 0 and have a serum sample sent for vitamin D analysis 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 VIDA 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 0, 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 VIDA Termination of Study Participation (P1_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 P1_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.

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.

The DCC will provide periodic reports of the data from the questionnaire for the QCC and the coordinators/investigators to review. Response rates will be compared across the performance sites to ensure that all sites are participating fully in the survey process.

## 2.40 Serum Calcium and Creatinine/eGFR Laboratory Tests

**Visit 1**
Obtain blood sample for serum calcium and creatinine/eGFR determinations (local lab) (one 3.5 ml SST) (P1_LAB, P1_ELIG3)

Near the end of Visit 1, for eligible participants, fill one 3.5 ml SST (serum separator tube) with blood for measurement of serum calcium and creatinine to determine if the participant meets related eligibility criteria. Samples will be analyzed at the performance site's local lab. Samples should be collected, labeled, and processed according to local lab requirements. In general, samples should be transported to the lab within 2 hours of the blood draw to yield reliable and accurate results.

Note that fasting is not required for these tests for VIDA.

**Total serum calcium**

Total serum calcium tests are being done at Visit 1 to ensure that participants do not have elevated levels (>10.2 mg/dl) at baseline, prior to starting study drug (vitamin D or placebo). Elevated serum calcium values later in the trial may be indicative of hypervitaminosis D. See below for further details on post-randomization serum calcium tests.

Drugs that can increase calcium levels include: calcium salts (found in some nutritional supplements and antacids), lithium, thiazide diuretics, thyroxine, and vitamin D.

Record the participant's serum calcium value in Q1040 on the VIDA Laboratory Results (P1_LAB) form. Note that values must be recorded in mg/dl. 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.

If the participant's serum calcium value is elevated, record this fact as an adverse event on the Clinical Adverse Events (AECLIN) form using ICD-9 code 275.42 (hypercalcemia). The date of the lab adverse event should correspond to the date the blood sample was collected.

**Serum creatinine**

Serum creatinine tests are being done at Visit 1 in order to estimate the participant's glomerular filtration rate (eGFR). The eGFR is a measure of how efficiently the kidneys

are filtering a waste product called creatinine which is formed by the normal breakdown of muscle cells. Healthy kidneys take creatinine out of the blood and put it into the urine to leave the body. When the kidneys aren't working as well as they should, creatinine builds up in the blood. Roughly, the eGFR corresponds to the percent of kidney function a person has available. Individuals whose Visit 1 eGFR is less than 30 ml/min are ineligible to continue in the study, as they have indications of impaired renal function.

Record the participant's serum creatinine value in Q1000 on the P1_LAB form. Note that values must be recorded in mg/dl. 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.

Several equations exist for computing the eGFR. The VIDA trial will employ the Cockcroft-Gault equation which uses the participant's serum creatinine measurement, along with age, weight, and gender to estimate GFR as follows:

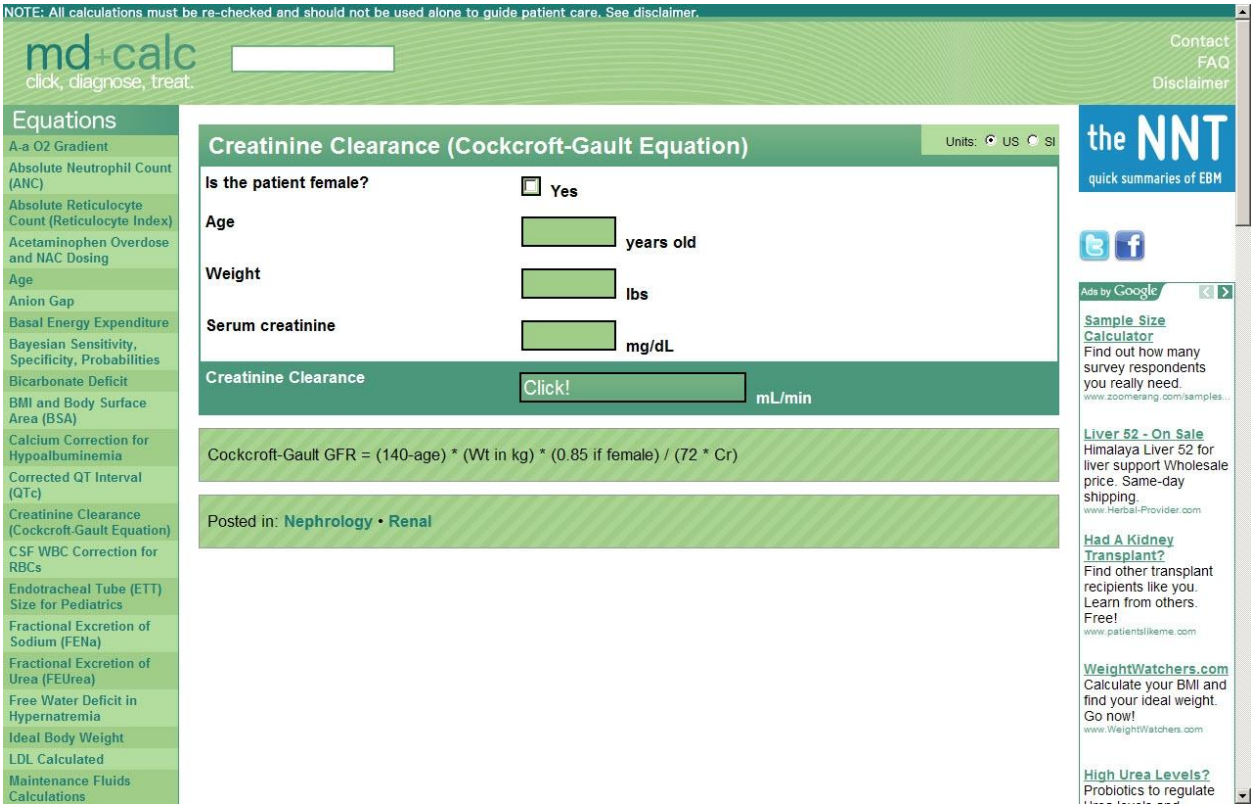
$$\text{eGFR (male)} = \frac{(140 - \text{age}) * (\text{weight})}{\text{creatinine} * 72}$$

where age is in years, weight is in kilograms, and serum creatinine is in mg/dl.

$$\text{eGFR (female)} = \text{eGFR (male)} * 0.85$$

To facilitate the eGFR calculation, the on-line calculator at mdcalc.com should be used. The full link to the calculator is:

http://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation




Before using the calculator the coordinator should complete the fields in the first 'Clinic Use Only' box on the P1_LAB form. This box contains spaces to record the participant's gender, current age (in whole years), and weight (in pounds), as required for input into the calculator. Note that the calculator requires weight in *pounds*. The weight measured at Visit 1 and recorded on the Adult Body Measurements (BODYMEAS_ADULT) form should be converted from kilograms to pounds by multiplying by 2.2. The converted weight should be recorded in the 'Clinic Use Only' box.

Enter the information from the P1_LAB form into the calculator. Verify that information was entered correctly, then click in the 'Creatinine Clearance' box. The participant's computed eGFR value will appear. Record this value rounded to one decimal place in Q1010 on the P1_LAB form.

Submit the original lab report with the serum creatinine value with the participant's Visit 1 packet. Ensure that all identifying information (name, medical record number, etc.) has been blackened out and the participant's VIDA ID number has been written at the top of the report. Retain a copy of the lab report in the participant's study folder at the performance site.

See section 4 of this manual for further details regarding completion of the P1_LAB form.

**Post-randomization total serum calcium determinations (as-needed for safety assessment)**

Following randomization and the initiation of blinded study capsules (4,000 IU vitamin D or placebo), participants will be monitored for hypervitaminosis D by having urine calcium to creatinine ratio ($U_{Ca}$:$U_{Cr}$ ratio) tests performed at Visits 6, 8 and 10. See the discussion of Urine Calcium:Creatinine Ratio Laboratory Test in this section for details on this test.

If a participant's $U_{Ca}$:$U_{Cr}$ ratio is elevated (> 0.37 when measured in mg:mg or >1.0 when measured in mmole:mmole), the participant will be instructed to increase hydration and a repeat measurement will be obtained 30 days later. If the repeat ratio is elevated, then the participant will be instructed to hold study capsules and to have serum calcium and serum vitamin D (25(OH)D) levels obtained. Results of the serum calcium test should be recorded on the VIDA Laboratory Results (P1_LAB) form in Q1040. If the participant's serum calcium level is elevated (>10.2 mg/dl), record an adverse event using ICD-9 code 275.42 (hypercalcemia) on the Clinical Adverse Events (AECLIN) form; the date of the lab adverse event should correspond to the date the blood sample was collected. If either the serum calcium level or vitamin D level is elevated, the participant will stop study drug for the remainder of the trial. If both the serum calcium and vitamin D levels are normal, then the participant will resume study drug. All changes in study capsule dosing must be recorded on a VIDA Change in Study Medications (P1_CHANGE_MEDS) form.

Submit the original lab report with the participant's data. Ensure that all identifying information (name, medical record number, etc.) has been blackened out and the participant's VIDA ID number has been written at the top of the report. Retain a copy of the lab report in the participant's study folder at the performance site. See section 4 in this manual for information on data entry of the P1_LAB form in these circumstances.

## 2.41 Serum Vitamin D Laboratory Test

**Visits 0, 6, 8, 10, 88, as-needed for safety follow-up between visits 6 and 10, and at early post-randomization termination visits (5-9)**
Obtain blood sample for serum vitamin D determination (one 5 ml red top tube)

**Supplies**

The following supplies are required to collect a vitamin D serum sample for the VIDA study:

| Item | Vendor | Catalog # | # Per Collection |
|---|---|---|---|
| 5 ml red-top vacutainer (BD #367814) | Fisher Sci. | 02-687-94 | 1 |
| Red-top vacutainer label (Avery #5160) | Staples | 209882 | 1 |
| 1.8 ml cryovial (Nunc #363401; no substitutes) | Fisher Sci. | 12-565-170N | 1 |
| Cryovial barcode label (KissCut Tough-Tags 1.28”x0.50”) | Diversified Biotech | TTLW-KK-20 | 1 |
| Sterile pipette | | | 1 |

Fill one 5 ml red-top 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: VIDA: Labels folder. Complete an entry for the blood draw on the VIDA Vitamin D Serum Sample Log (P1_VITD_SAMP_LOG). Complete the participant’s VIDA ID number, visit number, and collection date/time.

Allow the blood sample to clot at room temperature between 1 and 2 hours. At the end of the clotting period, complete the time spinning is initiated on P1_VITD_SAMP_LOG. Centrifuge the clotted blood at a minimum of 2800 RPMs for 15 minutes to separate the serum from the red blood cells. Using a sterile pipette, carefully remove the serum from above the clot and place it into a 1.8 ml Nunc cryovial. *The exact cryovial specified in the table above must be used for compatibility with Channing Lab’s equipment; no substitutions are allowed.*

Label the serum vial with a barcode label (KissCut Tough-Tags) generated through the Biological Sample Tracking (BST) module of the AsthmaNet database management system. The barcode label includes a preprinted 5-digit barcode number, starting with 10000, which is unique for every VIDA participant-sample. VIDA-VITD is printed on the label to identify the sample type. The sample type associated with the serum tubes in the BST module is "VIDA VITAMIN D." The last three digits of the participant's VIDA ID number should be written in the space on the side of the cryovial with a Sharpie marker. This extra identification information is necessary to ensure that the correct participant ID is linked to the barcode number in the database. A sample VIDA vitamin D serum barcode label follows:


Complete the cryovial barcode number and sample volume on P1_VITD_SAMP_LOG.

Immediately after labeling the serum vial, access the BST module and scan the barcode to insert a record for the sample. Input the participant ID information to link the barcode to the correct VIDA participant. It is imperative that all samples be scanned the day of collection so that the associated dates and times of the serum samples are available in the BST database. 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.

Store the serum sample at 4 degrees Celsius (refrigerated) until the shipment day. Record the date/time the sample is placed in the refrigerator and the current refrigerator temperature on P1_VITD_SAMP_LOG. Serum may be refrigerated no longer than 4 days prior to analysis for vitamin D level at Channing Lab.

A minimum of 0.30 ml of serum is required for the vitamin D assay. If a vial contains excess serum, Channing Lab staff will aliquot the extra serum into additional 0.5 ml cryovials and will store them at -80 degrees Celsius for future use by AsthmaNet researchers.

## Preparing Samples for Shipment to Channing Lab (every Monday and Thursday)

Sites should ship all available samples to Channing Lab each Monday and Thursday, priority overnight for AM receipt in Boston.

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, shipper 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.

An export file containing shipment information in .csv format will be e-mailed automatically to Channing Lab (to Roxanne Kelly (Roxanne.kelly@channing.harvard.edu) and Dan Cossette (redac@channing.harvard.edu)) following the performance site's confirmation of the shipment.

## Packaging Samples for Shipment to Channing Lab (every Monday and Thursday)

Before packaging available samples for shipment, they must be scanned into the BST system and an inventory of the shipment generated 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 |
|---|---|---|---|
| Styrofoam mailer (ThermoSafe 440) | Fisher Sci. | 03-528-10 | 1 |
| Corrugated cardboard mailing sleeve (Thermosafe 440KD) | Fisher Sci. | 03-520-7 | 1 |
| Convoluted foam padding (Thermosafe 441) | Fisher Sci. | 03-5206 | 2 |
| Biohazard specimen bags 6”x10” (Fisherbrand) | Fisher Sci. | 19-075-388D | 2 |
| Desiccant (Multisorb Drimop 0.5g liquid absorber 0201083CG08) | Fisher Sci. | NC9905534 | 1 for every 10 ml of sample (round up) |
| Gel packs (Thermosafe 8 oz 429) | Fisher Sci. | 03-528-6 | 1 |
| Packaging tape | Staples | 380107 | |
| Exempt Human Specimen labels Therapak 2.5”x2” | Fisher Sci. | 22-130-070 | 1 |
| Biohazard labels (large) 3”x3” | Fisher Sci. | 18-999-936 | 1 |
| Shipment inventory from BST | | | 1 |

Assembly instructions:

1. Place cryovials in a biohazard specimen bag. Add 1 desiccant pack for every 10 ml of sample and seal the bag tightly.
2. Further seal the specimen bag by securely taping it closed with packaging tape.
3. Place the sealed specimen bag inside a second biohazard specimen bag and seal the bag tightly.
4. Place 1 frozen gel pack in the bottom of the Styrofoam mailer. Cover with one sheet of the convoluted foam padding (egg carton side up).
5. Place the specimen bag on top of the foam padding and cover it with a second sheet of foam padding, egg carton side down. The specimen bag should be sandwiched between the sheets of foam.
6. Place a copy of the shipment inventory on top of the foam and close the Styrofoam mailer tightly. Use several loops of packaging tape to ensure that the mailer is secured and that it cannot leak if a sample tube opens during shipment.
7. Place the Styrofoam mailer inside a mailing sleeve. Attach one large "Biohazard" label and one "Exempt Human Specimen" sticker to the mailing sleeve. Address the shipment to:

   Roxanne Kelly
   Channing Lab
   221 Longwood Ave, EBRC 610
   Boston, MA 02115-5804

   Tel: (617) 732-5560
   Alternate Tel: (617) 732-5888

8. Specify priority overnight shipment for <u>AM receipt</u>.

**Receipt of Samples at Channing Laboratory (Tuesday and Friday mornings)**

Channing Lab will receive shipments on Tuesday and Friday mornings. Lab staff will scan the barcodes of all received samples into the AsthmaNet BST system to reconcile the shipments and identify/resolve any problems. Lab staff will generate an export file (.csv format) through the BST system that contains the following variables: barcode number, participant ID number, participant initials, visit number, collection date and shipment ID. Export files can be generated separately for each shipment ID, or a combined export file that includes all shipments received on a given day (or days) can be created.

Analysis for vitamin D levels will be performed on Tuesday and Friday afternoons, following receipt of shipments from all AsthmaNet sites that confirmed a shipment on a given Monday or Thursday.

Table 3 outlines shipment, analysis and result availability days.

**Table 3.**

| Collection Day | Shipment Day | Lab Receipt/ Analysis Day | Refrigeration Time (days) | Results Available by 2 PM ET |
|---|---|---|---|---|
| Monday | Monday | Tuesday | 1 | Wednesday |
| Tuesday | Thursday | Friday | 3 | Monday |
| Wednesday | Thursday | Friday | 2 | Monday |
| Thursday | Thursday | Friday | 1 | Monday |
| Friday | Monday | Tuesday | 4 | Wednesday |
| Saturday | Monday | Tuesday | 3 | Wednesday |
| Sunday | Monday | Tuesday | 2 | Wednesday |

## Vitamin D Result Availability

Results will be generated at Channing Lab every Tuesday and Friday afternoon, assuming that all shipments are received in Boston on time and no problems are encountered with the Diasorin platform or electronic reporting process.

Results will be posted to a secure file transfer protocol (SFTP) site provided by the DCC and accessible only by Channing personnel and designated database programmers at the DCC. DCC programmers will set up a process to retrieve the files and load them into the AsthmaNet database on Monday (for Thursday shipments) and Wednesday (for Monday shipments) mornings. For visit 0 serum, the eligibility status (eligible or not eligible) of each participant will be available to performance site personnel by 2 PM Eastern Time on Monday and Wednesday via the VIDA Participant Status Report.

Follow-up vitamin D levels (at Visits 6, 8, 10, early post-randomization termination visits, and as-needed for safety follow-up between visits 6 and 10) for randomized participants will be done to assess for hypervitaminosis D. These samples will be batch processed with the screen (Visit 0) samples on the schedule defined above.

Clinical site personnel will not be given numeric vitamin D levels (in ng/ml) for samples drawn at any visit, as maintaining the blind on the study capsules requires that the participant, site coordinators, investigators, and most DCC personnel not have access to this information. Only the database programmers at the DCC and Channing Lab staff will have access to the actual vitamin D levels throughout the study.

Participants also will not be supplied numeric vitamin D levels, even upon exit from the study. Channing Laboratory does not possess CLIA (Centers for Medicare & Medicaid Services Clinical Laboratory Improvement Amendments) certification; therefore, vitamin D levels generated during the VIDA trial are considered research and are not suitable for making clinical management decisions. Participants should be referred to their primary care physicians for follow-up testing and care. The VIDA vitamin D eligible termination letter has been supplied for this purpose. See the Withdrawals discussion in this section for more information.

## Post-Randomization Testing and Hypervitaminosis D Alerts

After the participant is randomized, he/she will have serum vitamin D tests performed at Visits 6, 8 and 10 for monitoring of hypervitaminosis D. The DCC has set up a process that will flag if a participant has a vitamin D value ≥120 ng/ml (the defined toxic level in the protocol) and will automatically e-mail the participant's performance site (principal investigator/site director as well as designated coordinator(s)) to alert staff to activate the protocol for potentially toxic vitamin D levels for this participant. The participant's

use of the study capsules should be suspended immediately upon notification and a VIDA Change in Study Medications (P1_CHANGE_MEDS) form should be entered and submitted to the DCC. An adverse event should be entered on the Clinical Adverse Events (AECLIN) form using ICD-9 code 278.4 (hypervitaminosis D); the date of the lab adverse event should correspond to the date of the participant's blood draw. The participant should be scheduled for a confirmatory vitamin D test within a week of notification of the elevated result. Under this scenario, it is possible for the same participant to have two vitamin D samples labeled with the same visit number (but different blood draw dates and different barcode numbers). If the elevation is confirmed by the repeat sample, then the participant should be kept off study capsules for the remainder of the study. If the repeat sample shows vitamin D levels in the normal range (<120 ng/ml), then the participant may resume taking study capsules, and another P1_CHANGE_MEDS form should be completed and forwarded to the DCC.

## Holiday Schedules

Vitamin D serum samples should not be collected during a visit if they will require refrigeration for more than 4 days prior to receipt and analysis at Channing Lab. Therefore, certain holidays when Channing Laboratory is closed will necessitate instituting 'blackout' dates on which no vitamin D serum samples can be collected. This holds for Visit 0 screens, as well as for safety follow-up samples collected at visits 6, 8 and 10. Lab closure dates will be communicated to the sites well in advance of any holidays that will affect vitamin D serum processing schedules.

Note that the same rule applies to closures at the performance sites. If a clinical site is closed for a Monday (or Thursday) holiday, such as Memorial Day or Labor Day, then no shipments will be made that day. Therefore, no samples should be collected in the days leading up to the holiday that would require refrigeration for more than 4 days prior to receipt and analysis at Channing Lab.

For example, Monday, May 30, 2011 is the Memorial Day holiday. If the clinical site is closed that day, then the next shipment to Channing Lab will occur on Thursday, June 2 for receipt at the lab on Friday, June 3. To ensure that samples are refrigerated no more than 4 days prior to analysis, no samples should be collected following the shipment to Channing Lab on Thursday, May 26 until the lab reopens on Tuesday, May 31. In other words, May 27 through May 30 are blackout dates for scheduling visits 0, 6, 8, 10. If a participant absolutely must be scheduled for a visit 6, 8, or 10 during a blackout period, arrangements must be made to have him/her return to the lab for a vitamin D serum blood draw as soon as possible once the blackout period has ended.

Channing Lab will be closed on the following dates in 2011:

| | |
|---|---|
| Memorial Day: | Monday, May 30, 2011 |
| Independence Day: | Monday, July 4, 2011 |
| Labor Day: | Monday, September 5, 2011 |
| Columbus Day: | Monday, October 10, 2011 |
| Thanksgiving: | Thursday, November 24, 2011 |
| Christmas: | Monday, December 26, 2011 |

None of these closure dates should affect receipt and processing of vitamin D shipments.

Channing Lab will be closed on the following dates in 2012:

| | |
|---|---|
| New Year's Day: | Monday, January 2, 2012 |
| Martin Luther King Day: | Monday, January 16, 2012 |
| President's Day: | Monday, February 20, 2012 |
| Memorial Day: | Monday, May 28, 2012 |
| Independence Day: | Wednesday, July 4, 2012 |
| Labor Day: | Monday, September 3, 2012 |
| Columbus Day: | Monday, October 8, 2012 |
| Thanksgiving: | Thursday and Friday, November 22-23, 2012 |
| Christmas: | Tuesday, December 25, 2012 |

Channing Lab will be closed on the following dates in 2013:

| | |
|---|---|
| New Year's Day: | Tuesday, January 1, 2013 |
| Martin Luther King Day: | Monday, January 21, 2013 |
| President's Day: | Monday, February 18, 2013 |
| Memorial Day: | Monday, May 27, 2013 |
| Independence Day: | Thursday, July 4, 2013 |
| Labor Day: | Monday, September 2, 2013 |
| Columbus Day: | Monday, October 14, 2013 |
| Thanksgiving: | Thursday and Friday, November 28-29, 2013 |
| Christmas: | Wednesday, December 25, 2013 |

Note: FedEx closes for major holidays, as well. Before preparing a shipment, check the lab closure schedule and the FedEx holiday schedule at www.fedex.com to be sure your package will be picked up and delivered as expected.

## Channing Lab Contacts

Names: Roxanne Kelly (roxanne.kelly@channing.harvard.edu)
Kevin Lundgren (rektl@channing.harvard.edu)
Dan Cossette (redac@channing.harvard.edu)

Address: 181 Longwood Avenue EBRC112
Boston, MA 02115

Telephone: (617) 732-5560 (Roxanne) or (617) 732-5888 (Dan and Kevin)
Fax: (617) 264-5135

## 2.42 Significant Asthma Exacerbation

**Visit 3-10, 88, 90-92**
Complete Significant Asthma Exacerbation form (P1_SIGEX), if applicable

**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 criteria for treatment failure AND one or more of the following:

1. Failure to respond within 48 hours to treatment failure rescue algorithm.

   See the discussion of Treatment Failure in this section for the treatment failure rescue algorithm. If the participant requires additional treatment above the escalated dose of study inhaled corticosteroids (ICS), he/she is considered a non-responder and is categorized as having a significant asthma exacerbation.

2. $FEV_1$ <50% of the baseline pre-bronchodilator $FEV_1$ at Visit 3 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 Spirometry Testing (SPIRO) form at Visit 3. This value is used for assessing treatment failure and asthma exacerbation criteria for the remainder of the participant's study participation.

   A participant will meet this criterion if he/she experiences pre-bronchodilator $FEV_1$ values that are <50% of the Visit 3 baseline $FEV_1$ value at two consecutive visits during the post-randomization period. This criterion can be met for the following comparisons:

   - Visit 5 and Visit 6
   - Visit 6 and Visit 7
   - Visit 7 and Visit 8
   - Visit 8 and Visit 9
   - Visit 9 and Visit 10

   The participant will also meet this criterion if the following set of circumstances occurs:

If the pre-bronchodilator $FEV_1$ value at a visit is <50% of the baseline pre-bronchodilator value obtained at Visit 3, and the participant does not meet other treatment failure or exacerbation criteria, the participant should be given levalbuterol (≥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 treatment failure and exacerbation. The additional visit scheduled for repeat spirometry is referred to as an '$FEV_1$ re-assessment visit.' No additional provocative procedures (e.g., methacholine challenge, sputum induction) scheduled for the original visit day should be performed. The site coordinator or designee should telephone the participant every 24 hours to assess his/her condition in the event that treatment failure or 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 3; if not, the participant will be considered as having an asthma exacerbation at that time. Note that the participant may meet the $FEV_1$ criterion for treatment failure without meeting exacerbation criteria.

Note that this portion of the $FEV_1$ criterion may also be applied at Visit 4 (end of oral corticosteroid (OCS) response period). While unlikely, if the participant meets treatment failure or exacerbation criteria during the OCS response period, he/she will be ineligible for randomization at Visit 4.

Note: The $FEV_1$ criterion will not be evaluated during the run-in period (Visit 2-Visit 3) due to lack of a consistent baseline $FEV_1$ for all participants during this period of the study.

See the Extra Study Visits discussion in this section for more details on $FEV_1$ re-assessment visits.

3. 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 at two consecutive visits during the post-randomization period. The visit comparisons and $FEV_1$ re-assessment visit described in 2 above also apply to this criterion.

Note: This criterion will not be assessed at Visits 2 and 3. If the participant's pre-bronchodilator $FEV_1$ value is <40% of predicted at these visits, the participant is ineligible to continue in the trial and must be terminated from further participation.

4. Use of ≥ 16 puffs of PRN "as needed" levalbuterol per 24 hours for a period of 48 hours.

   This criterion is assessed through a review of the participant's spirotel® e-diary data on the Spirotel® Participant Visit Report generated at a given visit. Specifically, answers to Q17 (# RESCUE puffs 24) should be reviewed to determine if the participant meets this criterion.

5. Use of oral/parenteral corticosteroids for asthma.

6. Experiencing an exacerbation of asthma in the opinion of study investigator or personal physician.

## Documentation

When a participant experiences an asthma exacerbation during the VIDA study, he/she should notify the performance site as soon as possible, preferably within 24 hours. Timely reporting ensures that the exacerbation is documented accurately and that the participant receives appropriate treatment. Once the significant asthma exacerbation has been confirmed, the following forms should be completed:

- Clinical Adverse Events (AECLIN)

  All significant asthma exacerbations should be documented on AECLIN using ICD-9 code 493.92. Because exacerbations automatically qualify as treatment failure events, as well, a separate entry for treatment failure using ICD-9 code 000.00 should also be made.

  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 escalated ICS treatment, the date corresponding to the second day of

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.

Treatment failure and exacerbation dates may differ, depending on which of the criteria are met.

- Concomitant Medications for Asthma/Allergy and Adverse Events (CMED)

  Any non-study medications used to treat the exacerbation event should be recorded on the CMED form. Examples include oral or parenteral corticosteroids (e.g., rescue prednisone). Nebulized beta-agonist administered in a doctor's office or at the performance site should be recorded by the participant in his/her e-diary counting each nebulizer treatment as two puffs of beta-agonist.

  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.

- VIDA Treatment Failure Checklist and Treatment Failure Information (P1_TXFAIL_CHK, P1_TXFAIL)

  Exacerbations automatically qualify as treatment failure events. Treatment failure forms (P1_TXFAIL_CHK and P1_TXFAIL) must be completed any time a participant experiences an exacerbation.

- VIDA Significant Asthma Exacerbation (P1_SIGEX)

  P1_SIGEX must be completed any time the participant meets the criteria for an asthma exacerbation. This form is always treated as a single form.

  The exacerbation date is recorded in Q1060. This date is critical for analysis of time to exacerbation. It should correspond to the date exacerbation criteria were confirmed for the current event. For example, if a participant experienced two pre-bronchodilator $FEV_1$ values <50% of his/her baseline $FEV_1$ value from Visit 3, the date of the second measurement should be recorded as the exacerbation date. If multiple criteria for exacerbation are met, record the earliest date any of the applicable criteria were met.

  If a participant meets asthma exacerbation criteria during the run-in (between Visit 2 and Visit 3) or during the oral corticosteroid response period (between

Visit 3 and Visit 4), P1_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 phases of the trial, P1_SIGEX should be completed as a single form and data entered with the participant's visit packet (regular visit or Visit 90-92).

- 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.

### Significant Asthma Exacerbation Rescue Algorithm

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.

Participants who are not responsive to the treatment failure rescue algorithm (see the Treatment Failure discussion in this section) or those who develop asthma exacerbations 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.

Levalbuterol (study RESCUE Xopenex®) and oral prednisone are the principal medications for rescue management. At Visit 2, participants will be dispensed RESCUE Xopenex®. At Visit 4, randomized participants will be given a course of prednisone to keep at home for rescue use, only as directed by a study physician. Participants will be instructed in their use for home management. Oral prednisone will be used if alteration of the inhaled corticosteroid (ICS) dose does not resolve the exacerbation. For severe acute episodes of asthma, treatment will be administered according to the best medical judgment of the treating physician.

Home Care

Asthma exacerbations will be recognized by decreases in peak flow and/or an increase in levalbuterol (Xopenex®) 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% of baseline will use levalbuterol by MDI, 2-4 puffs, every 20 min up to 60-90 min if needed and then every 4 hours, or less, if needed. Participants will be instructed to use the "Rescue Xopenex®" inhaler for treatment.

If the PEF does not increase to >65% of 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 levalbuterol to control or maintain PEF >65% of baseline 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 min over the first 60-90 min.

If the PEF increases to >65% of baseline after the first 60-90 min, 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 (60 mg prednisone orally; methylprednisolone 60 mg iv bolus). Monitoring of PEF or spirometry should continue every hour. Within 4 hours of treatment, a decision should be made regarding participant disposition. The participant should restart his/her Alvesco® at least at the Phase I (ICS stable) dose.

If PEF increases to >65% of baseline within 4 hours, the participant can be discharged to continue treatment at home. Home treatment should include an 8-day course of prednisone (see below).

If PEF remains >40% but ≤65% of baseline, 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 acute exacerbations cannot be controlled by albuterol therapy and alteration of ICS dosing. Indications for prednisone therapy include the following:

- For follow-up management after discharge from the physician's office, emergency department, or hospital for an acute exacerbation.
- For home management when asthma symptoms remain clinically significant for 48 hours or longer and the participant is taking ≥ 16 puffs of levalbuterol plus alteration of inhaled corticosteroid dose.
- When PEF falls to <50% of baseline despite levalbuterol and inhaled corticosteroid treatment.

The recommended dose of prednisone used during an acute exacerbation shall consist of 60 mg as a single dose every day for 3 days, followed by a 10 mg/day taper over the next 5 days. The decision to initiate or to continue a course of prednisone beyond 8 days is left to the discretion of the physician.

At the point when prednisone or parenteral corticosteroid treatment is initiated, the participant should revert to the ICS stable dose of Alvesco® (2 puffs BID) and remain on this dose for the rest of his/her trial participation. Complete a VIDA Change in Study Medications (P1_CHANGE_MEDS) form to document the dose change.

## Study Participation Following an Asthma Exacerbation

Participants experiencing an asthma exacerbation during the screening, run-in, or oral corticosteroid response period of the study are ineligible to continue in the trial. A VIDA Termination of Study Participation (P1_TERM) form should be completed. See the discussion of Withdrawal Due to Treatment Failure or Exacerbation in the Treatment Failure section for further details.

For safety reasons, all participants will be seen within 1 week of the date of an exacerbation, sooner if possible. If a regular visit is not already scheduled in this timeframe, the participant should be seen for a Visit 90-92. See the Extra Study Visits discussion in this section for further details.

Following clinical assessment and appropriate medical management, regular study visits will continue in accordance with the participant's visit schedule.

Note: If a participant meets exacerbation criteria at the time of Visit 6, he/she should not proceed with methacholine challenge testing and sputum induction at the visit. If the participant has experienced a recent significant asthma exacerbation, a study physician must be consulted for approval before attempting these procedures at the visit.

## Inhaled Corticosteroid (ICS) Dosing Following an Exacerbation

If a participant experiences a significant asthma exacerbation, maintenance ICS dosing depends on the prescribed treatment and the phase in which the event occurred. If the exacerbation occurs during Phase I and no oral/parenteral corticosteroid is initially prescribed, then the dose of ICS will be doubled (to 4 puffs BID) for 7 days. If, after 7 days, the event is clinically-resolved, the dose will be reduced back to the ICS stable dose (2 puffs BID) for the remainder of the study, and visits will continue as per protocol. The participant will not be eligible for any ICS dose tapers during Phase II.

If the exacerbation occurs during Phase II and no oral/parenteral corticosteroid is initially prescribed, then the dose of ICS will be increased to the ICS stable dose (2 puffs BID) and maintained for the remainder of the study (assuming at least 1 ICS taper has been done; if not, then the dose would be doubled to 4 puffs BID and instructions for Phase I dosing should be followed). Additional treatment for exacerbations is allowed at the treating physician's discretion. The participant will not be eligible for any additional ICS dose tapers.

If prednisone/parenteral corticosteroid therapy is initiated, the participant should revert back to the ICS stable dose of Alvesco® (2 puffs BID) on the day the first prednisone

dose is taken. The participant should remain on the ICS stable dose for the rest of his/her study participation. The participant is ineligible for any future ICS dose tapers.

## 2.43 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 VIDA trial.

The Sinonasal Questionnaire (SNQ)[13] 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. 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 VIDA from Dr. Anne Dixon, one of the instrument's original authors.

**Visit 3, 6**
Administer Sinonasal Questionnaire (SNQ)

The administration of the SNQ 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 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

[13] 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.

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 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.

## 2.44 Skin Testing

**Visit 2**
Perform allergy skin test (SKIN_TEST)

The allergy skin test provides baseline medical information. Only clinical personnel who have completed the AsthmaNet allergy skin test certification outlined in the AsthmaNet Skin Testing Manual of Operations (located in appendix 3 of the AsthmaNet General Manual of Operations) are qualified to conduct the skin testing procedure and, subsequently, to complete the Allergy Skin Test Results (SKIN_TEST) form.

Previously obtained allergy skin test results may be used to satisfy the skin testing requirements for the VIDA study if both of the following conditions are met:

1. Prior skin testing was performed by an AsthmaNet certified coordinator or technician using AsthmaNet procedures and allergens. ACRN skin tests may not be substituted for AsthmaNet skin tests.

2. Prior skin testing occurred within 3 years of the current visit date. Skin test results that are more than 3 years old are invalid. In this case, skin testing must be repeated.

Substituting an old skin test in lieu of repeating one is useful if a participant re-enrolls in the VIDA study and had completed a skin test during his/her initial enrollment. See section 10 of the AsthmaNet General Manual of Operations for instructions for submission and data entry of previously collected skin test data.

If a participant has had a significant adverse reaction to the skin testing procedure in the past (urticaria, angioedema, asthma, hypotension, etc.), regardless of where or when testing was performed, repeat skin testing should NOT be carried out. Complete page 1 of the SKIN_TEST form providing this information. Skin test data will be missing for this participant. ImmunoCap procedures will not be done as a substitute for skin testing in the VIDA study.

If the participant has had an anaphylactic reaction to egg, peanut, or milk, do not administer the applicable allergen when performing the skin test. Results for the applicable allergen should be missing on the SKIN_TEST form.

The majority of skin tests should be completed during Visit 2. Confirm that the medications listed in the AsthmaNet Skin Testing Manual of Operations have been avoided for the designated washout periods before beginning the skin testing

procedures. If the participant completed a methacholine challenge at the visit, then the last $FEV_1$ post-challenge should be used to qualify the participant for skin testing (i.e., the final post-reversal $FEV_1$). If the participant did not perform spirometry and methacholine challenge at Visit 2, then the participant's baseline pre-bronchodilator $FEV_1$ from Visit 1 may be used to qualify the participant for skin testing at the coordinator's discretion. If the coordinator determines that too much time has elapsed between visits or that the participant's clinical status at the time of Visit 2 requires repeat spirometry, then spirometry should be performed on the day of Visit 2 for the sole purpose of qualifying the participant for skin testing. The report from this spirometry session should be kept in the participant's study folder at the performance site; do not data enter the information or submit it to the DCC. Answer Q1040 on the SKIN_TEST form on the basis of this spirometry session and provide a comment on the form explaining how the participant was qualified.

If the participant is not able to be tested at Visit 2 because of medication use or a low $FEV_1$, reschedule the testing for an upcoming visit as soon as possible. Skin testing may be done at an alternate VIDA visit and submitted later in the study as a single form. Use the results of the spirometry session closest to skin testing during the visit to qualify the participant at the chosen visit.

## 2.45 SmartProbe 400 (melanin measurements)

**Visit 3, 10**
Complete Melanin Test (P1_MELANIN)

**Background**

The SmartProbe 400 (IMS inc. Milford, CT) is a handheld device that measures skin tone (degree of pigmentation or melanin in the skin) by reflectance colorimetry. It is very simple to use and provides three measurements, designated L*, a* and b* (specified by the International Commission on Illumination). For the purposes of the VIDA trial the “L” value is the most important, although all three values are measured by the device automatically. The “L” value is a measure of the lightness or darkness (pigmentation) of the skin (0=black, 100=white). The “a” value is a measure of redness and the “b” value is a measure of yellowness. The “a” and “b” measurements are not felt to be relevant to the trial as they are not likely to affect UVB absorption or vitamin D synthesis in the skin. In general, the range of human skin tone for the “L” measurement is from 30 to 70 (but values outside this range are possible). “L” is a measure of reflectance, with whiter skin yielding a higher number (i.e., more light is reflected). After tanning, a person typically will have a lower “L” and higher “a” and “b” measurements.

The SmartProbe will be connected to the performance site’s (non-spirometry) computer via a data cable and a USB adapter and readings will automatically populate into an Excel spreadsheet using the SmartConnect software provided with the device. The DCC has provided a template spreadsheet (the VIDA Melanin Recording Form (P1_MELANIN) saved as p1_melanin.xls) that should be used for each participant visit when melanin levels are measured (Visits 3 and 10). Participant ID, initials, visit number, visit date, and coordinator ID are entered into the spreadsheet by the coordinator taking the measurements and the remaining fields are completed automatically by the device. The spreadsheet will serve as the data collection form for these measurements; values will be entered into the AsthmaNet database directly from the spreadsheet. See section 4 of this manual for information on connecting the device to the computer for data transfer and accessing the spreadsheet with the SmartProbe for melanin data collection.

Note: In order to use the non-spirometry AsthmaNet computer for transfer of the SmartProbe data to a spreadsheet, coordinators must have administrator privileges to their machines.

## Monthly Calibration with Skin Tone Chart

Each SmartProbe device is accompanied by an IMS Human Skin Tone Chart. This chart should be used to calibrate the device monthly, following the steps outlined below. Results should be stored in the SmartProbe Skin Tone Chart Calibration Spreadsheet (smartprobecal.xls) and saved on the performance site's desktop (non-spirometry computer) or printed and stored in a calibration folder. Calibration results will be subject to audit during a VIDA data quality site visit.

Calibration steps:

1. Open calibration spreadsheet (p1_smartprobecal.xls) and type in the current date in the field at the top. The spreadsheet is located on the secure website in folder Forms:VIDA:Admin Forms.
2. Locate the IMS Human Skin Tone Chart.
3. Do an initial white tile calibration measurement; do not record this measurement in the spreadsheet.
4. Take one reading from each of the nine different skin tones, in numerical order, storing each in the spreadsheet in the designated cells.
5. Compare the results to the first month's readings. All measurements of the same tone should be within 0.1-0.2 of the first month's measurement for the device to pass calibration.

If this is the first time the SmartProbe is being calibrated against the skin tone chart, take a second set of readings (that is, open a second calibration spreadsheet and follow steps 1-3 above). All readings must be within 0.1-0.2 of each other for the device to pass.

Note: The skin tone chart must be stored protected from light so the color blocks do not fray or fade. If this happens, the device could fail the calibration check in error.

## Calibration with White Tile (Performed with each use)

Before the SmartProbe is used to take measurements from a study participant, the device must be calibrated against the white tile provided in the case with the device. White tile calibration readings will be recorded in the spreadsheet that contains the participant's data from the visit (p1_melanin.xls). Follow the steps outlined below:

1. Connect the device to the site computer (non-spirometry) and plug in (see instructions in section 4 of this manual, if needed).
2. Open the p1_melanin.xls spreadsheet. Complete the participant's ID, participant's initials, visit number, visit date, and coordinator ID.
3. Place cursor on the "L" field for the first white tile calibration measurement.

4. Clean white tile calibration plate gently with an alcohol pad.
5. Remove cap from device.
6. Clean device gently with alcohol pad.
7. Turn device on (|). The message 'Set Cal. Plate → Measure' will appear.
8. Place plexiglas plate flat against white calibration tile.
9. Press measurement button (on side of device) once. Press a second time to register the first calibration reading.
10. L, a, b numbers will appear on the LCD display screen and in the spreadsheet. They should match those written on the inside of the case of the calibration plate (within 0.1-0.2).
11. Ensure that the cursor is on the "L" field for the second white tile calibration measurement. Press measurement button on side of device once to perform a second white tile calibration reading.
12. If L, a, b, numbers from the second calibration test match the values on the inside of the tile plate case (within 0.1-0.2), the probe is ready to use with the participant.

Note: The device will chirp twice if something is wrong. For example, if the first reading is not performed on the white tile calibration plate, the device will protest and require the calibration to be performed.

Be aware that light coming through the side of the plexiglas may also affect readings.

### Location of Measurements on a Participant

At visits 3 and 10 each participant will have two readings taken from each of the following four body areas: exposed forehead, upper inner arm, outer forearm, and abdomen. For standardization across visits and clinical sites, readings should be taken from the right side of the participant's body (i.e., the participant's right). If readings are mistakenly made from the left side of the participant's body, this protocol deviation should be noted on the spreadsheet and in the participant's study folder so that subsequent measurements are made from the same locations.

It is important to take readings in areas of skin that appear uniform and to avoid areas of hyper- or hypo-pigmentation, freckles and freckly areas, tattoos, dirty areas, and areas with dark hair as these will all affect the readings. If a participant is wearing heavy makeup, be sure to clean the area prior to taking measurements.

If an individual participant needs to have the location of certain measurements adjusted slightly (due to hair, hyper/hypo-pigmented area or other reasons), changes should be

noted on the spreadsheet and in the participant's study folder so that readings at Visit 10 are taken from the same locations.

The four body areas where measurements are taken are (Figure 1):

1. Exposed forehead:

   Reading should be taken in the center of the forehead, approximately 1 inch above the eyebrow line. If the participant is wearing makeup, use an alcohol swab to clean the area and allow to dry completely prior to taking the measurements.

2. Upper, inner arm:

   Reading should be taken from the inner surface of the arm which is nearest to the body if the participant is standing with palms facing forward. Measurement should be taken approximately 2 inches up from the elbow joint.

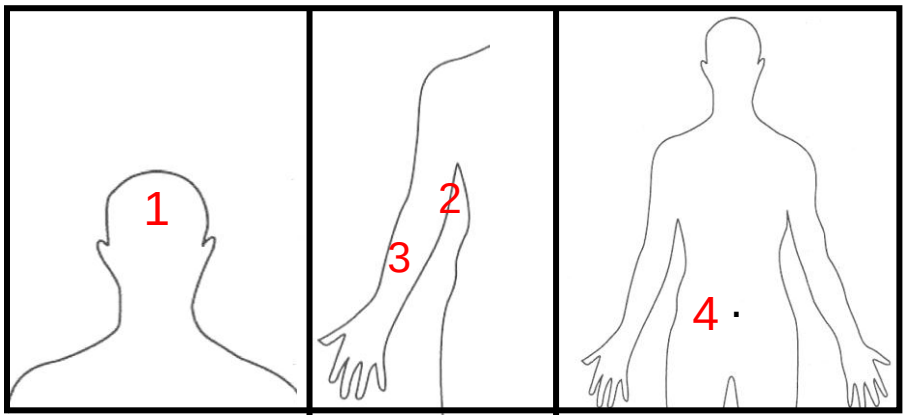
3. Outer forearm:

   Reading should be taken from the surface of the arm that is continuous with the back of the hand, approximately halfway between the wrist joint and the elbow joint. This is an area that may have more hair and/or freckles. Be careful to avoid areas with a significant amount of dark hair.

4. Abdomen:

   Reading should be taken one inch to the participant's right (reader's left) of the umbilicus.

Figure 1. Locations for Melanin Measurements



## Taking Measurements on a Participant

Two measurements will be taken from each body location at each applicable visit. Perform the following steps:

1. Take the cap off the probe and clean it with an alcohol pad gently prior to each use. This includes swabbing the plexiglas plate. Allow to dry completely.
2. Locate the white calibration tile and clean it with an alcohol pad. Allow to dry.
3. Hook the device up to the non-spirometer computer and plug it in. See instructions in section 4 of this manual, if needed.
4. Turn on device (|).
5. Open the p1_melanin.xls spreadsheet. Type in the participant's ID and initials, visit number, visit date, and coordinator ID.
6. Click on the cell where the "L" value will be input for the first white tile calibration measurement ("a" and "b" will automatically populate the two cells to the right).
7. Perform the first white tile reading (press the measurement button the side of the device once, then a second time to register a set of measurements).
8. Ensure that the cursor is on the "L" field for the second calibration reading.
9. Perform the second white tile reading (press the measurement button once until you hear a beep).
10. Compare white tile readings to the values on the inside of the tile's case. If they are all within 0.1-0.2 of the posted measurements, the device is ready to perform measurements on the participant. If not, the device should not be used.
11. Identify the area on the participant to be read and place the cursor in the spreadsheet at the "L" field for this location.
12. Hold the device so that the plexiglas plate is flat against and in complete contact with the participant's skin, but is not pressed too firmly against him/her. Pressing too firmly may affect the light that comes through the plexiglas and obscure the reading.
13. Press the measuring button once until you hear a beep (less than 1 second).
14. The readings should automatically be input into the spreadsheet.
15. Ensure that the cursor is at the "L" field for the next measurement and continue with the remaining measurements. Two measurements will be taken from each of the four body locations.
16. When all measurements are complete, print a copy of the spreadsheet for inclusion in the participant's visit packet.
17. Save a copy of the participant's results to a local folder. Name the spreadsheet p1_melanin_1pppppp_nn.xls where 1pppppp is the participant's VIDA ID number and nn represents the visit number (3 or 10).

If a problem is encountered connecting to the computer and accessing the spreadsheet, values can be handwritten from the LCD display on the device. This is not ideal due to the possibility of transcription error and should only be done if absolutely necessary.

### Caring for the SmartProbe

- Any time there is a problem, the device will chirp twice. Most often this will be caused by attempting to use the device without first having calibrated it with the white tile. Check the screen for an error message (see below).
- Handle the device with extreme care. Be especially careful never to drop the device.
- Take care not to allow liquid to get on the device.
- Do not direct the probe towards your face or the participant's face. This may cause damage to the eyes.
- Although the device can be battery operated (batteries are supplied with the device), the AC adapter should always be used to ensure adequate power.
- Always turn off, disconnect and repack the device and white tile calibration plate to protect them when not in use.

### Error Messages and Corrective Actions

| Message | Cause | Corrective Action |
|---|---|---|
| Measure Again | Measurement was not taken correctly; instrument was moved during measurement; ambient light entered device aperture, etc. | Take measurement again, making sure plexiglas plate is flat against the skin and that the instrument is not moved until the beep has sounded |
| Sample Too Dark | Reflectance of specimen is low | Specimens with low reflectance cannot be measured |
| Change Battery | Battery power is almost exhausted | Replace batteries or use AC adapter |
| Illumination Error | Lamp filament is broken or measurement circuit is malfunctioning | Contact the DCC to receive a replacement device |
| Cal Again | Calibration was performed using something other than the white calibration tile | Use only the white tile included with the device. |

## Replacement Devices

If a SmartProbe fails to calibrate or is otherwise malfunctioning, it should not be used to take participant measurements. In this case, contact the DCC for a replacement device. As the purchaser of the devices, the DCC will facilitate communications with the manufacturer.

## Contact

For technical questions related to the use of the device, contact Peter Sottery at IMS Inc. Phone: (203) 915-8502 (cell) or (207) 773-1044 (office).

## 2.46 Spirometry

**Visits 1-10, 88, 90-92**
Complete Pulmonary Procedure Checklist (P1_PULMONARYCHK)
Perform Spirometry Testing (SPIRO)

Spirometry procedures are carried out at all VIDA visits, with the exception of Visit 0. Individuals who meet the $FEV_1$ reversibility criterion at Visit 1 do not need to perform spirometry testing or methacholine challenge at Visit 2. Pulmonary function data are very important, as they confirm the participant's eligibility for the study and provide data for assessment of treatment failure criteria.

**General Instructions**

The VIDA trial 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 Maximum Reversibility Testing (MAXREV) 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 VIDA Pulmonary Procedure Checklist (P1_PULMONARYCHK). 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. For the VIDA study, two exceptions to this rule are acceptable:

1. If the participant is present at a post-randomization visit and has already met treatment failure criteria based on other parameters, then the participant may proceed with spirometry testing, even if some of the required holds on medications (such as rescue levalbuterol) are not met.

2. If the participant was seen for a post-randomization visit and did not meet treatment failure criteria, but his/her $FEV_1$ was ≤80% of the Visit 3 value for the first time, then he/she is rescheduled for another visit for $FEV_1$ assessment in 1-4 days. If the participant fails to meet all the required medication holds at the $FEV_1$ reassessment visit, then he/she may still proceed with spirometry testing.

When one of the exceptions outlined above is implemented, Q1150 on P1_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.

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. Heights for these individuals will be recorded on the P1_PULMONARYCHK form at all visits, with the exception of Visits 1 and 10 when height is recorded for all participants on the Adult Body Measurements (BODYMEAS_ADULT) form. The height value for participants who are under age 21 should be updated in the spirometry software for all sessions. Participants who are at least 21 years old will have their height measured and updated in the spirometry system only twice during the study (at Visit 1 and Visit 10). Once a participant is over the age of 21, he/she should not be re-measured until Visit 10.

The participant's spirometry race/ethnicity designation and gender 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. Both race and gender have a large influence on a participant's predicted lung function values.

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.

Care must be taken to enter the participant's identification (e.g., participant ID number, initials, etc.) and demographic information into the spirometry software correctly. A technician ID must also be included for each test that is performed. Failure to provide complete and accurate information in the MedGraphics system may result in the assignment of a protocol deviation.

**Visits 1-10, 88, 90-92**
Complete the Pulmonary Procedure Checklist (P1_PULMONARYCHK)
Perform Spirometry Testing (SPIRO)

Baseline spirometry at Visits 1, 2 and 3 is used to determine study eligibility. These results are recorded on the Spirometry Testing (SPIRO) form and are referenced on VIDA Eligibility Checklists (P1_ELIG3, P1_ELIG4, P1_ELIG5) at each of the visits.

Original protocol:

Individuals whose $FEV_1$ improved ≥ 12% in response to four puffs of levalbuterol (as part of the maximum reversal procedure) at Visit 1 must have a baseline $FEV_1$ at each of visits 1 and 3 that is between 50% and 90% of predicted, inclusive, to be eligible. These individuals will not undergo spirometry or methacholine challenge testing at Visit 2.

Individuals whose $FEV_1$ did not improve ≥12% in response to four puffs of levalbuterol (as part of the maximum reversal procedure) at Visit 1 must have a baseline $FEV_1$ at each of visits 1, 2, and 3 that is between 50% and 85% of predicted, inclusive, to remain eligible.

Modified protocol:

In January 2012 the AsthmaNet Data and Safety Monitoring Board (DSMB) approved requested modifications to the VIDA inclusion criteria such that participants qualify with $FEV_1$ ≥ 50% of predicted at Visits 1, 2 and 3, regardless of presence or absence of bronchodilator responsiveness. Only individuals whose $FEV_1$ did not improve ≥12% in response to four puffs of levalbuterol (as part of the maximum reversal procedure) at Visit 1 may need to undergo spirometry and methacholine challenge testing at Visit 2 to establish eligibility.

Baseline spirometry at Visit 3 will be considered the participant's 'baseline' for the remainder of the study. The $FEV_1$ obtained at Visit 3 serves as the participant's reference value for determining if he/she meets treatment failure criteria. See the Treatment Failure discussion in this section for further details.

Baseline spirometry at Visit 4 is used to determine the participant's response to 5-7 days of oral corticosteroid (prednisone) therapy. This is an important phenotypic variable. Responders and non-responders will be defined for stratification during data analyses.

Baseline spirometry at Visits 3 and 6 is used to qualify the participant for methacholine challenge at these visits. If the participant's baseline $FEV_1$ ≥ 55% of predicted and baseline $FEV_1$ ≥ 1.0 liter, and all other criteria on the Adult Methacholine Challenge Testing Checklist (METHACHK_ADULT) are met, then he/she is eligible to proceed with the challenge at the visit.

At Visits 4-10, 88, and 90-92, $FEV_1$ from baseline spirometry will be compared to the $FEV_1$ from Visit 3 (baseline) to determine if the participant meets the $FEV_1$ criterion for treatment failure. See the Treatment Failure discussion in this section for further details.

**Visit 1**
Perform Maximum Reversibility Testing (MAXREV)

Note: Participants who do not meet the baseline $FEV_1$ criterion at Visit 1 should not proceed with maximum reversibility testing at the visit. They should be terminated from the trial and a VIDA Termination of Study Participation (P1_TERM) form completed.
At Visit 1 all participants who remain eligible for the study at that point in the visit will undergo maximum response/reversibility testing following the procedure outlined in the Spirometry Manual of Operations. During this procedure the participant completes baseline spirometry (recorded on the Spirometry Testing (SPIRO) form) and is then administered 4 puffs of levalbuterol. After 10-15 minutes of rest, spirometry is repeated. The $FEV_1$ (liters) from the post-bronchodilator spirometry session is recorded on the Maximum Reversibility Testing (MAXREV) form in Q1030. This value is compared to the $FEV_1$ (liters) from baseline spirometry at the visit recorded in Q1030 on the SPIRO form to determine if the participant has reversed at least 12%. See the Eligibility Criteria discussion in this section for further details on reversibility calculations.

Participants who reverse at least 12% to 4 puffs of levalbuterol (without rounding) do not need to perform spirometry or methacholine challenge at Visit 2. Those who do not reverse at least 12% must perform spirometry and methacholine challenge at Visit 2 to confirm their eligibility for the study.

All participants who initiate the maximum response/reversibility procedure should complete the procedure at Visit 1 according to the steps outlined in the Spirometry Manual.This holds regardless of whether or not they meet the reversal criterion for eligibility after 4 puffs of bronchodilator.

Participants should dose from levalbuterol (Xopenex®) inhalers taken from bulk supply (log on VIDA Drug Dispensing Log: Xopenex® (RESCUE) Inhaler (P1_DRG_XOP)). Actuators should be sterilized between participants, allowing for multiple participant use.

**Visit 3, 6**
Administer 4 puffs of levalbuterol, wait 10-15 minutes, and perform post-bronchodilator testing
Complete Post-Albuterol (4 puffs) Spirometry Testing form (PALB4_SPIRO)

At Visit 3, participants who did not perform a methacholine challenge and complete reversal from the procedure with levalbuterol should be given 4 puffs of levalbuterol 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 at these visits.

Participants should dose from their levalbuterol (RESCUE Xopenex®) inhalers for this test. Levalbuterol puffs taken as part of this visit procedure should not be included in the RESCUE puffs the participant records in his/her spirotel® device the evening after the visit.

Note that at Visit 6, only those participants who are deemed eligible to continue with sputum induction (via the VIDA Participant Status Report) and who have not reversed from a methacholine challenge procedure at the visit should perform these extra procedures.

**$FEV_1$ Re-assessment Visits (Visits 4-10, 90-92)**
Complete Pulmonary Procedure Checklist (P1_PULMONARYCHK)
Perform Spirometry Testing (SPIRO)

Starting at Visit 4, participants will be monitored for treatment failure conditions applying the $FEV_1$ criterion. This criterion requires $FEV_1$ values ≤80% of the baseline value from Visit 3 on two consecutive spirometric determinations made 1-4 days apart to be deemed a treatment failure. If a participant is present for a visit and his/her $FEV_1$ at the visit is ≤80% of the baseline $FEV_1$ from Visit 3, but the participant meets no other failure criteria at the time, then he/she is rescheduled for follow-up, confirmatory spirometry in 1-4 days. At the $FEV_1$ re-assessment visit, a new VIDA Pulmonary Procedure Checklist (P1_PULMONARYCHK) must be completed with the current date (using the same visit number as the prior visit). Spirometry should be completed at the re-assessment visit, even if not all of the washouts on the P1_PULMONARYCHK form have been met.

At the re-assessment visit, participants must complete baseline spirometry testing to determine if their $FEV_1$ continues to be ≤80% of baseline, thus meeting the treatment failure criterion. Results of this spirometry session should be recorded on a new Spirometry Testing (SPIRO) form with the current date (using the same visit number as the prior visit).

All data collected on the P1_PULMONARYCHK and SPIRO forms for both parts of the visit should be entered into the study database. See section 4 of this manual for further details on entry of the various forms involved in this type of visit.

## 2.47 Spirotel®

The spirotel® is a peak flow meter and electronic diary (e-diary) combined into one device. Participants will be given a device and trained in its use at the beginning of the run-in period, near the end of Visit 2. 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 uploaded to the MedGraphics database during each visit to the performance site. After the most recent data have been uploaded, clinical personnel will generate and print reports to review with the participant.

This section covers VIDA-specific spirotel® information. For additional information on the spirotel® device, refer to appendix 6 of the AsthmaNet General Manual of Operations.

### Participant Instruction

**Visit 2**
Instruct participant in use of spirotel® (use demo device) (HTSPIROTEL, P1_SPIROTEL_REF)

The DCC will provide each performance site two demonstration (demo) devices loaded with the VIDA demo program. These devices are only for instructional purposes; they should not be dispensed to participants for use during the trial. Demo devices do not store data.

Demo devices have been programmed with the VIDA e-diary questions (AM and PM) and an alert to “Take Your Meds” following each scheduled AM and PM session. If the participant answers “Yes” to the “Have cold today?” question, then the alert “Complete WURSS Tonight” will appear.

At Visit 2 when the spirotel® is first introduced to the participant, clinical personnel should review the information on the How to Use Your spirotel® Electronic Diary and Peak Flow Meter (HTSPIROTEL) handout. 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, clinical personnel should introduce the participant to the demo device. When the device is turned on, three options will appear: AM, PM and PEF. Press the “0” button 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. Press the “1” button to take the participant through a scheduled evening session with e-diary questions and peak flow maneuvers. Press the “3” button 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 upload 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 VIDA-specific handout (VIDA Spirotel® Reference Card (P1_SPIROTEL_REF)) has been created to fit into the spirotel®’s case for quick reference by the participant at home during a session. This reference includes each question abbreviation (i.e., the up to 16 character 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 not to include pre-activity preventive bronchodilator puffs (taken routinely prior to exercise and other strenuous activities) in the rescue use values recorded in the e-diary, 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 2**
Complete Spirotel® Performance Checklist (SPIROTEL_PERF , P1_ELIG4) (use demo device)

After the participant has had a chance to experiment with the VIDA demo device, he/she should undergo a formal spirotel® performance assessment using the steps on the Spirotel® Performance Checklist (SPIROTEL_PERF). He/she must pass the performance check with a score of 13 to remain eligible for the study. Results of the performance check are recorded in Q1200 on VIDA Eligibility Checklist 4 (P1_ELIG4).

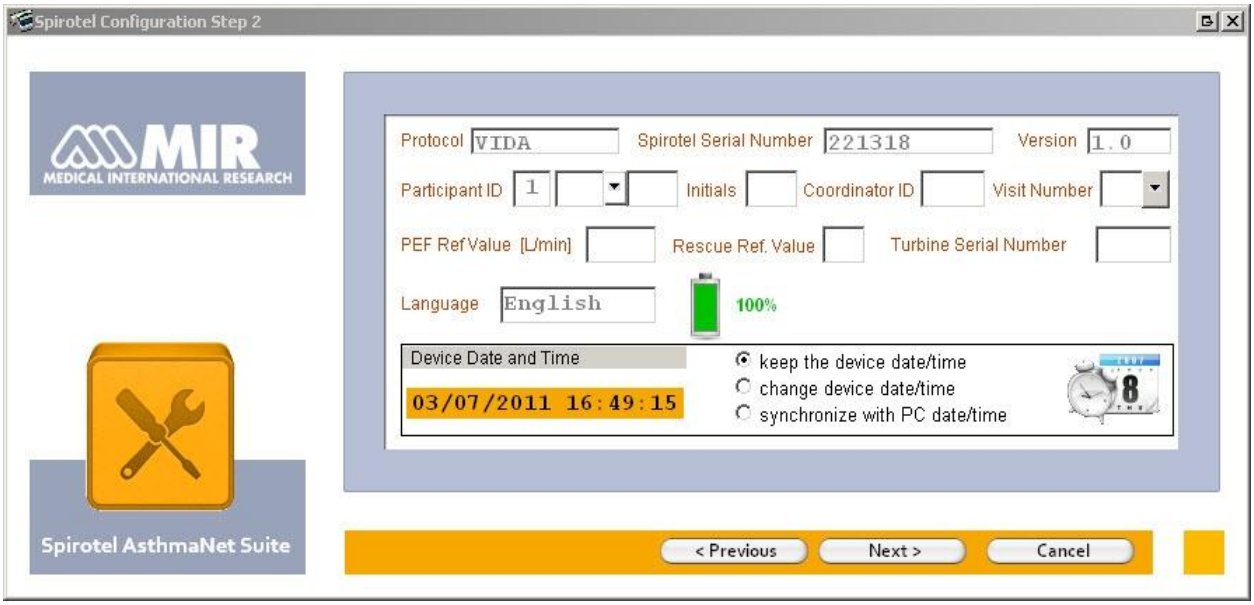
If a participant fails to perform all the steps on the performance checklist correctly, he/she may be retrained and undergo another assessment. There is no limit on the number of times the participant may attempt to pass the checklist. Store all completed SPIROTEL_PERF forms in the participant’s VIDA study folder at the performance site; they should not be forwarded to the DCC.

## Loading the VIDA Program and Preparing Device for Participant Use

### Visit 2

Load VIDA program into participant's assigned spirotel® device

Determine which spirotel® device will be assigned to the participant. Load the VIDA program into the device. The following setup screen will appear with the protocol name (VIDA), device serial number, software version number, first digit of the participant ID (1), and English language pre-filled.




### Visit 2

Program spirotel® with participant's information, including baseline peak flow and rescue use

After the VIDA program has been loaded into the participant's device, several participant-specific pieces of information must be entered by clinical personnel, including:

Participant ID: This is the participant's assigned VIDA ID number. The ID is broken into three sections: protocol number (1 pre-completed), performance site number, and ID number. Clinical personnel must complete the site number and ID number portions.

Coordinator ID: This is the 4-digit identification number belonging to the person who is setting up the participant's device

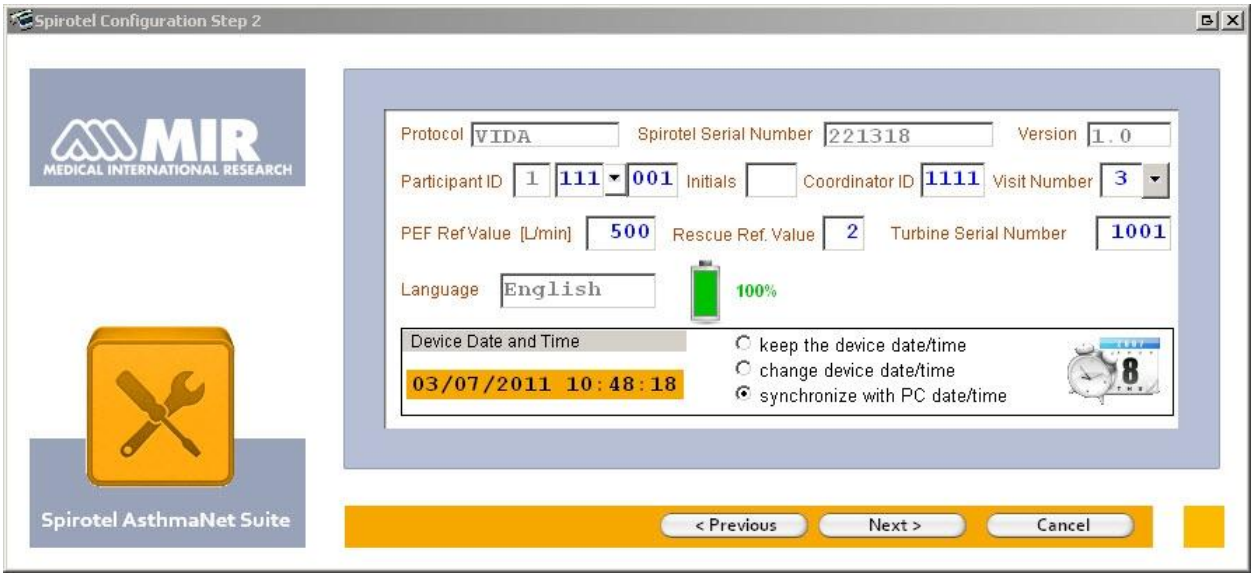
Visit Number: The return visit number should be entered. At Visit 2 the return visit number should be specified as 3. This value will be updated by clinical personnel at each regular visit.

PEF Ref Value [L/min]: This is the participant's baseline peak flow value. The value recorded in Q1000 on the VIDA Baseline PEF and Rescue Use Values (P1_BASELINE) form at Visit 2 should be entered. See the Baseline Peak Flow and Rescue Use Values discussion in this section for details on the derivation of these measurements. Note that the baseline peak flow is being entered; not the 65% of baseline treatment failure reference value.

Rescue Ref. Value: This is the participant's baseline rescue use value in puffs/day. The value recorded in Q1010 on the VIDA Baseline PEF and Rescue Use Values (P1_BASELINE) form at Visit 2 should be entered. See the Baseline Peak Flow and Rescue Use Values discussion in this section for details on the derivation of these measurements. Note that the baseline daily rescue use value is being entered; not the participant's 'high rescue inhaler use' value used to define treatment failure events.

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 1-111-001at Visit 2 follows.


Spirotel Configuration Step 2
MIR
MEDICAL INTERNATIONAL RESEARCH
Protocol VIDA
Spirotel Serial Number 221318
Version 1.0
Participant ID 1 111 001
Initials
Coordinator ID 1111
Visit Number 3
PEF Ref Value [L/min] 500
Rescue Ref. Value 2
Turbine Serial Number 1001
Language English
100%
Device Date and Time
03/07/2011 10:48:18
keep the device date/time
change device date/time
synchronize with PC date/time
Spirotel AsthmaNet Suite
< Previous
Next >
Cancel

**Visit 3**
Update baseline PEF and rescue use in spirotel®

At Visit 3 the participant's baseline peak flow and rescue use values are updated using information stored in the spirotel® device between Visit 2 and Visit 3. See the Baseline Peak Flow and Rescue Use Values discussion in this section for the definition of these measurements. The updated values are recorded on the VIDA Baseline PEF and Rescue Use Values (P1_BASELINE) form.

After the updated reference values have been determined, they must be programmed into the participant's device for use in determining when treatment failure alerts should appear. The following fields should be updated:

PEF Ref Value [L/min]: This is the participant's new baseline peak flow value for use during the remainder of the study. The value recorded in Q1000 on the P1_BASELINE form at Visit 3 should be entered. Note that the baseline (average) peak flow is being entered; not the 65% of baseline treatment failure reference value.

Rescue Ref. Value: This is the participant's new baseline rescue use value in puffs/day. The value recorded in Q1010 on the P1_BASELINE form at Visit 3 should be entered. Note that the baseline (average) daily rescue use value is being entered; not the participant's 'high rescue inhaler use' value used to define treatment failure events.

**Visits 3-9**
Update return visit number in spirotel® device

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 3, the visit number setting in his/her device must be incremented to 4 before he/she leaves the visit. This setting ensures that all stored data will be associated with the correct visit number.

Note: If a participant is discharged from the performance site because he/she has a low $FEV_1$ at the visit and does not meet any other treatment failure criteria, he/she will be returning to complete the visit in 1-4 days. In that case the return visit number in his/her device should not be updated until the return ($FEV_1$ re-assessment) visit. All accumulated data should register in the device under the visit he/she is in the process of completing.

Note: Return visit numbers should not be altered in the device when a participant is seen for an 'extra' treatment failure visit (Visit 90-92). All accumulating data should register with the visit number associated with the next regular visit.

## Spirotel® Quality Control Procedures

### Visits 2-10, 88
Perform spirotel® QC (participant's assigned device) (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 out 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 forward them to the DCC.

Spirotel® quality control procedures may be performed in advance of the Visit 2 date to prepare the device for the visit.

## Initializing the Run-In Visit Interval

### Visit 2
Have participant do one unscheduled PEF maneuver on his/her spirotel®.

After the participant's device has been set up with his/her information and has passed the quality control process, have the participant do one unscheduled peak flow maneuver using it. This measurement will be used to define the Visit 2 date in the device for purposes of generating spirotel® reports at Visit 3.

## Logging Dispensation and Return of Spirotel® Equipment

### Visit 2
Log/dispense spirotel® (SPIROTEL_DEVICE, SPIROTEL_TURBINE)
### Visits 10, 88 or whenever a participant leaves the study
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 VIDA 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, SPIROTEL_DEVICE and SPIROTEL_TURBINE must be updated to reflect receipt of these items. At the time of the termination visit, 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, note the date the device was shipped back to Respitech and/or the date Respitech was contacted for a replacement turbine.

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.

## VIDA Asthma Monitoring Log (P1_ASTHMA_LOG)

The Asthma Monitoring Log (P1_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 P1_ASTHMA_LOG is the only reference the participant will have to assess how his/her lung function and rescue Xopenex® use may have changed over recent days, possibly signaling the onset of a treatment failure. The log also includes space to record unscheduled peak flows, 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 P1_ASTHMA_LOG form was 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 2-9**
Complete and distribute Asthma Monitoring Log (P1_ASTHMA_LOG)

At each of visits 2 through 9 a new P1_ASTHMA_LOG form should be completed with participant information in the key fields area and dates, starting with the date of the current visit. The participant's '65% Baseline PEF' value from the Participant ID Card (P1_ID) should be recorded in the first two blank fields in the text at the top of the form. The participant's 'High Rescue Inhaler Use' value from P1_ID should be recorded in the third blank field in the text. The form should be given to the participant to complete until the next regularly scheduled visit.

**Visits 3-10, 88, 90-92**
Collect Asthma Monitoring Log (P1_ASTHMA_LOG)

Near the beginning of each visit, the participant's completed P1_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 VIDA study folder at the performance site; these forms should not be forwarded to the DCC.

Note: If a participant is discharged from the performance site because he/she has a low $FEV_1$ at the visit and does not meet any other treatment failure criteria, he/she will be

returning to complete the visit in 1-4 days. In that case the P1_ASTHMA_LOG form should be returned to the participant for completion until the return visit. See below for special procedures regarding Visits 90-92.

**Visits 90-92**
Return Asthma Monitoring Log (P1_ASTHMA_LOG) to participant

If a participant is being seen for an 'extra' treatment failure visit between regularly-scheduled visits, his/her P1_ASTHMA_LOG form should be collected and reviewed near the beginning of the visit, as usual. Before the participant leaves the visit, the form should be returned to him/her for completion until the next regularly scheduled visit.

## Uploading the spirotel®

**Visits 3-10, 88, 90-92**
Upload spirotel®

At each visit to the performance site, the data stored in the participant's spirotel®'s memory will be uploaded to the MedGraphics database. Once the data have been uploaded successfully, they will no longer be available on the participant's device. Data must be uploaded from a device before it can undergo the quality control process at a visit.

Note that data must be uploaded prior to generating reports at a visit. If a participant is present for an 'extra' treatment failure visit (visit 90-92), data should be uploaded from his/her device in order to generate a Participant Visit Report to review peak flow and diary data for treatment failure criteria. Note that at these visits, the return visit number must not be changed in the device. At the next regular visit, all data associated with that visit number will be included in updated reports.

If the participant forgets to bring his/her spirotel® to a visit, arrange for him/her to bring it to the clinic as soon as possible for upload 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, 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 upload. Further, it is possible that a treatment failure event on the basis of peak flow or rescue use criteria may have been missed, which will not be detected until the device is available for upload at a later date, which is not ideal for the study. Participants must be reminded to bring their devices with them to every study visit.

If a participant was discharged from a visit due to low $FEV_1$ and is now present for an $FEV_1$ re-assessment visit, his/her spirotel® must be uploaded at the current visit. Visit reports must be regenerated to include the data that accumulated over the past 1-4 days between visits.

## Compliance Assessments

### Visits 3-10

Print and review Spirotel® Participant Compliance Report (P1_COMPLY)

The e-diary questions serve as a daily log that should be completed by the participant twice a day, every day starting with the Visit 2 date, 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 peak flow is part of the VIDA treatment failure assessment, and increases in symptoms (recorded in the e-diary) often signal impending treatment failure, which is the primary outcome for VIDA. 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 in VIDA 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 3-10, the participant's spirotel® device will be uploaded to the MedGraphics database. The Spirotel® Participant Compliance Report for the current visit should be generated through the Breeze software. This report includes all data collected between the previous visit number and the current visit number. If multiple uploads were performed between visits and the return visit number was correctly specified, all data from the combined uploads will be used in the compliance assessment.

The Spirotel® Participant Compliance Report summarizes three values that will be recorded on the VIDA Compliance Checklist (P1_COMPLY):

- 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. This value is recorded in Q1100 on P1_COMPLY.

- 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

were answered and at least one peak flow maneuver was 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 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 at Visit 3. See the Eligibility Criteria discussion in this section for more information. This value is recorded in Q1110 on P1_COMPLY.

- Percent compliance: This value is computed as the number of e-diary complete days divided by the number of full days x 100. This value is recorded in Q1120 on P1_COMPLY.

## 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 and 6. This timing during the study was chosen because these are long visits at which the cleaning process can be accomplished without delaying the participant. These visits also mark the beginning of critical phases of the study during which the participant needs to receive accurate feedback on his/her peak flows to determine if treatment failure conditions are met. 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, 6**
Remove turbine from spirotel® device and clean
Replace cleaned turbine into spirotel® device

Near the beginning of Visit 3 and Visit 6, 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 Visit 3 and Visit 6, 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.

## VIDA Spirotel® Reports

### Visits 3-10
Print and review Spirotel® Participant Visit Report
Print and review Spirotel® Participant Compliance Report (P1_COMPLY)

### Visit 3
Print and review Spirotel® VIDA Eligibility and Baseline Report (P1_ELIG5)

Three spirotel® reports will be generated and consulted during the VIDA trial. Reports are accessed through the MedGraphics Breeze Suite software after a participant's spirotel® data are uploaded at a given visit by doing the following: 1) Open the Breeze Suite software. The 'Open Patient' screen will display. 2) Select the radio button 'PEF Only.' 3) Select the applicable participant ID and hit the 'Open' button. A list of visits for this participant will appear. 4) Select the desired visit and hit the 'Open Visit' button. 5) Select 'Quick Print' from the toolbar. 6) Three options are available for printing: All Reports, the Participant Visit Report, the Participant Compliance Report, or the VIDA Participant Eligibility and Baseline Report (available only at Visit 3).

Descriptions of the VIDA reports follow.

- Spirotel® Participant Visit Report: 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, baseline peak flow value, baseline rescue use value, turbine and device serial number, and upload date. If multiple uploads occur between visits, data from each upload are summarized separately.

  The body of the report shows all the data entered into the device sorted by trial date, trial type (AM session, PM session, extra PEF), and time each trial started. Variables include: trial date, trial type, time trial started (military time), VIDA diary questions Q1-Q19, number of peak flow maneuvers completed during a session, FVC, FEV1, PEF, FEF25-75, and FET. VIDA diary questions correspond to the order in which the participant answers them in the device. Refer to the VIDA Spirotel® Coordinator Reference Card (P1_SPIROTEL_CREF) when reviewing the report with a participant. Questions and their possible responses are listed below:

Q1: Number of times you woke up last night due to asthma (0-9)
Q2: Number of puffs you will take from your Alvesco® inhaler this morning (0-9)
Q3: Number of scheduled capsules you will take this morning (0-9)
Q4: Have you taken any puffs from your RESCUE Xopenex® inhaler during the past 4 hours? (3=yes, 0=no)
Q5: Shortness of breath score (during the night) (0,1,2,3)
Q6: Chest tightness score (during the night) (0,1,2,3)
Q7: Wheezing score (during the night) (0,1,2,3)
Q8: Cough score (during the night) (0,1,2,3)
Q9: Phlegm/mucus score (during the night) (0,1,2,3)
Q10: Number of puffs you will take from your Alvesco® inhaler tonight (0-9)
Q11: Have you taken any puffs from your RESCUE Xopenex® inhaler during the past 4 hours? (3=yes, 0=no)
Q12: Shortness of breath score (since awakening) (0,1,2,3)
Q13: Chest tightness score (since awakening) (0,1,2,3)
Q14: Wheezing score (since awakening) (0,1,2,3)
Q15: Cough score (since awakening) (0,1,2,3)
Q16: Phlegm/mucus score (since awakening) (0,1,2,3)
Q17: Number of RESCUE Xopenex® puffs taken during past 24 hours (0-40)
Q18: Number of times used RESCUE Xopenex® during past 24 hours (0-20)
Q19: Did you have a cold today? (3=yes, 0=no)

The Spirotel® Participant Visit Report should be reviewed with the participant at each visit, starting with Visit 3, to ensure that no treatment failure events were missed. Coordinators should carefully examine peak flow and rescue use (puffs) values for treatment failure criteria.

Coordinators should review the participant's answers to Q17 and Q18 (rescue Xopenex® use information) to ensure that the participant is using Xopenex® for primary treatment of asthma symptoms appropriately, and to confirm that he/she understands the difference between the two questions and how to calculate each.

Coordinators should review Q2 and Q10 (Alvesco® inhaler use) at each visit to ensure that the participant is following instructions for inhaled corticosteroid dosing as dictated by the protocol. Because the participant's dose will change over the course of the study, it is important to confirm that he/she is following the instructions during each study phase.

If a participant is seen for a treatment failure visit (Visit 90-92) 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 with the Visit 90-92 packet. At the next regular visit, following uploading of the participant's data, a new report should be generated. This report will show the data from both uploads and should be submitted to the DCC with the regular visit packet.

- Spirotel® Participant Compliance Report: This report summarizes a participant's compliance with completing his/her e-diary questions and peak flows in the interval between visits. If multiple uploads are done between visits, all data corresponding to a given visit number will be included in one summary report.

  See the compliance section above for further details on this report.

- Spirotel® VIDA Eligibility and Baseline Report: This report is used only at Visit 3 to establish the participant's baseline peak flow and rescue inhaler use values and to determine if his/her e-diary/peak flow compliance and symptoms meet the VIDA eligibility criteria.

  The top of the report shows the participant's VIDA ID number and initials.

  The 'PEF Baseline Value' section shows the participant's updated peak flow (PEF) baseline value using data entered between Visit 2 and Visit 3. The baseline peak flow value is the average pre-bronchodilator AM PEF value recorded during the last 2 weeks (14 days) of the run-in, including the AM PEF from the morning of Visit 3. Any peak flows obtained within 4 hours of using rescue Xopenex® puffs are excluded from the calculation. Missing values are also ignored. The PEF Baseline Value section shows the number of AM sessions (out of the 14 leading up to the visit) used in the calculation. It also shows the Baseline PEF, which is the average of the eligible, pre-bronchodilator AM peak flow values, and the participant's 65% Baseline PEF reference value for determining when treatment failure conditions are met. The report defines the baseline value that should be programmed into the spirotel® device at Visit 3.

  The 'Rescue Use Baseline Value' section shows the participant's updated rescue use baseline value using data entered between Visit 2 and Visit 3. The baseline rescue use value is the average number of Xopenex® RESCUE puffs used during the 14 days prior to Visit 3. Missing values in the 14-day period are ignored. The Rescue Use Baseline Value section shows the number of PM sessions (out of the 14 day period) that were used in the calculation. It also shows the Baseline Rescue Use value and the participant's High Rescue Use value (defined as 8+Baseline Rescue Use Value) used for determining when

treatment failure conditions are met. The report defines the baseline value that should be programmed into the spirotel® device at Visit 3.

The next two sections of the report determine whether or not the participant meets the e-diary/peak flow compliance and symptom eligibility criteria. Data on the report provide answers to Q1000 and Q1010 on VIDA Eligibility Checklist 5 (P1_ELIG5).

The Q1000 section shows the answer to Q1000 based on the participant's e-diary/peak flow compliance, along with the number of compliant days out of the 14 days prior to the visit. The day of Visit 3 is not included in the calculations. In order for a day to be considered 'compliant', the participant had to complete at least one of the scheduled AM and/or PM sessions that day, including all e-diary questions and at least one peak flow maneuver.

The Q1010 section shows the answer to Q1010 based on the participant's reported symptom scores for Q5-Q9 (nighttime symptoms) and Q12-Q16 (daytime symptoms) during the 2 weeks (14 days) prior to Visit 3. The report divides the 14 days prior to Visit 3 into two 7-day weeks leading up to the day of the visit, not including the morning of Visit 3. For each defined week, it computes the number of days when at least one daytime symptom (with score 1, 2, or 3) was reported. For each defined week, it computes the number of days when at least one nighttime symptom (with score 1, 2, or 3) was reported. The report then computes the average number of days with daytime symptoms across the two weeks (average days per week with symptoms). It also calculates the average number of nights across the two weeks with nighttime symptoms reported (average nights per week with symptoms). Average days per week and nights per week with symptoms are shown on the report. If the participant reported asthma symptoms on at least two days or one night per week, on average, then he/she meets the eligibility criterion.

## VIDA Spirotel® Alerts

Several alert messages have been programmed into the VIDA spirotel® device in an effort to improve participant compliance with taking study medications, recognizing treatment failure events, and completing the WURSS-21 survey when a cold is experienced. Alerts appear following a completed scheduled AM or PM session when certain criteria are met. Alert definitions follow.

- "Take Your Meds/If Instructed" Alert

  This alert appears after every scheduled AM and PM session is complete, including three peak flow maneuvers.

  Note that there may be points in the study when a given participant is not instructed to take any PM medications. Clinic personnel need to be sure the participant is clear on his/her dosing instructions and that this alert should be ignored in that case. This is a major training issue. The PM alert will have a second line that reads "If Instructed" to help guide the participant.

- "Peak Flow Low/Call Clinic ASAP" Alert

  This alert appears after a completed scheduled AM or PM session when the participant meets the peak flow criterion for treatment failure at that session. That is, if 2 out of 3 consecutive scheduled AM and/or PM peak flows are ≤65% of the participant's baseline peak flow that is programmed into his/her spirotel® device, and the completed session triggers the treatment failure criterion, then the alert will appear.

- "RESCUE Use High/Call Clinic ASAP" Alert

  This alert appears after a completed scheduled PM session when the participant meets the rescue use criterion for treatment failure at that session. That is, if it is the second consecutive scheduled PM session where the participant indicates in e-diary Q17 that he/she used at least as many puffs as his/her 'high rescue inhaler use' value (defined as 8 + the baseline rescue use value that is programmed into the participant's spirotel® device), the alert will appear. The participant must indicate high rescue inhaler use (in puffs/day) for two consecutive calendar days for the alert to trigger.

- "Complete WURSS/Tonight" Alert

  This alert is triggered following a completed scheduled PM session when the participant answers e-diary Q19 (Have cold today?) 'yes.' The participant will have a supply of the WURSS-21 surveys at home to complete daily when he/she has a cold during the post-randomization phases of the study. It is possible that the participant will receive this alert prior to randomization if he/she experiences a cold during the run-in or oral corticosteroid response periods of the study. He/she should be instructed that the alert should be ignored in this case.

  The participant will receive a handout with instructions for completion of the WURSS-21 survey (P1_WURSS21_INST). He/she will be asked to complete the survey for two extra days beyond the end of the cold event (i.e., when the "Have cold today? " question is answered 'no'). No alert will be triggered on the spirotel® device for these days to remind the participant to complete the survey. This is a training issue. See the Wisconsin Upper Respiratory Symptom Survey-21 discussion in this section for additional details.

## Spirotel® Traffic Light Settings

The spirotel® device has red, orange, yellow, and green zones on its display. Zones have been defined as follows for the VIDA study:

Green: Highest PEF > 80% of baseline PEF
Yellow: 65 < Highest PEF ≤ 80% of baseline PEF
Red: Highest PEF ≤ 65% of baseline PEF

Note that no 'orange' zone has been defined in the spirit of the 'traffic light' interpretation of peak flows.

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 baseline value.

If the participant's highest peak flow during a scheduled session is in the red zone, he/she should be cognizant of possible treatment failure conditions. A spirotel® alert will appear if this is the second consecutive session out of three where his/her highest peak flow is in the red zone.

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 VIDA Asthma Monitoring Log (P1_ASTHMA_LOG) as another source of information when reviewing spirotel® reports at a visit.

## 2.48 Sputum Induction

**Visit 3, 6**
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 provides important secondary outcome variables for the VIDA study. 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.

**Quotas for sputum induction**

All participants should attempt to qualify for sputum induction at Visit 3. Due to budgetary constraints, only half of the 400 randomized participants (~200) will proceed with sputum induction at Visit 6. In order to be eligible to qualify for the Visit 6 sputum induction, individuals must have had a successful sputum induction at Visit 3, resulting in a sample that was deemed adequate by the overreader in San Francisco. Adequate samples are defined as having less than 80% squamous cells and the presence of a %eosinophils reading on the sputum overread report.

The status of each participant's Visit 3 sputum sample will be communicated to the performance sites via the VIDA Participant Status Report. If the 'Sputum Status at V3' column on the report is coded 'Adequate', then the participant may attempt to qualify for the Visit 6 sputum induction, as long as the sample size of 200 Visit 6 inductions has not yet been achieved. The VIDA Accrual Report will include a table that summarizes the number of Visit 6 sputum inductions that have been completed at each clinical center partnership and Network-wide. For additional details on the Participant Status Report, see the related discussion in this section.

Note: As the Network approaches the target of 200 Visit 6 sputum inductions, the DCC will monitor the distribution of the treatment arms (vitamin D or placebo) for those who have completed the extra sputum induction. If significant imbalance is present, the DCC may need to approve each subsequent participant identified as eligible for the Visit 6 induction in an effort to restore balance.

### Pre-sputum induction spirometry

Individuals who complete the methacholine challenge at Visit 3 and Visit 6 should be reversed with 4 puffs of levalbuterol as the standard reversal if they are being qualified for sputum induction at the visit. 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.

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 $FEV_1$ % of 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 'FEV1 absolute' column on the Methacholine Report. Multiply the result by 100% and round to the nearest %.

Individuals who do not complete the methacholine challenge at Visit 3 or Visit 6 and who are eligible to qualify for sputum induction at the visit (as described above) must undergo reversal with 4 puffs of levalbuterol to be assessed for procedure eligibility. Results of the reversal testing are recorded on the Post-Albuterol (4 puffs) Spirometry Testing (PALB4_SPIRO) form. The Spirometry Report generated through the MedGraphics system (Pre/Post report) provides the % predicted value needed to complete the Sputum Induction Checklist (SPUTUMCHK) form and assess the participant for eligibility for the sputum induction procedure.

The $FEV_1$ value (in liters) after final 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.

### Treatment Failures and Exacerbations at Visit 6

Participants who meet criteria for a significant asthma exacerbation at Visit 6 should not proceed with sputum induction at the visit. If a participant meets treatment failure criteria but does not meet exacerbation criteria, he/she may proceed with the sputum induction as long as all criteria on SPUTUMCHK are met and as long as the study physician has cleared the participant for the procedure.

## 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 shipments to San Francisco

Slides

For the VIDA trial, all accumulated Visit 3 and Visit 6 sputum slides should be shipped to San Francisco the second Tuesday of each month for overnight receipt. The scheduled shipment dates follow:

| 2011 | 2012 | 2013 |
|---|---|---|
| May 10 | January 10 | January 8 |
| June 14 | February 14 | February 12 |
| July 12 | March 13 | March 12 |
| August 9 | April 10 | |
| September 13 | May 8 | |
| October 11 | June 12 | |
| November 8 | July 10 | |
| December 13 | August 14 | |
| | September 11 | |
| | October 9 | |
| | November 13 | |
| | December 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 slides on an alternate date; slides should not be held until the next month's shipment date. It is imperative that slides are shipped on the monthly schedule to ensure that overreading results are available in time to qualify participants for the Visit 6 sputum induction.

Supernatant/pellets

For the VIDA trial, sputum supernatant and pellets should be shipped to San Francisco on the following dates (i.e., every 6 months) for overnight receipt:

2011 December 13

2012 June 12
December 11

2013 Final shipment date to be determined

## 2.49 Study Handout Folder

At the end of Visit 0 the participant should be given one handout, the VIDA Clinic Contact Information (P1_CLINFO) form. This form provides contact information for clinical personnel in the event that the participant needs to get in touch with the performance site before his/her Visit 0 vitamin D eligibility status is known. See the Contact Information discussion in this section for further details.

Starting with their entry into the run-in period at Visit 2, VIDA 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. 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 VIDA participation. The folder should be brought to each study visit so that clinical personnel can review and/or update handouts, as necessary.

**VIDA Study Handout Folder Contents**

- VIDA Daily Activities (P1_DAILYACT2) – distributed at Visit 2
- VIDA Daily Activities (P1_DAILYACT3) – distributed at Visit 3
- VIDA Daily Activities (P1_DAILYACT4) – distributed at Visit 4
- VIDA Daily Activities (P1_DAILYACT6) – distributed at Visit 6
- VIDA Daily Activities (P1_DAILYACT8) – distributed at Visit 8

“Daily Activities” handouts contain simple summaries of the activities the participant should carry out each day during the VIDA study. Other handouts provide details on the execution of these activities. The “Daily Activities” handouts also list the participant’s peak flow and high rescue inhaler use reference values. They prompt the participant to contact clinical personnel when they may be experiencing a treatment failure event. See the Daily Activities Handout discussion in this section for further details.

- If Your Asthma Gets Worse (P1_ASWORSE)
- Participant Identification Card (P1_ID)

These references facilitate the identification and treatment of asthma exacerbations and treatment failure events according to the protocol, both by the participant and by healthcare providers. The P1_ASWORSE handout is introduced at Visit 2 and reviewed at subsequent visits, as needed. P1_ID is introduced at Visit 2 and updated at Visit 3 with new reference peak flow and high rescue inhaler use values. The ID card contains

reference values for defining exacerbations and treatment failures and 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.

- VIDA DOSER™ Instructions (P1_DOSERINST)

This handout instructs participants on proper use of the DOSER™ device with his/her study Alvesco® inhaler(s). It is introduced at Visit 2.

- 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 2.

- VIDA How to Use Your MEMS®6 Cap (P1_MEMSINST)

This handout provides instructions on the correct use of the MEMS®6 cap with VIDA study drugs. For additional information on the MEMS®6 cap, see the MEMS®6 Cap discussion in this section. This handout is introduced at Visit 2.

- How to Use Your Spirotel® Electronic Diary and Peak Flow Meter (HTSPIROTEL)
- VIDA Spirotel® Reference Card (P1_SPIROTEL_REF)

HTSPIROTEL is a standard handout that provides instructions for home use of the spirotel® e-diary and peak flow meter. P1_SPIROTEL_REF is a VIDA-specific reference card that gives the participant additional information on the VIDA e-diary questions and alerts. This reference is printed as a tri-fold card that fits in the spirotel®'s carrying case. These handouts are introduced at Visit 2. For more information see the spirotel® discussion in this section.

- VIDA Visit Preparation Checklist (P1_VISPRP)

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 P1_VISPRP 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 2.

- VIDA Wisconsin Upper Respiratory Symptom Survey – 21 (WURSS-21) Instructions (P1_WURSS21_INST)

This handout instructs the participant on when and how to complete the WURSS-21 survey in the event that he/she experiences a cold during the study. It is distributed at Visit 4. See the Wisconsin Upper Respirator Symptom Survey-21 discussion in this section for further details.

- VIDA 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.

## 2.50 Study Medications

During the VIDA trial, participants will receive the following study medications:

- ciclesonide HFA (Alvesco®; 80 mcg per puff), an inhaled corticosteroid (ICS) to be used 2 puffs BID every day through the run-in, oral corticosteroid (OCS) response period and Phase I. ICS dose will be tapered for Phases IIa and IIb for participants who qualify for the taper. See the Inhaled Corticosteroid Dose Taper discussion in this section for details.

  Alvesco® is labeled 'VIDA Inhaler – Alvesco®' throughout the trial. It is supplied with a brown plastic actuator with a red dust cap. Labels for these inhalers are white. This is an open-label medication that will be dispensed from bulk supplies provided by the DCC.

- levalbuterol rescue drug (Xopenex®), an inhaled beta-agonist to be used as-needed throughout the VIDA trial, starting at Visit 2, to treat asthma symptoms.

  Xopenex® rescue drug will be labeled 'VIDA Xopenex® (RESCUE) Inhaler.' It is supplied with a blue plastic actuator with a red dust cap. Labels for these inhalers are red. Xopenex® will be dispensed from bulk supplies provided by the DCC.

- run-in scheduled daily capsules, single-blind placebo capsules. Capsule vials will be labeled 'VIDA Capsule Vial – Run-In Scheduled Daily Capsules' and dispensed at Visit 2 from bulk supplies provided by the DCC. Each vial contains 35 placebo capsules. Participants will take 1 capsule each morning.

- oral corticosteroid (OCS) response period scheduled daily capsules, single-blind placebo capsules. Capsule vials will be labeled 'VIDA Capsule Vial – OCS Response Period Scheduled Daily Capsules' and dispensed at Visit 3 from bulk supplies provided by the DCC. Each vial contains 14 placebo capsules. Participants will take 1 capsule each morning.

- oral corticosteroid (OCS) response period prednisone. Tablet vials will be labeled 'VIDA Tablet Vial – OCS Response Period Prednisone' and dispensed at Visit 3 from bulk supplies provided by the DCC. Each vial contains 14 20 mg prednisone tablets to be taken 2 per day in the morning for 5-7 days until Visit 4.

- rescue prednisone, an oral steroid 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 following randomization at Visit 4. See the Significant Asthma Exacerbation discussion in this section for taper details.

- loading dose double-blind vitamin D/placebo. Capsule vials will be labeled 'VIDA LOADING DOSE Capsule Vial', will contain two capsules, and will be dispensed at Visit 4. Loading dose vials are numbered and their contents are blinded (either 50,000 IU vitamin D capsules or placebo). The number of the loading dose vial to assign to a given participant is provided by the VIDA Randomization Module. Participants will take both loading dose capsules from their assigned vial the morning following Visit 4. For details on randomization procedures, see the Randomization discussion in this section and section 3 of this manual.

- regular dose double-blind vitamin D/placebo. Capsule vials will be labeled 'VIDA REGULAR DOSE Capsule Vial – Scheduled daily capsules', will contain 52 capsules, and will be dispensed at Visits 4-9. Regular dose vials are numbered and their contents are blinded (either 4,000 IU vitamin D capsules or placebo). The number of the regular dose vial to assign to a given participant at each applicable visit is provided by the VIDA Randomization Module. Participants will take one capsule from their assigned vial each morning, with the exception of the day following randomization. For details on randomization procedures, see the Randomization discussion in this section and section 3 of this manual.

Procedures related to drug dispensation and participant education on use of these medications are given under the appropriate visits below. See section 5 of this manual for detailed drug-related instructions.

**Visit 2-9, 90-92**
Log/Dispense Xopenex® (RESCUE) inhaler (P1_DRG_XOP)
Check supply of Xopenex® and log/dispense a new inhaler, if needed (P1_DRG_XOP)

Every participant should receive a new levalbuterol rescue inhaler (labeled 'VIDA Xopenex® (RESCUE) Inhaler') at Visits 2, 4, 6, and 8. At all other visits through Visit 9, including Visits 90-92, the participant's rescue use should be reviewed and a new inhaler dispensed, if necessary. The participant must be assured an adequate supply of rescue medication throughout the trial. When dispensing a rescue inhaler to a participant, the next available row on the VIDA Drug Dispensing Log: Xopenex® (RESCUE) Inhaler (P1_DRG_XOP) should be completed by the person dispensing the medication. See sections 4 and 5 for details on completion of this log.

**Visit 2**
Instruct participant on use of Xopenex® (RESCUE) inhaler (HTMDI, P1_ASWORSE)

Review the closed-mouth inhalation technique described in the "How to Use Your Metered Dose Inhaler (MDI)" (HTMDI) handout and demonstrate the method. The participant will have an opportunity to practice his/her inhalation technique with a placebo inhaler at this visit. Clinical staff will assess the participant's technique via the MDI Inhalation Technique Checklist (Without Spacer) (TECH_MDI_NOSP). See the Inhalation Technique Assessment discussion in this section for further details.

Show the participant the label on the levalbuterol inhaler and explain that the RESCUE inhaler is to be used on an as-needed basis whenever he/she experiences asthma symptoms and needs relief. Emphasize that the levalbuterol RESCUE inhaler should be carried with the participant at all times and that he/she should not use other inhalers for rescue medication.

Review the "If Your Asthma Gets Worse" (P1_ASWORSE) handout with the participant. Ensure that the participant knows his/her reference peak flow and rescue use values and how to identify a potential treatment failure or exacerbation event. Ensure that he/she understands how to initiate treatment and how to contact the clinical site in an emergency. Further details regarding exacerbations and treatment failures can be found in the Significant Asthma Exacerbation and Treatment Failure discussions in this section.

**Visit 4, 6, 8, 10, 88 and any time a Xopenex® inhaler is collected**
Collect/log Xopenex® (RESCUE) inhaler (P1_DRG_XOP)

Used rescue inhalers must be collected and accounted for. When collecting a rescue inhaler from a participant, its row on the VIDA Drug Dispensing Log: Xopenex® (RESCUE) Inhaler (P1_DRG_XOP) should be identified and updated by the person collecting the medication. See sections 4 and 5 for details on completion of this log.

**Visit 2-9, 90-92**
Log Alvesco® inhaler(s) and log/set DOSER™ (P1_DRG_ALV, P1_DRG_ALV_DOU, DOSER_LOG, P1_DRG_SCH)
Check supply of Alvesco® and dispense additional inhalers, if needed (P1_DRG_ALV, P1_DRG_SCH, P1_DRG_ALV_DOU)
Attach DOSER™ to one of the Alvesco® inhalers; dispense

Each participant will be dispensed a new supply of open-label Alvesco® inhalers at each visit 2-9 (and visits 90-92, if necessary). When dispensing Alvesco® inhalers to a participant, the next available row on the VIDA Drug Dispensing Log: Alvesco® ICS

Inhaler (P1_DRG_ALV) should be completed by the person dispensing the medication. This log maintains a balance of available inhalers at the performance site. Each time Alvesco® inhalers are dispensed following randomization (at Visits 4-9, 90-92), they also need to be logged on the participant-specific VIDA Drug Dispensing Log: Post-Randomization Study Medications (P1_DRG_SCH). If Alvesco® inhalers are dispensed at Visit 90-92, record them in the row for the last regular visit.

The VIDA Alvesco® Dates of Use Worksheet is used to determine the dates of use for each inhaler when multiple inhalers are being dispensed at a given visit. This worksheet helps to ensure that the capacity of each inhaler is not exceeded.

See sections 4 and 5 for more details on completion of the drug logs and dates of use worksheet.

See the DOSER™ discussion in this section for details on setting the DOSER™ and attaching it to one of the dispensed Alvesco® inhalers.

**Visit 2**
Instruct participant on how to use Alvesco® inhaler (HTMDI, P1_DAILYACT2)

Review the "VIDA Daily Activities (Visit 2)" (P1_DAILYACT2) handout with the participant. This handout covers dosing with the open-label Alvesco® inhaler that should take place twice a day, every day, until Visit 3.

**Visit 3-10, 88**
Collect/log Alvesco® inhalers (P1_DRG_ALV, P1_DRG_SCH)

All used Alvesco® inhalers must be collected and accounted for. When collecting an Alvesco® inhaler from a participant, its row on the VIDA Drug Dispensing Log: Alvesco® ICS Inhaler (P1_DRG_ALV) should be identified and updated by the person collecting the medication. Following randomization, returned Alvesco® inhalers also need to be logged on the participant-specific VIDA Drug Dispensing Log: Post-Randomization Study Medications (P1_DRG_SCH). See sections 4 and 5 for details on completion of these logs.

**Visit 6, 8**
Determine participant's ICS dosing schedule and number of inhalers to dispense (P1_ALV_DIST_REF)

At Visits 6 and 8 participants are eligible for tapering of their ICS dose if they meet stability criteria. The Alvesco® Distribution Reference Card (P1_ALV_DIST_REF)

serves as a guide for determining the number of Alvesco® inhalers to dispense according to the participant's current ICS dose.

**Visit 2**
Log/Dispense run-in capsule vial (P1_DRG_RUNIN_CAPS)

When dispensing a run-in capsule vial to a participant at Visit 2, the next available row on the VIDA Drug Dispensing Log: Run-In Scheduled Capsules (P1_DRG_RUNIN_CAPS) should be completed by the person dispensing the medication. This log maintains the balance of capsule vials available at the performance site. See sections 4 and 5 for details on completion of this log.

**Visit 2**
Instruct the participant on how to take the run-in capsules (P1_DAILYACT2)

Review the "VIDA Daily Activities (Visit 2)" (P1_DAILYACT2) handout with the participant. This handout covers dosing with the scheduled daily capsules every day until Visit 3.

**Visit 3**
Collect/log run-in capsule vial (P1_DRG_RUNIN_CAPS)

All used run-in capsule vials must be collected and accounted for. When collecting a run-in capsule vial from a participant at Visit 3, its row on the VIDA Drug Dispensing Log: Run-In Scheduled Capsules (P1_DRG_RUNIN_CAPS) should be identified and updated by the person collecting the medication. See sections 4 and 5 for more details on completion of this log.

**Visit 3**
Log/dispense OCS response period capsule vial (P1_DRG_OCS_RESP_CAPS)

When dispensing an oral corticosteroid response period capsule vial to a participant at Visit 3, the next available row on the VIDA Drug Dispensing Log: OCS Response Period Scheduled Capsules (P1_DRG_OCS_RESP_CAPS) should be completed by the person dispensing the medication. This log maintains the balance of capsule vials available at the performance site. See sections 4 and 5 for details on completion of this log.

**Visit 4**
Collect/log OCS response period capsule vial (P1_DRG_OCS_RESP_CAPS)

All used oral corticosteroid response period capsule vials must be collected and accounted for. When collecting a capsule vial from a participant at Visit 4, its row on the VIDA Drug Dispensing Log: OCS Response Period Scheduled Capsules (P1_DRG_OCS_RESP_CAPS) should be identified and updated by the person collecting the medication. See sections 4 and 5 for more details on completion of this log.

**Visit 3**
Dispense open-label prednisone 7-day supply for OCS response evaluation (P1_DRG_OCS_RESP_PRED)

When dispensing an oral corticosteroid response period prednisone tablet vial to a participant at Visit 3, the next available row on the VIDA Drug Dispensing Log: OCS Response Period Prednisone (P1_DRG_OCS_RESP_PRED) should be completed by the person dispensing the medication. This log maintains the balance of tablet vials available at the performance site. See sections 4 and 5 for details on completion of this log.

**Visit 4**
Collect/log any leftover OCS response period prednisone (P1_DRG_OCS_RESP_PRED)

All used oral corticosteroid response period prednisone tablet vials must be collected and accounted for. When collecting a tablet vial from a participant at Visit 4, its row on the VIDA Drug Dispensing Log: OCS Response Period Prednisone (P1_DRG_OCS_RESP_PRED) should be identified and updated by the person collecting the medication. See sections 4 and 5 for more details on completion of this log.

**Visit 4**
Log/dispense rescue prednisone (P1_DRG_RESC_PRED)

During the VIDA trial, participants will be taking a standard (low) dose of Alvesco® with the potential for tapering of the dose at Visits 6 and 8. Levalbuterol will be available for use as the participant's primary rescue medication.

At some point during the study, the participant may experience a significant asthma exacerbation and may require therapy in addition to his/her levalbuterol (Xopenex® (RESCUE)) inhaler and an escalation of study inhaled corticosteroids. Prednisone will be used when, in the judgment of the investigator, an acute exacerbation cannot be controlled by albuterol and inhaled corticosteroid therapy. Prednisone will be used at the investigator's discretion and under his/her direction only.

To ensure prompt treatment should an exacerbation occur at home, each participant will be given one 8-day course of oral prednisone to store at home. At Visit 4 clinical personnel should dispense a course consisting of 60 mg as a single dose every day for 3 days, followed by a 10 mg/day taper over the next 5 days. This medication should be dispensed in childproof packaging.

Prednisone should be obtained from the local clinical pharmacy for dispensation as a rescue medication; it will not be supplied by AsthmaNet. Proper labeling is the responsibility of the performance site.

The decision to initiate or to continue a course a prednisone beyond 8 days is left to the discretion of the investigator.

When dispensing rescue prednisone to a participant at Visit 4, the next available row on the VIDA Drug Dispensing Log: Rescue Prednisone Tablets (P1_DRG_RESC_PRD) should be completed by the person dispensing the medication. See sections 4 and 5 for details on completion of this log.

**Visit 4**
Randomize participant
Log assigned Loading Dose and Regular Dose capsule vial numbers (P1_LOG)
Log/dispense Loading Dose and Regular Dose capsule vials (P1_DRG_SCH)
Confirm medication dispensation (P1_MED)

Eligible participants are randomized at Visit 4. The VIDA Randomization Module presents the participant's assigned loading dose and regular dose capsule vial numbers. These vial numbers are logged on VIDA Drug Dispensing Log: Post-Randomization Study Medications (P1_DRG_SCH) and on the Participant Assignment Log (P1_LOG). The person dispensing the vials should complete this information. See the Randomization discussion in this section and section 3 of this manual for details on the Randomization Module.

Each time a post-randomization capsule vial is dispensed, a VIDA Scheduled Capsules (P1_MED) form must be completed to confirm the dispensation in the VIDA database. See sections 4 and 5 of this manual for details on the completion of this form and related logs.

**Visit 5**
Collect/log Loading Dose capsule vial (P1_DRG_SCH)

At Visit 5 the participant's loading dose capsule vial is returned to the performance site. The person collecting the vial should update the Visit 4 row on the VIDA Drug

Dispensing Log: Post-Randomization Study Medication (P1_DRG_SCH) log with information on the collection. See sections 4 and 5 of this manual for details on the completion of this log.

**Visit 5-10, 88**
Collect/log Regular Dose capsule vial (P1_DRG_SCH)

At each scheduled post-randomization visit the participant returns a regular dose capsule vial to the performance site. The person collecting the vial should update the appropriate row on the VIDA Drug Dispensing Log: Post-Randomization Study Medication (P1_DRG_SCH) with information on the collection. See sections 4 and 5 of this manual for details on the completion of this log.

**Visit 5-9**
Generate new Regular Dose capsule vial number via randomization module
Log assigned Regular Dose capsule vial number (P1_LOG)
Log/dispense Regular Dose capsule vials (P1_DRG_SCH)
Confirm medication dispensation (P1_MED)

At Visits 5-9 the VIDA Randomization Module is accessed in order to generate a new regular dose capsule vial number for the participant. The module may be accessed up to 5 calendar days in advance of the visit to generate the vial number and prepare for the visit. This vial number is logged on VIDA Drug Dispensing Log: Post-Randomization Study Medications (P1_DRG_SCH) and on the Participant Assignment Log (P1_LOG). The person dispensing the vial should complete this information. See the Randomization discussion in this section and section 3 of this manual for more details on the Randomization Module.

Each time a post-randomization capsule vial is dispensed, a VIDA Scheduled Capsules (P1_MED) form must be completed to confirm the dispensation in the VIDA database. See sections 4 and 5 of this manual for details on the completion of this form and related logs.

## 2.51 Study Treatment Questionnaires

**Visit 10 (or last post-randomization contact at Visits 5-9, 88, or 90-92)**
Have participant complete Participant Study Treatment Questionnaire (P1_PARTTXQX)
Complete Coordinator Study Treatment Questionnaire (P1_CTXQX)

The study treatment questionnaires are used to assess how well the masking of the scheduled capsules was carried out. The Participant Study Treatment Questionnaire (P1_PARTTXQX) was developed to evaluate the blind from the participant's perspective. The Coordinator Study Treatment Questionnaire (P1_CTXQX) was developed to evaluate the blind from the study coordinator's perspective. These questionnaires are completed at the participant's final post-randomization study visit. Questions on the forms address the treatment the participant or study coordinator thought the participant received since starting blinded, randomized treatment at Visit 4.

If a participant withdraws from the study following randomization and prior to Visit 10, 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 P1_PARTTXQX questionnaire over the phone. In this case, no source documentation will be recorded.

**Participant Study Treatment Questionnaire**

Near the conclusion of Visit 10, the participant should complete a Participant Study Treatment Questionnaire (P1_PARTTXQX). This form is designed to determine how well the blind on the VIDA scheduled capsules performed with respect to the participant's perceptions of the study medication (i.e., active vitamin D versus placebo) he/she received since randomization at Visit 4. 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 regular dose capsule vial.

This questionnaire is participant-completed. It is relatively short and should take no longer than five minutes to complete. Study personnel should not help the participant to answer questions on the questionnaire, as such assistance could influence the participant's responses and result in bias. Participants 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 should initial and date the source documentation box on page 2.

## Coordinator Study Treatment Questionnaire

Near the end of Visit 10, the study coordinator who was primarily responsible for the participant's VIDA study visits since randomization at Visit 4 should complete a Coordinator Study Treatment Questionnaire (P1_CTXQX). This form is designed to determine how well the blind on the VIDA scheduled capsules performed with respect to the coordinator's perceptions of the study medication (i.e., active vitamin D versus placebo) the participant received since randomization. The coordinator should complete this form before reviewing the participant's questionnaire (P1_PARTTXQX) 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 P1_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 is unavailable during Visit 10 or the participant's early withdrawal visit, the P1_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.

If a randomized participant is lost to follow-up or withdraws early and is unavailable to complete the P1_PARTTXQX form, the study coordinator still should complete a P1_CTXQX form, as long as the participant had at least one follow-up visit during the double-blind treatment period. In this case the P1_CTXQX form should be submitted as a single form as part of a Visit 88 packet, along with any other information that might be available.

See Section 4 in this manual for further details regarding the completion of the P1_CTXQX and P1_PARTTXQX forms.

## 2.52 Sun Exposure Questionnaire

Vitamin D is produced endogenously when ultraviolet (UV) rays from sunlight strike the skin and trigger vitamin D synthesis. To quantify each VIDA participant's UV exposure history, a modification of the UV exposure questionnaire used in the Nurses' Health Study[14] has been developed into the VIDA Sun Exposure Questionnaire (SEQ). This questionnaire inquires about the participant's average hours per day spent outdoors in summer and winter, the frequency the participant is outdoors for activities in summer and winter, and sunscreen and tanning salon habits. This questionnaire is administered prior to randomization and again at the end of the trial to determine if the participant's sun exposure habits changed over the course of the trial. Because the frame of reference for the original survey is the past 3 years, two versions of the VIDA questionnaire have been developed: 1) the P1_SEQ_3 questionnaire is administered at Visit 3 and addresses sun exposure over the last 3 years; 2) the P1_SEQ_10 questionnaire is administered at Visit 10 and addresses sun exposure since the participant was randomized in the VIDA trial (roughly 7 months). Information from the melanin skin readings will be interpreted in conjunction with the SEQ results. See the SmartProbe 400 discussion in this section for further details on melanin readings.

**Visit 3**
Administer Sun Exposure Questionnaire (P1_SEQ_3)
**Visit 10**
Administer Sun Exposure Questionnaire (P1_SEQ_10)

Both forms of the SEQ are completed by the participant. Ensure that all questions are answered, with exactly one response per question. If the participant requests help with a question, offer guidance.

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. Check that the participant's responses are clearly marked.

[14] Han J, Colditz GA, Hunter DJ. Risk factors for skin cancers: a nested case-control study within the Nurses' Health Study. International Journal of Epidemiology 2006; 35:1514-1521.

Note that Q1050 on both versions of the SEQ addresses tanning salon patronage. If a participant visits a tanning salon for the sole purpose of spray tanning, this question should be answered 'No.' Spray tanning does not afford any change in vitamin D synthesis as it does not involve the transference of UV light.

## 2.53 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. VIDA-specific considerations follow.

- Participant Assignment Log: Complete the participant ID number and other information on the Participant Assignment Log (P1_LOG) (Not Pre-Filled) version. Maintain this log with the site-specific VIDA log. The participant should retain his/her original ID that was assigned at the originating site.

- 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 participant's device should be reconfigured to reflect the new performance site at his/her first visit at the new site.

  The new site should download the participant's spirotel® data to the site's Breeze Suite database and upload spirotel® data to the central database at MedGraphics following normal procedures. If the first visit at the new site is a visit 4-10, the new site will need to contact the DCC to generate the appropriate spirotel® reports for the visit. Once the first download is stored on the site's local machine, subsequent downloads and reports may be printed as usual (provided the visit data downloaded at the new site reside on the same MedGraphics machine each time).

- Randomization: In the VIDA 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

capsule bottle 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).

- DOSER™: The originating site should put a note in the Comments section of the DOSER™ Tracking Log (DOSER_LOG) indicating that the DOSER™ went to the new site with the participant. The new site should increment their DOSER™ balance by 1 on their DOSER_LOG and contact the originating site for the device's 'wake up date.' The DOSER™ will not be returned to the originating site (unless the participant returns to the originating site).

- MEMS®6 Cap: The originating site should put a note in the Comments section of the MEMS®6 Monitor Log (MEMS_LOG) indicating that the MEMS®6 cap went to the new site with the participant. The new site should increment their MEMS®6 balance by 1 on their MEMS_LOG and record the cap's information. The cap will not be returned to the originating site (unless the participant returns to the originating site).

- Baseline Peak Flow and Rescue Use Values: The originating site should provide the new performance site a photocopy of the most recent Baseline PEF and Rescue Use Values (P1_BASELINE) form (Visit 2 or Visit 3). In addition, if the participant is beyond Visit 3, the originating site should confirm the participant's reference $FEV_1$ value.

- Current Dosing Information and Exacerbation/Treatment Failure History: The originating site should supply the new site details of the participant's current Alvesco® dose. The originating site should supply the new site a summary of all treatment failure and exacerbation events the participant has experienced in the study, along with their dates and any ongoing treatment (primarily increased Alvesco® dosing and/or prednisone). 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 .

- 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. The height and weight recorded on this form should be referenced when entering participant characteristics into the MedGraphics PC.

- Green Mechanistic Study Participation: If the participant transfers between Visit 2 and Visit 3 (during the run-in), the originating performance site should send the new site a copy of the local lab report confirming normal hematocrit levels. The new site should reference the VIDA Participant Status Report for the participant's enrollment site for the participant's mechanistic study participation status beyond Visit 3. This assumes that appropriate database permissions have been requested/granted. The new site should confirm the participant's consent to continue in the study based on his/her responses on the local consent document.

- Sputum Status: The new site should refer to the VIDA Participant Status Report for the participant's enrollment site for the status of the participant's Visit 3 sample when planning for Visit 6. This assumes that appropriate database permissions have been requested/granted.

- Physical Exams: The originating site should send copies of the short and long physical exam forms (LEXAM_ADULT, SEXAM_ADULT) to the new site.

- Evaluation of Spirometry-Related Outcomes: Significant asthma exacerbation $FEV_1$-related criteria (SIGEX Q1020 and Q1030) and treatment failure $FEV_1$-related criterion (TXFAIL_CHK Q1030) are evaluated by observing if consecutive $FEV_1$ values have fallen below a defined limit. Assuming appropriate database permissions have been requested/granted, the new site may use the Participant Data module to view the Spirometry Testing (SPIRO) form data for previous visits completed at the originating site.

- Skin Testing: If allergy skin testing was deferred to a later visit and has not yet been completed, the originating site should notify the new site.

- 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: If the participant has been randomized, the new site should verify that he/she has a supply of rescue prednisone on hand. If he/she does not, a new supply should be dispensed.

## 2.54 Treatment Failure

**Visit 3-10, 88, 90-92**
Assess participant for treatment failure (P1_TXFAIL_CHK, P1_TXFAIL)

The primary hypothesis of the VIDA trial is: In individuals 18 years and older with persistent asthma who remain symptomatic despite low dose inhaled corticosteroid and are vitamin D insufficient (<30 ng/ml), the addition of vitamin D is superior to placebo in reducing treatment failures.

The occurrence and timing of treatment failure events are the primary outcome variables for the VIDA trial. Treatment failure is a well-defined asthma outcome reflecting overall asthma control that has been used previously in multiple clinical trials, including Asthma Clinical Research Network (ACRN) studies. Treatment failure as defined in the VIDA protocol is consistent with the ATS/ERS definition of a moderate exacerbation (that is, a deterioration in symptoms and/or lung function with increased rescue bronchodilator use that lasts 2 days or more).

Participants in the VIDA trial may experience multiple treatment failure events over the course of the trial, depending on when they occur. See the Withdrawal Due to Treatment Failure discussion below for details.

**Treatment Failure Definition**

A participant will have experienced a treatment failure event if he/she meets at least one of the following criteria:

*At-home measurements*

1. Pre-bronchodilator peak flow (PEF) ≤65% of baseline PEF on any 2 of 3 consecutive scheduled AM and/or PM measurements.

   Definition of the baseline PEF value is summarized in the Baseline Peak Flow and Rescue Use Values discussion in this section. Only PEFs measured during the scheduled AM and PM sessions are considered for this criterion; unscheduled (extra) PEFs performed during the day are ignored.

   This criterion compares individual PEF values to the 65% of baseline PEF reference value. A scheduled PEF value is considered low if it is ≤65% of the baseline PEF value. The criterion is satisfied if:

- AM PEFs for two consecutive days are low
- PM PEFs for two consecutive days are low
- AM and PM PEFs for the same day are both low
- PM and AM PEF for two consecutive days are both low

Note that days with low PEFs must be consecutive in terms of calendar dates for the criterion to be met (e.g., 5/22/11 and 5/23/11 are consecutive dates).

The participant's spirotel® device has been programmed to provide an alert if he/she meets this criterion. The alert will read 'Peak Flow Low/Call Clinic ASAP.' In addition, the participant should be instructed to monitor his/her scheduled PEFs on his/her VIDA Asthma Monitoring Log (P1_ASTHMA_LOG) to pick up the occurrence of this criterion. The 65% of baseline PEF value is written at the top of this form, as well as on other participant handouts, to guide the participant in recognizing treatment failure events at home.

2. An increase in PRN (as-needed) levalbuterol use (i.e., RESCUE Xopenex® use) of 8 or more puffs per 24 hours over baseline use for a period of 48 hrs.

   Calculation of the baseline rescue use value is summarized in the Baseline Peak Flow and Rescue Use Values discussion in this section. The participant's 'High Rescue Inhaler Use' value is calculated by adding 8 to his/her baseline rescue use value.

   This criterion is satisfied if the participant uses at least the number of puffs specified by his/her 'High Rescue Inhaler Use' value for two consecutive days. Days must be consecutive in terms of calendar dates (e.g., 5/22/11 and 5/23/11 are consecutive dates). This criterion relies on the answers the participant supplies to Q17 in his/her spirotel® e-diary (# RESCUE Puffs 24).

   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 daily RESCUE puffs on his/her VIDA Asthma Monitoring Log (P1_ASTHMA_LOG) to pick up the occurrence of this criterion. The 'High Rescue Inhaler Use' value is written at the top of this form, as well as on other participant handouts, to guide the participant in recognizing treatment failure events at home.

Participants should be trained that one nebulizer use is equivalent to two puffs of RESCUE Xopenex® when calculating their daily number of RESCUE puffs. Participants should also be trained to exclude any preventive puffs they take (e.g., pre-medication for exercise) and any bronchodilator puffs administered as part of study visit procedures from their daily totals. This information is included in the VIDA Spirotel® Reference Card (P1_SPIROTEL_REF) that is included in the case with the spirotel® device.

*In-clinic measurements*

3. Pre-bronchodilator $FEV_1$ values on 2 consecutive sets of spirometric determinations that are ≤ 80% of the baseline pre-bronchodilator value obtained at Visit 3.

   The baseline pre-bronchodilator $FEV_1$ value (in liters) should be taken from Q1030 on the participant's Spirometry Testing (SPIRO) form at Visit 3. This value is used for assessing treatment failure for the remainder of the participant's study participation.

   A participant will meet this criterion if he/she experiences pre-bronchodilator $FEV_1$ values that are ≤80% of the Visit 3 baseline $FEV_1$ value at two consecutive visits during the post-randomization period. This criterion can be met for the following comparisons:

   - Visit 5 and Visit 6
   - Visit 6 and Visit 7
   - Visit 7 and Visit 8
   - Visit 8 and Visit 9
   - Visit 9 and Visit 10

   The participant will also meet this treatment failure criterion if the following set of circumstances occurs:

   If the pre-bronchodilator $FEV_1$ value at a visit is ≤80% of the baseline pre-bronchodilator value obtained at Visit 3, and the participant does not meet other treatment failure criteria, the participant should be given levalbuterol (≥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 treatment failure. The additional visit scheduled for repeat spirometry is referred to as an '$FEV_1$ re-assessment visit.' No additional provocative procedures (e.g., methacholine challenge, sputum induction) scheduled for the original visit day should be performed. The site coordinator or designee should telephone the participant every 24 hours to assess his/her condition in the event that treatment failure 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 >80% of the baseline pre-bronchodilator value obtained at Visit 3; if not, the participant will be considered a treatment failure at that time. If treatment failure criteria are not met, all procedures for the previously scheduled visit shall be performed, including methacholine challenge and sputum induction, if applicable and the participant meets the normal requirements for the procedures, and the participant will continue on his/her study medications, as usual. If treatment failure criteria are met and the visit includes provocative procedures, the study physician should be consulted regarding the ability of the participant to complete the procedures. Individuals who have had a significant asthma exacerbation confirmed at the time of the re-assessment visit should not proceed with methacholine challenge or sputum induction.

Note that this portion of the $FEV_1$ criterion may also be applied at Visit 4 (end of oral corticosteroid (OCS) response period). While unlikely, if the participant meets treatment failure criteria during the OCS response period, he/she will be ineligible for randomization at Visit 4.

Note: The $FEV_1$ criterion will not be evaluated during the run-in period (Visit 2-Visit 3) due to lack of a consistent baseline $FEV_1$ for all participants during this period of the study.

Note: If a participant is released from the performance site due to a low $FEV_1$ value and he/she never returns for an $FEV_1$ re-assessment visit, the VIDA scientific coordinator should be notified. Clinical personnel should continue to try to contact the participant in order to assess his/her condition and to ensure that he/she has an adequate supply of medication.

See the Extra Study Visits discussion in this section for more details on $FEV_1$ re-assessment visits.

If a participant arrives for a regular visit, has not met all of the medication and substance holds on the VIDA Pulmonary Procedure Checklist (P1_PULMONARYCHK), and does not meet other treatment failure criteria to proceed with spirometry testing at the visit, then Q1030 on P1_TXFAIL_CHK should be marked 'Not evaluated.' Likewise, if the participant has one $FEV_1$ value that is ≤80% of the baseline value, but he/she is not evaluated at an $FEV_1$ re-assessment visit to confirm whether or not the criterion is met, then Q1030 should be marked 'Not evaluated.'

4. Any use of additional inhaled or oral/parenteral corticosteroids related to the treatment of the participant's asthma and prescribed by the study or treating physician.

   If non-study inhaled corticosteroids (ICS) (i.e., any ICS other than Alvesco®) were prescribed or oral/parenteral steroids were administered, these drugs should be recorded on the Concomitant Medications for Asthma/Allergy and Adverse Events (CMED) form. If the dose of study Alvesco® was altered, the change should be documented on the VIDA Change in Study Medications (P1_CHANGE_MEDS) form.

   Total ICS taken over the course of the study will be calculated for each participant and used in analysis; it is important that any and all changes to the participant's study ICS dose be documented, as well as use of any non-study ICS medications.

   If oral/parenteral steroids were prescribed, then the event also qualifies as a significant asthma exacerbation and a VIDA Significant Asthma Exacerbation (P1_SIGEX) form should be completed. Note that this designation may change the participant's ICS maintenance dose. See the Significant Asthma Exacerbation discussion in this section for details.

5. Need for emergency treatment at a medical facility that is related to, or complicated by, the participant's asthma and which results in systemic corticosteroid treatment or hospitalization for an acute asthma exacerbation.

   If systemic corticosteroid treatment is administered, record these drugs on the CMED form. If the participant is hospitalized for an asthma exacerbation, complete a Serious Adverse Event Reporting Form (SERIOUS) and a VIDA Significant Asthma Exacerbation (P1_SIGEX) form.

6. Participant refusal to continue study drugs because of lack of satisfaction with treatment.

7. Physician clinical judgment for safety reasons.

   This criterion is usually reserved for use only when a participant does not meet any other treatment failure criteria and the performance site physician feels that an increase in the participant's dose of Alvesco® is warranted for treatment of the participant's symptoms.

8. 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 VIDA trial. If the participant meets the criteria for a significant asthma exacerbation, a P1_SIGEX form should be completed.

Note: If the participant satisfies criteria for an asthma exacerbation, then the event also qualifies as a treatment failure. Not all treatment failure events will qualify as asthma exacerbations.

**Withdrawal Due to Treatment Failure or Exacerbation**

Participants who develop treatment failure during the run-in period or OCS response period (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. Once the treatment failure has resolved for at least two weeks, the participant may be re-screened at Visit 0 for entry into the study at the discretion of the local investigator. See the Re-Enrollment discussion in this section for further details.

Participants who experience two treatment failures during the run-in period or OCS response period (one each during two separate enrollments prior to randomization) will not be allowed to participate in the study further. This will enrich the study population with individuals who are likely to remain stable during the stable inhaled corticosteroid dose phase (Phase I) with the bulk of treatment failures likely to occur during the inhaled corticosteroid tapering phases (Phases IIa and IIb).

Once randomization has occurred at Visit 4, intention-to-treat principles apply. As treatment failure is the primary outcome, and since treatment failure criteria are consistent with a less severe worsening of asthma than experienced during an exacerbation, participants will not be terminated from study participation until more than two treatment failures or exacerbations have occurred. Once achieving the third

treatment failure or exacerbation event, the participant will be withdrawn from the blinded phase of the trial and will be seen at the performance site for a final termination visit. If this occurs, Q1205 on the VIDA Termination of Study Participation (P1_TERM) form should be marked 'yes', and letter 'm' should be listed as the primary reason for study termination in Q1230.

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. 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.

**Documentation of Treatment Failure Events**

When a participant experiences a treatment failure event, he/she should notify the study coordinator immediately (within 24 hours) and be seen at the performance site as soon as possible, definitely within 1 week of the date of the event. Timely reporting ensures that the treatment failure is documented accurately and that the participant receives appropriate treatment. 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. If the event also qualified as a significant asthma exacerbation, then it should also be recorded using code 493.92 in a separate entry.

  The start date recorded should correspond to the date treatment failure criteria were confirmed. For example, if a participant only meets the 'high rescue inhaler use' criterion that requires increased RESCUE Xopenex® use for a 2-day period, the second day of elevated use should be recorded as the start date. If multiple criteria for treatment failure are met, record the earliest date any of the applicable criteria were met. The start dates for entries for an event that meets both treatment failure and exacerbation criteria may differ depending on the criteria that were met.

- Concomitant Medications for Asthma/Allergy and Adverse Events (CMED)

  Any non-study medications used to treat the treatment failure event should be recorded on the CMED form. Examples include oral or parenteral corticosteroids

(e.g., rescue prednisone) and non-study inhaled corticosteroids (i.e., anything other than Alvesco®). Nebulized beta-agonist treatments administered in a physician's office or other care facility should be captured in the participant's daily diary recording two puffs per treatment.

RESCUE Xopenex® inhaler puffs and Alvesco® puffs should not be recorded on CMED. Alterations to the dose of Alvesco® should be documented on the VIDA Change in Study Medications (P1_CHANGE_MEDS) form (see below). Study RESCUE use should be recorded in the participant's spirotel® e-diary.

Medications used for treatment of treatment failure events and exacerbations and listed on the CMED form should be linked to the applicable adverse event recorded on the AECLIN form. If an event qualifies as both a treatment failure and an exacerbation, link the medication to the exacerbation adverse event entry; otherwise, link the medication to the treatment failure event entry.

- VIDA Change in Study Medications (P1_CHANGE_MEDS)

  When a participant experiences a treatment failure event, his/her dose of study Alvesco® is normally increased for a period of time (see the Treatment Failure Rescue Algorithm discussion below). Alterations to the dose of Alvesco® are recorded on P1_CHANGE_MEDS. Each time a change is made, whether increasing the dose for rescue treatment or decreasing back to the previous dose, a new P1_CHANGE_MEDS form should be completed. If adjustments are being made to treat a treatment failure or exacerbation event, answer Q1000 'Adverse Event' and provide the number of the related adverse event on AECLIN. If the event qualifies as both an exacerbation and a treatment failure, link the change in medications to the exacerbation event number.

  While not part of the treatment failure rescue algorithm, if the participant's scheduled study capsules are being discontinued, this change should also be captured on P1_CHANGE_MEDS.

- VIDA Treatment Failure Checklist (P1_TXFAIL_CHK)

  The P1_TXFAIL_CHK form captures the criteria the participant meets for treatment failure. It is completed at each regular visit, starting at Visit 3, and 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.

The treatment failure date is recorded in Q1100. 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 meets the 'high rescue inhaler use' criterion that requires increased RESCUE Xopenex® use for a 2-day period, the second day of elevated use 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 a participant is seen for an extra treatment failure visit (Visit 90-92), the P1_TXFAIL_CHK form is also completed as part of the visit packet. If the participant does not meet any treatment failure criteria when assessed at an extra visit, then the data packet should not be entered or submitted to the DCC.

If a participant meets treatment failure criteria during the run-in (between Visit 2 and Visit 3) or during the oral corticosteroid response period (between Visit 3 and Visit 4), P1_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. In this situation, the participant is ineligible and must be terminated from further study participation.

- VIDA Treatment Failure Information (P1_TXFAIL)

  P1_TXFAIL is completed only when a participant meets treatment failure criteria as recorded on P1_TXFAIL_CHK. P1_TXFAIL records details of the medical care the participant received for his/her condition, medications taken, and the study physician's opinion of the effectiveness of the treatment failure definition for this particular event. The physician must supply source documentation (signature, date and time) on page 3 of the form after providing his/her input. P1_TXFAIL is always a single form.

- VIDA Significant Asthma Exacerbation (P1_SIGEX)

  If the participant's treatment failure event also qualifies as a significant asthma exacerbation, a P1_SIGEX form should be completed. This form is always treated as a single form.

  The exacerbation date is recorded in Q1060. This date is critical for analysis of time to exacerbation. It should correspond to the date exacerbation criteria were confirmed for the current event. For example, if a participant experienced two pre-bronchodilator $FEV_1$ values <50% of his/her baseline $FEV_1$ value from Visit 3, the date of the second measurement should be recorded as the exacerbation

date. If multiple criteria for exacerbation were met, record the earliest date any of the applicable criteria were met.

If a participant meets asthma exacerbation criteria during the run-in (between Visit 2 and Visit 3) or during the oral corticosteroid response period (between Visit 3 and Visit 4), P1_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 phases of the trial, P1_SIGEX should be completed as a single form and data entered with the participant's visit packet (regular visit or Visit 90-92).

- Serious Adverse Event Reporting Form (SERIOUS)

  If a participant is hospitalized due to a treatment failure/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, 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.

**Treatment Failure Rescue Algorithm**

Home Care

Participants will be educated to recognize treatment failures as early as possible to facilitate prompt treatment and to lessen morbidity. Several participant handouts have been developed for this purpose, including "If Your Asthma Gets Worse" (P1_ASWORSE), "Daily Activities" handouts (P1_DAILYACT), and the "Participant Identification Card" (P1_ID). The participant's VIDA Asthma Monitoring Log (P1_ASTHMA_LOG) also includes instructions for identifying and treating the onset of treatment failure.

Participants who recognize increased symptoms and/or a fall in peak flow (PEF) to ≤65% of baseline will use levalbuterol by MDI, 2-4 puffs, every 20 min up to 60-90 min, if needed, and then every 4 hours, or less, if needed. Participants will be instructed to use the Rescue Xopenex® inhaler for treatment.

If the PEF does not increase to >65% of 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 levalbuterol to control or maintain PEF >65% of baseline may be indicative of an asthma exacerbation requiring further medical management. See the Significant Asthma Exacerbation discussion in this section for further details.

Adjustment of Trial Medication

When a participant meets criteria for treatment failure status post-randomization, the dose of study inhaled corticosteroid (Alvesco®) will be doubled and continued for 7 days. For treatment failures occurring during Phase I (inhaled corticosteroid (ICS) stable period), the dose will be 4 puffs BID. For treatment failures occurring during Phase IIa or IIb (ICS tapering periods), the dose will be increased to the dose the participant was receiving prior to the initiation of his/her most recent ICS taper. Doubled ICS doses should be implemented as outlined in Table 4 below.

**Table 4. ICS dose escalation for treatment of treatment failure**

| ICS Dose at Time of TF | Doubled ICS Dose |
|---|---|
| 2 puffs BID (ICS stable dose) | 4 puffs BID |
| 2 puffs AM (1st tapered dose) | 2 puffs BID |
| 1 puff AM (2nd tapered dose) | 2 puffs AM |

If, after 7 days of increased ICS treatment, the treatment failure episode is clinically-resolved, the ICS stable dose (for treatment failures during Phase I) or pre-failure tapering dose (for treatment failures during Phase II for participants who have undergone tapers) of ICS will be resumed and study visits will continue as per protocol.

If a participant experiences a treatment failure event that also meets the criteria for a significant asthma exacerbation, ICS dosing depends on the phase in which the event occurred. If the exacerbation occurs during Phase I, the dose of ICS will be doubled (to 4 puffs BID) for 7 days. If, after 7 days, the event is clinically-resolved, the dose will be reduced back to the ICS stable dose (2 puffs BID) for the remainder of the study, and visits will continue as per protocol. The participant will not be eligible for any dose tapers during Phase II. If the exacerbation occurs during Phase II, the dose of ICS will be increased to the ICS stable dose and maintained for the remainder of the study. Additional treatment for exacerbations is allowed at the treating physician's discretion. See the Significant Asthma Exacerbation discussion in this section for further details.

If a participant is prescribed oral/parenteral corticosteroids for treatment of the significant asthma exacerbation, then the ICS dose should revert back to the ICS stable

dose on the first day that prednisone or parenteral corticosteroids are used. The participant should remain on the ICS stable dose for the rest of the trial.

During medical management of a treatment failure event, study scheduled capsules will be continued, unless the treating physician considers it appropriate to suspend such therapy until the event resolves.

Any changes to the participant's ICS dose or scheduled study capsule status must be recorded on the VIDA Change in Study Medications (P1_CHANGE_MEDS) form. It is crucial that this information be entered into the study database in order to determine each participant's total ICS dose during the trial, an important secondary outcome measure.

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 (P1_TXFAIL_CHK, P1_TXFAIL). The participant should be reminded to monitor his/her peak flows and rescue use at home and to alert the study coordinator if he/she has meet failure criteria between visits. This is important for the participant's safety, as well as for the integrity of the study data.

### Post-Randomization Study Visits Following Treatment Failure

For safety reasons, all participants will be seen within 1 week of the date of a treatment failure or exacerbation, sooner if possible. If a regular visit is not already scheduled in this timeframe, the participant should be seen for a Visit 90-92. See the Extra Study Visits discussion in this section for further details.

Following treatment failure assessment and appropriate medical management, regular study visits will continue in accordance with the participant's visit schedule.

Note: If a participant meets treatment failure criteria at the time of Visit 6, he/she may proceed with the methacholine challenge and sputum induction at the visit, as long as he/she meets all of the requirements on the Adult Methacholine Challenge Testing Checklist (METHACHK_ADULT) and/or Sputum Checklist (SPUTUMCHK). If the participant has experienced a recent significant asthma exacerbation, a study physician must be consulted for approval before proceeding with these procedures at the visit. If the participant is experiencing an asthma exacerbation at the time of the visit, these procedures should not be attempted.

## 2.55 Urine Calcium:Creatinine Ratio Laboratory Test

**Visit 1, 3, 5, 6, 8, 10**
Obtain (clean catch) urine sample for calcium:creatinine ratio determination (local lab) (P1_LAB)

Urine calcium to creatinine ratios ($U_{Ca}$:$U_{Cr}$) are being done at Visit 1 and Visit 3 to ensure that participants do not have elevated levels (>0.37 when calcium and creatinine are expressed in mg) at baseline, prior to starting study drug (vitamin D or placebo). Ratios measured later in the trial will be used to monitor for hypervitaminosis D.

At each designated visit, provide the participant a urine specimen cup and instruct him/her in clean catch procedures before he/she provides the urine sample. Samples will be analyzed at the performance site's local lab. Samples should be collected, labeled, and transported according to local lab requirements. Note that fasting and 24-hour urine collections are not required for these tests for VIDA. We will obtain results from random, spot urine samples.

If a urine pregnancy test is required for a woman of childbearing potential at a visit when a $U_{Ca}$:$U_{Cr}$ test is also being done, the participant may be asked to void once, filling the urine specimen cup. An aliquot may be extracted from the specimen cup to complete the pregnancy test in the clinic. Follow local procedures when coordinating two urine tests at the visit. See the Pregnancy Test discussion in this section for further details.

Urinary calcium and creatinine are recorded in Q1020 and Q1030, respectively, on the VIDA Laboratory Results (P1_LAB) form. Clinical personnel will need to compute the ratio manually by dividing the calcium measurement by the creatinine measurement. A 'Clinic Use Only' box has been provided on the form for this purpose.

Individuals whose Visit 1 ratio is elevated are technically ineligible. However, at the local investigator's discretion, if the participant meets all other eligibility criteria at the visit, he/she may be allowed to continue in the pre-randomization phases of the study, pending the results of follow-up $U_{Ca}$:$U_{Cr}$ ratio testing at Visit 3. The participant should be advised to increase fluid intake in the interim. Note that local investigator approval must be obtained before proceeding with this exception. See the Eligibility Criteria discussion in this section for details on documenting the exception.

If a participant's Visit 3 ratio is elevated, he/she is ineligible for continued study participation. In this case a VIDA Termination of Study Participation (P1_TERM) form must be completed.

While others have found the dose of 4,000 IU/day vitamin D to be safe and effective at raising vitamin D (25(OH)D) levels, participants will have their $U_{Ca}$:$U_{Cr}$ ratio monitored during the post-randomization period (Visits 5, 6, 8, 10). Elevation in $U_{Ca}$:$U_{Cr}$ ratio is the earliest abnormality detected, and this test is the most non-invasive way of monitoring for hypervitaminosis D.

If a post-randomization $U_{Ca}$:$U_{Cr}$ ratio is greater than 0.37 (urinary calcium and creatinine expressed in mg), the participant will be instructed to increase hydration and a repeat measurement will be obtained 30 days later. If the repeat $U_{Ca}$:$U_{Cr}$ ratio is elevated, then the participant will be instructed to hold study drug and will have a serum calcium and vitamin D (25(OH)D) level obtained. Serum calcium values should be reported in Q1040 on P1_LAB. If either the calcium or vitamin D level is elevated (Ca > 10.2 mg/ml and/or vitamin D ≥120 ng/ml), the participant will stop study drug for the remainder of the trial. If the calcium and vitamin D levels are normal, then the participant may resume study drug. All changes in study drug dosage (e.g., drug stopped, drug resumed) must be documented on the VIDA Change in Study Medications (P1_CHANGE_MEDS) form. If a participant requires a $U_{Ca}$:$U_{Cr}$ ratio test at a visit that does not include this test in its visit procedures, complete a single P1_LAB form.

If the participant's $U_{Ca}$:$U_{Cr}$ ratio (or follow-up serum calcium test) is elevated at any point in the trial, record this fact as an adverse event on the Clinical Adverse Events (AECLIN) form using ICD-9 code 275.42 (hypercalcemia). No specific code exists for hypercalciuria. The date of the adverse event should correspond to the date the urine sample was collected.

Note: If urinary calcium and creatinine are measured in mmole rather than mg, the appropriate cutoff for eligibility assessment and determination of elevated values is 1.0. Values must be converted to mg/L before completing the P1_LAB form.

Submit the original lab report with the participant's visit packet. Ensure that all identifying information (name, medical record number, etc.) has been blackened out and the participant's VIDA ID number has been written at the top of the report. Retain a copy of the lab report in the participant's study folder at the performance site.

See section 4 of this manual for further details regarding completion and entry of the P1_LAB form.

## 2.56 Visit Schedule

**Visits 2, 3, 4, 6, 8**
Run VIDA 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 VIDA study visits. The visit scheduler is run at Visits 2, 3, 4, 6 and 8. The visit scheduler at Visit 2 creates the participant's schedule, based on the Visit 2 date, for visit 3 (run-in period). The Visit 3 scheduler creates the participant's schedule, based on the Visit 3 date, for Visit 4 (oral corticosteroid response period). The visit scheduler at Visit 4 creates the participant's schedule, based on the Visit 4 date, for the entire post-randomization portion of the study, including scheduled phone contacts, through Visit 10. Because Visits 6 and 8 begin phases IIa and IIb of the trial and they cannot be missed, a new visit scheduler must be run for all participants at these visits to ensure adequate and standardized follow-up periods in each phase. The Visit 6 and 8 schedulers create the participant's schedule for all remaining visits, through Visit 10.

The visit scheduler has been created in five pieces to adjust the dates for each participant such that each phase has appropriate follow-up and spacing between visits, per protocol. Resetting the schedule at the beginning of each study phase is necessary in situations when visit windows are used for the first visit in the phase. Visit schedulers should be run for all participants at Visits 3, 4, 6, and 8 even if extended windows have not been utilized.

Visit Scheduler Reports should be run near the end of the applicable visits (2, 3, 4, 6, 8) and reviewed with the participant. Reports are customized for each participant in that his/her actual visit dates (2, 3, 4, 6, 8) are entered so that ideal dates and visit windows for all subsequent visits can be calculated and displayed on the report.

If clinical staff and the participant desire to see the ideal schedule for all subsequent visits at the time of Visit 2, the following procedures should be followed. First, generate the participant's Visit 2 report by entering the participant's Visit 2 date. Next, review the Visit 2 report and find the ideal date for the participant's Visit 3. Enter this Visit 3 date into the Visit 3 portion of the scheduler to generate a second report. Next, review the Visit 3 report and find the ideal date for the participant's Visit 4. Enter this Visit 4 date into the Visit 4 portion of the scheduler to generate a third report. The three reports combined show the participant's complete schedule for the study. Be sure to explain to the participant that alterations to this schedule will be necessary if his/her Visit 3, 4, 6, and/or 8 occur earlier or later than the ideal date on the reports.

Note that no visit scheduler is available for the screening visits (Visits 0-2). The protocol allows for flexible scheduling of these visits with the only constraint being that no more than 8 weeks can elapse between Visit 0 and Visit 2. Performance site staff will be responsible for ensuring that this constraint is met or the participant will be deemed ineligible at the time of Visit 2. Ideally screening visits will take place over a very short period of time (i.e., 1-2 weeks).

Instructions for accessing and generating the VIDA Visit Scheduler Reports on the AsthmaNet secure website can be found in Section 3 of this manual.

A copy of the VIDA 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.

## 2.57 Visit Windows

Table 5 summarizes the regular and extended windows allowed by protocol around the ideal visit date for each of the VIDA study visits. Screening visits have flexible timing and are not subject to formal visit scheduling constraints; however, Visit 2 must be scheduled within 8 weeks of the participant's Visit 0 to ensure that his/her vitamin D results do not 'age out.' The run-in is 4 weeks long, followed by the oral corticosteroid response period which is ideally 5-7 days long. Post-randomization visits occur approximately every 4-6 weeks.

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, the VIDA 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.

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 at Visit 1.If a participant cannot be scheduled in the spirometry windows, contact the scientific coordinator at the DCC to seek an exception.

**Table 5. Regular and Extended Windows for VIDA Study Visits**

| Visit Number | Study Week | Regular Window (days) Lower \| Upper | | Extended Window (days) Lower \| Upper | |
|---|---|---|---|---|---|
| Screening 0 & 1 | -0 | Must occur no more than 8 weeks prior to Visit 2 | | | |
| 2 | 0 | | | | |
| 3 | 4 | -- | +3 | -- | +7 |
| 4 (randomization) | 5 | -2 | -- | -- | +7 |
| Phone Contact | 8 | -3 | +3 | -5 | +5 |
| 5 | 11 | -3 | +3 | -5 | +5 |
| Phone Contact | 14 | -3 | +3 | -5 | +5 |
| 6 | 17 | -3 | +3 | -5 | +5 |
| 7 | 21 | -3 | +3 | -5 | +5 |
| 8 | 25 | -3 | +3 | -5 | +5 |
| 9 | 29 | -3 | +3 | -5 | +5 |
| 10 | 33 | -3 | +3 | -5 | +5 |

Visit 3 marks the end of the VIDA run-in period. Each participant must have no less than 4 weeks on standardized low dose inhaled corticosteroid therapy in the run-in. Windows for Visit 3 have been established to allow for up to an extra week in the run-in if an individual cannot be seen on his/her ideal Visit 3 date; no earlier visits (i.e., no lower windows) are allowed for this visit.

Visit 4 marks the end of the oral corticosteroid response phase of the study. Participants will be given 5-7 days of prednisone to take between Visit 3 and Visit 4. Visit 4 must be performed on day 5, 6, or 7 of prednisone therapy to establish the participant's corticosteroid response. If a participant has extenuating circumstances that prevent him/her from being seen on day 5, 6, or 7 post-Visit 3, then Visit 4 can be delayed for up to one additional week. The extended window allows for Visit 4 to be scheduled at most 2 weeks after Visit 3. If a participant must utilize the extended window, then data collected at the visit will not be used to establish his/her corticosteroid response; this will be missing data for the analysis. Visit 4 **must** be scheduled in the regular window if at all possible. The DCC will monitor the number of participants who are missing corticosteroid response data at each performance site.

Ideal visit dates and regular and extended visit windows have been programmed into the VIDA 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 screening phase visits multiple times may not be good prospects for randomization, as most of the VIDA study visits cannot be missed. If counseling by the site coordinator during the screening and run-in phases does not seem to improve the situation, the coordinator should consider terminating the participant from further study participation by filing a VIDA Termination of Study Participation (P1_TERM) form.

## 2.58 Vitamin D Intake Questionnaire

The VIDA Vitamin D Intake Questionnaire (P1_VITD_INTAKE) was developed to gauge the amount of vitamin D the participant ingests through supplementation and some of the most common dietary sources of vitamin D. This form is by no means intended to be as accurate as a food diary; it is meant to collect a crude estimate of the amount of additional vitamin D the participant ingests at the beginning and end of the study to determine if his/her diet or supplementation habits changed significantly over the course of the trial.

**Visit 3, 10**
Administer Vitamin D Intake Questionnaire (P1_VITD_INTAKE)

This questionnaire is completed by participant interview. The participant should bring his/her vitamins and supplements, in their original containers, to each study visit. At Visits 3 and 10, coordinators should use the information on the containers to answer Questions 1a-1c on the questionnaire. If the participant uses only one or two supplements, leave the remaining fields blank.

Note that Q1150 asks about the participant's use of cod liver oil in capsule form, which is high in vitamin D. Cod liver oil and 'fish oil' commonly taken for heart health are both rich in omega 3 essential fatty acids; however, 'fish oil' is not a good source of vitamin D. When reviewing a participant's use of fish oils, be sure to determine exactly what type of oil the participant is taking before assuming it is cod liver oil.

## 2.59 Wisconsin Upper Respiratory Symptom Survey – 21

The Wisconsin Upper Respiratory Symptom Survey (WURSS)[15] 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 VIDA trial will employ the WURSS-21 (form name WURSS_21). Collection of data on participant-reported respiratory tract infections will allow for secondary analyses examining the impact of vitamin D supplementation on the incidence and severity of colds.

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 VIDA 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 4**
Introduce WURSS-21 questionnaire (P1_WURSS21_INST)
Distribute WURSS-21 questionnaires (21 forms) (WURSS_21)

At Visit 4 the participant is introduced to the WURSS-21 for the first time. The study coordinator should review the "VIDA Wisconsin Upper Respiratory Symptom Survey – 21 (WURSS-21) Instructions" handout with the participant at this visit. The participant should be instructed to complete one survey per day, starting the first day cold symptoms are experienced. 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. All completed surveys should be returned to the study coordinator at the participant's next VIDA study visit.

The participant should be given 21 copies of the WURSS-21 to keep at home in the event that he/she experiences a cold event between visits.

[15] 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.

If the participant is experiencing cold symptoms at the time of Visit 4 and has had these symptoms for more than one day, he/she should not complete the WURSS-21 for this cold event. Instruct the participant to start completing the form at the onset of his/her next cold, if another is experienced during the study.

**Visit 5-9**
If participant experienced a cold between visits:
Collect and review WURSS-21 forms
Replenish participant's WURSS-21 supply (WURSS-21)

If a participant experiences a cold between visits, he/she should bring completed WURSS-21 forms to the next visit. Collect and review the forms to be sure dates have been completed at the top of every form. Also ensure that the participant's VIDA ID number is on each form.

If the visit occurs 'mid-cold', collect the forms the participant is returning and store them in his/her VIDA study folder until the balance of the WURSS forms for the same cold event have been returned. Enter the forms with the visit for which all forms are present; do not separate WURSS forms for a single cold event among multiple visits.

After collecting completed WURSS-21 forms, give the participant a new supply of forms to keep at home for completion if he/she experiences another cold event during the study. Ensure that the participant has an adequate supply at all times.

Be sure to record the cold event on the participant's Clinical Adverse Events (AECLIN) form.

**Visit 10, 88**
If participant experienced a cold between visits:
Collect and review WURSS-21 forms

If a participant experiences a cold between visits, he/she should bring completed WURSS-21 forms to the next visit. Collect and review the forms to be sure dates have been completed at the top of every form. Also ensure that the participant's VIDA ID number is on each form.

Because the forms are being returned at a study termination visit, it is possible that they may be turned in mid-cold. Collect the available forms and data enter them even if the cold was not completely resolved (i.e., last two days recorded as 'Not sick'. The participant should not provide data beyond his/her study termination date.

## 2.60 Withdrawals

**Early Study Withdrawal**
Complete VIDA Termination of Study Participation form (P1_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 0 successfully, a VIDA Termination of Study Participation (P1_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 P1_TERM form.

In addition to the P1_TERM form, participants who are withdrawn from VIDA 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 P1_TERM form and as part of the Visit 10 and 88 packets. 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.

**Visit 0 Screen Failures**

At any point during Visit 0 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 0 and have a blood sample drawn for serum vitamin D determination should have data entered into the study database and forms forwarded to the DCC.

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 0. See the Re-Enrollment discussion in this section for further details.

### Visit 0 Vitamin D Ineligible

Participants whose Visit 0 serum vitamin D (25(OH)D) level is ≥30 ng/mL are ineligible for continued study participation. Clinical personnel will be notified of each participant's eligibility status via the VIDA Participant Status Report posted to the secure AsthmaNet website and updated in real time. If the participant's Vitamin D Eligible status is 'No', then the participant must be informed that he/she is ineligible for VIDA. All participants who are vitamin D ineligible must be mailed or given a copy of the "VIDA vitamin D ineligible" form letter posted on the secure website in the Forms:VIDA:Handouts:Visit 0 folder. The letter should be customized with the performance site's information and signed by the site's principal investigator or site director. Once the participant has been notified of his/her study status, a VIDA Termination of Study Participation (P1_TERM) form should be completed and data entered, indicating 'yes' for Q1020 and 'yes' for Q1030. These participants should also be sent an AsthmaNet Satisfaction Questionnaire (SATQX) with pre-addressed, postage paid envelope.

### Withdrawals during the Pre-Randomization Phases (Screening, Run-in and Oral Corticosteroid Response Phases) (Visit 0 through Visit 4)

The primary purpose of the screening (Visit 0 through Visit 2) and run-in phases (Visit 2 through Visit 3) is to identify an appropriate group of participants for randomization in the VIDA trial. These phases give clinical personnel an opportunity to review eligibility criteria and adherence to study procedures for each participant before he/she is randomized. For the VIDA 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 their diaries and peak flows in their spirotel® devices are non-compliant. These participants should not be randomized at Visit 4, as their lack of adherence can affect the results of the study adversely and may jeopardize their safety if they cannot recognize treatment failure conditions. Thus, the screening and run-in phases are the optimal times to identify and withdraw inappropriate participants.

The short oral corticosteroid response phase of the study (between Visits 3 and 4) leads up to randomization at Visit 4. While no formal eligibility criteria are assessed at Visit 4, clinical personnel may determine that the participant has not been compliant with study procedures between visits, or the participant may not be able to schedule Visit 4 in the window required by the protocol. Additionally, in the rare event that a participant would

experience a treatment failure between Visits 3 and 4, he/she is ineligible for randomization. In these cases, the participant must be withdrawn from the study prior to randomization.

When a participant is withdrawn from the screening, run-in or oral corticosteroid response phase or withdraws consent prior to randomization at Visit 4, a VIDA Termination of Study Participation (P1_TERM) form should be submitted to the DCC along with any study data that have been collected. If a participant withdraws between visits prior to randomization, the number of the last completed visit should be indicated as the visit number on the P1_TERM form.

In addition to the P1_TERM form, participants who are withdrawn after successfully completing Visit 0 and prior to randomization 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.'

Upon exiting the study, all participants who were vitamin D eligible at the time of Visit 0 must be mailed or given a copy of the "VIDA vitamin D eligible termination" form letter posted on the secure website in the Forms:VIDA:Handouts folder. The letter should be customized with the performance site's information and signed by the site's principal investigator or site director. This letter informs the participant that his/her initial vitamin D value was low (<30 ng/ml), and it refers him/her to his/her primary care provider for follow-up care. All sites should use the standardized letter supplied on the website; no site-specific letters should be employed for this purpose. IRB approval must be obtained before any letters are distributed to participants.

Any blood, urine or sputum samples that are collected during the participant's termination visit should be forwarded to the appropriate labs as outlined in this manual.

Any spirotel® data collected between visits should be uploaded and transmitted to MedGraphics for inclusion in the VIDA dataset.

Minimum data requirements for individuals terminated at Visit 3 include:

- Eligibility Checklist 5 (P1_ELIG5)
- Compliance Checklist (P1_COMPLY)
- Treatment Failure Checklist (P1_TXFAIL_CHK)
- MEMS6 Monitor Quality Control (MEMSQC) and MEMS Report (MEMS_RPT)
- Spirotel Quality Control (SPIROTELQC) and Spirotel Reports

Additional data, such as the spirometry forms (P1_PULMONARYCHK, SPIRO) and reports, should be forwarded to the DCC for participants who complete these study procedures.

### Early Withdrawals after Randomization

The intention-to-treat principle applies to the VIDA 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 capsule vials at Visit 4, 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

- Three Treatment Failure or Exacerbation Events

  If a participant experiences three documented treatment failure and/or exacerbation events (combined total events) during the post-randomization period of the study, he/she must be terminated from further study participation for safety reasons.

- 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 VIDA Termination of Study Participation (P1_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, diary and peak flow completion in the spirotel® device, 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 P1_TERM form; it may not be used as the primary reason for termination.

*Withdrawal at a regular visit (5-10) or visit 90-92*

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 and forwarded to the DCC. A serum vitamin D sample should be drawn, even if this procedure is not part of the visit structure at the applicable visit (i.e., at visits 5, 7, 9). A VIDA Termination of Study Participation (P1_TERM) form should be submitted. The participant should be asked to complete the VIDA Participant Study Treatment Questionnaire (P1_PARTTXQX) and the coordinator should complete the VIDA Coordinator Study Treatment Questionnaire (P1_CTXQX). If termination is occurring at visits 5-9, 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.

Upon exiting the study, all participants who were vitamin D eligible at the time of Visit 0 must be mailed or given a copy of the “VIDA vitamin D eligible termination” form letter posted on the secure website in the Forms:VIDA:Handouts folder. The letter should be customized with the performance site’s information and signed by the site’s principal investigator or site director. This letter informs the participant that his/her initial vitamin D value was low (<30 ng/ml), and it refers him/her to his/her primary care provider for follow-up care. All sites should use the standardized letter supplied on the website; no site-specific letters should be employed for this purpose.

Any blood, urine or sputum samples that are collected during the participant’s termination visit should be forwarded to the appropriate labs as outlined in this manual.

*Withdrawal between regular visits (visit 88)*

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. Early termination visits are designated by visit number 88 and have their own visit procedure checklist (P1_VISITK) and their own packet structure defined in the database. Early termination visit procedures include:

- Asthma Control Questionnaire (ACT) completion
- Collection of WURSS-21 forms, if applicable
- Compliance assessment (P1_COMPLY)
- Spirometry (P1_PULMONARYCHK, SPIRO)
- Treatment failure assessment (P1_TXFAIL_CHK)
- Treatment failure documentation (P1_TXFAIL), if applicable
- Participant Study Treatment Questionnaire (P1_PARTTXQX) completion
- Coordinator Study Treatment Questionnaire (P1_CTXQX) completion
- Serum vitamin D measurement

Participants should be asked to complete all Visit 88 procedures, if at all possible. If this is not possible, any partial data should be submitted as part of the packet and remaining forms should be marked missing. At a minimum, the VIDA Termination of Study Participation (P1_TERM) form must be completed and must indicate in Q1000 the number of the last regular visit the participant completed. In addition, a VIDA Coordinator Study Treatment Questionnaire (P1_CTXQX) should be 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 with MEMS®6 cap and DOSER™ back to the site. Data on the participant's spirotel® device should be uploaded as soon as the device is returned. Compliance should be estimated as best possible from the returned compliance devices and recorded on the VIDA Compliance Checklist (P1_COMPLY). A partial treatment failure assessment should be done with the available information and recorded on the VIDA Treatment Failure Checklist (P1_TXFAIL_CHK). 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 VIDA Participant Study Treatment Questionnaire (P1_PARTTXQX) over the phone, if the participant is agreeable. No source documentation will be available on the form in this case.

All participants should be given or sent a copy of the vitamin D eligible termination letter customized on clinical site letterhead. See above for further details of this letter.

**General Note:**

After a participant has been terminated from the VIDA 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, then spirotel® quality control (SPIROTELQC) may take place after the termination date without penalty.

## 2.61 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). 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[16]. The WPAI:Asthma is being used for the VIDA study.

For more details on the WPAI, see http://www.reillyassociates.net.

**Visit 2, 10**
Administer Asthma-Specific Work Productivity and Activities Impairment Questionnaire (WPAI_ASTHMA)

The administration of the WPAI_ASTHMA questionnaire is one of the first procedures performed at an applicable visit. Study coordinators should observe the order of procedures as they are laid out on the visit procedure checklists.

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 WPAI_ASTHMA 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. Responses must reference the seven days leading up to the current visit date. 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 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

[16] 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.

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., schoolteachers 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.