

Protocol C3291001

**A PHASE 2A, RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED
STUDY, TO CHARACTERIZE THE MECHANISM OF ACTION OF
CRISABOROLE OINTMENT 2%, BY EVALUATION OF EFFICACY AND
CHANGES IN SKIN BIOMARKERS, IN ADULT SUBJECTS WITH MILD TO
MODERATE ATOPIC DERMATITIS, WITH A 4 WEEK OPEN-LABEL
EXTENSION**

Statistical Analysis Plan
(SAP)

Author: PPD
Version: 2
Date: 1-Jun-2018

TABLE OF CONTENTS

TABLE OF CONTENTS.....	2
LIST OF TABLES.....	4
1. VERSION HISTORY.....	5
2. INTRODUCTION	6
2.1. Study Objectives	6
2.1.1. Primary Objectives	6
2.1.2. Secondary Objectives	6
CCI	
2.2. Study Design	7
3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS	7
3.1. Primary Endpoint(s)	7
3.2. Secondary Endpoint(s)	7
CCI	
3.4. Baseline Variables.....	8
3.5. Safety Endpoints	9
3.5.1. Adverse Events	9
3.5.2. Laboratory Data	9
4. ANALYSIS SETS	9
4.1. Full Analysis Set	9
4.2. Per Protocol Analysis Set.....	9
4.3. Safety Analysis Set.....	9
4.4. Other Analysis Sets	9
5. GENERAL METHODOLOGY AND CONVENTIONS.....	10
5.1. Hypotheses and Decision Rules	10
5.2. General Methods	10
5.2.1. Analyses for Binary Data.....	10
5.2.2. Analyses for Continuous Efficacy Data	10
5.2.3. Analyses for Biomarkers	11
5.2.4. Analyses for Categorical Data	12
5.3. Methods to Manage Missing Data	12
6. ANALYSES AND SUMMARIES	12

6.1. Primary Endpoint(s)	12
6.1.1. Change In Lesion TSS From Baseline To Day 15	12
6.1.2. Change in Key Skin Biomarkers (S100A12, CCL17, CCL18, CCL22, K16, elafin/PI3 and IL-13 expression level) From Baseline to Day 15	14
6.2. Secondary Endpoint(s)	14
6.2.1. Change in The Lesion TSS From Baseline to Day 8	14
6.2.2. Changes in Key Skin Biomarkers From Baseline to Day 8	14
6.2.3. Correlation Between Biomarkers Change And Lesion TSS Change	14
6.2.4. Change From Baseline to Day 8 and Day 15 in ISGA	15
6.2.5. Change From Baseline To Visits Up To Day 15 In Pruritus Numerical Scale	15
CCI	
.....	
.....	
.....	
.....	
.....	
.....	
.....	
.....	
6.4. Subset Analyses	18
6.5. Baseline and Other Summaries and Analyses	19
6.5.1. Baseline Summaries	19
6.5.2. Study Conduct and Subject Disposition	19
6.5.3. Study Treatment Exposure and Compliance	19
6.5.4. Concomitant Medications and Non-Drug Treatments	19
6.6. Safety Summaries and Analyses	19
6.6.1. Adverse Events	19
6.6.2. Laboratory Data	20
6.6.3. Vital Signs	20
6.6.4. Physical Examination	20
7. INTERIM ANALYSES	20

8. REFERENCES	21
9. APPENDICES	22
9.1. Definition and Use of Visit Windows in Reporting	22
CCI	

LIST OF TABLES

Table 1. Summary of Major Changes in SAP Amendments	5
-----------------------------------------------------------	---

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study C3291001¹ is based on the protocol dated 02May2017.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
2	<p>Additional Day 15 visit window for ISGA (global), CCI [REDACTED] and pruritus NRS (global) was added</p> <p>AR(1) variance-covariance matrix was added to Section 5.2.2 for mixed model.</p> <p>Summary of pruritus NRS change from Day 15 to Day 43 was updated as change from Day 15 to Day 16 through Day 43.</p> <p>TEAE definition was updated</p> <p>CCI [REDACTED]</p> <p>Line plots for mean change (\pm SE) from baseline up to Day 15, and mean change (\pm SE) from Day15 to Day 16 through Day 43 in pruritus NRS were added.</p>	<p>No Day 8 assessments for these endpoints</p> <p>In case there is convergence issue for unstructured variance-covariance matrix.</p> <p>Pruritus NRS was collected daily.</p> <p>Per Pfizer Standard</p>

2. INTRODUCTION

Crisaborole, also referred to as PF-06930164 and AN2728, is a low molecular weight benzoxaborole anti-inflammatory phosphodiesterase-4 (PDE-4) inhibitor. The safety and efficacy of crisaborole has been demonstrated in two phase 3 studies (AN2728-AD-301 and AN2728-AD-302) and one long term open-label study (AN2728-AD-303). The 2% dose strength of crisaborole ointment is approved in the US for the treatment of mild-moderate atopic dermatitis (AD) for subjects ≥ 2 years.

The specific mechanism(s) by which crisaborole exerts its therapeutic action is not well defined. In this study, skin biopsies will be collected to characterize the mechanism of action, by evaluation of efficacy and changes in key skin biomarkers, of crisaborole ointment 2% over vehicle, applied twice a day in adult subjects with AD with maximum treatable BSA of 10%. The skin biopsy samples will be analyzed using immunohistochemistry (IHC) and gene expression, which will be done using TLDA PCR for 48 genes including housekeeping genes as well as single gene PCR for a few genes that are below detection level on TLDA.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study C3291001.¹ This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives

2.1.1. Primary Objectives

- To evaluate the efficacy of crisaborole ointment 2% vs vehicle in subjects with mild to moderate AD.*
- To evaluate change in key skin biomarkers of AD in target lesions treated with crisaborole ointment 2% or vehicle.*

2.1.2. Secondary Objectives

- To evaluate change in other skin biomarkers of atopic dermatitis in target lesions treated with crisaborole ointment 2% or vehicle.*
- To evaluate normalization of biomarker and gene expression levels in lesional skin treated with crisaborole ointment 2% or vehicle.*
- To evaluate changes in AD clinical sign and symptom severity in target lesions treated with crisaborole ointment 2% or vehicle.*
- To assess the safety and local tolerability of crisaborole ointment 2% in subjects with mild to moderate AD.*

CCI

- CCI

2.2. Study Design

This is a Phase 2a randomized, double-blind, vehicle-controlled study to characterize the mechanism of action, by evaluation of efficacy and changes in key skin biomarkers, of crisaborole ointment 2% in subjects with mild to moderate atopic dermatitis. After completing screening activities, including meeting eligibility criteria, approximately 40 subjects will be treated. In the double-blind treatment period, each subject will be randomly assigned to be treated with crisaborole ointment 2% for one target lesion. The other target lesion will receive vehicle.

The double-blind treatment period will last from Baseline/Day 1 to Day 15 skin biopsy collection and will include twice daily visits to the site for IP application and study assessments, where applicable. The open-label treatment period will start from the Day 15 skin biopsy collection and last until Day 43 (end of treatment/early termination); during this time, subjects will be able to treat all AD skin areas (except scalp), at home, with crisaborole ointment 2%.

Scheduled (outpatient) study visits for all subjects will occur at Screening (up to 30 days prior to Day 1/Baseline), Days 1 to 14 (twice daily), Day 15, and Day 43 (end of treatment/early termination). On Day 71 (end of study), a follow-up telephone call will be made by site staff to assess for AEs that may have occurred since the last visit.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

- *Change from baseline in TSS in target lesions treated with crisaborole ointment 2% or vehicle on Day 15.*
- *Change from baseline in key skin biomarkers of AD (S100A12, CCL17, CCL18, CCL22, K16, elafin/PI3 and IL-13 expression level) in target lesions treated with crisaborole ointment 2% or vehicle at Day 15.*

3.2. Secondary Endpoint(s)

- *Change from baseline in other skin biomarkers in target lesions treated with crisaborole ointment 2% or vehicle at Day 15.*
- *Biomarker and gene expression level in lesional skin treated with crisaborole ointment 2% or vehicle at Day 15 and levels in non-lesional skin at Baseline.*
- *Change from baseline in lesion severity as measured by TSS, ISGA, and Pruritus Numerical Rating Scale at each visit up to Day 15.*
- *The incidence of treatment emergent AEs and SAEs.*

CCI [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

3.4. Baseline Variables

Demographic and baseline characteristics include:

- Age (in years);
- Sex;
- Race;
- Ethnicity;
- Height (in cms);
- Weight (in kg);
- Body Mass Index;
- Duration of disease (in years);
- ISGA (global and target lesions);
- CCI [REDACTED]
- CCI [REDACTED]
- TSS (target lesions);
- CCI [REDACTED]
- Pruritus numerical scale (global and target lesions).

3.5. Safety Endpoints

3.5.1. Adverse Events

- *All adverse events (AEs), including serious adverse events (SAEs).*

An AE is considered treatment emergent relative to a given treatment if:

- The event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment (eg, during the screening period), or
- The event was seen prior to the start of treatment but increased in severity during treatment, or
- The event was seen and was resolved prior to the start of treatment but reported again during treatment.

3.5.2. Laboratory Data

- Clinically significant abnormal laboratory parameters.
- Clinical laboratory values and change from screening at Day 43/Early Termination.

4. ANALYSIS SETS

4.1. Full Analysis Set

The full analysis set (FAS) includes all subjects who are randomized and receive at least one dose of investigational product.

4.2. Per Protocol Analysis Set

The Per Protocol Analysis Set (PPAS) will be a subset of subjects from FAS. PPAS *includes any subject randomized and receiving ≥ 1 dose of investigational product, with both Day 1 and Day 15 biopsies done, and without protocol violations that were thought to impact the biomarker expression during the vehicle controlled period. All protocol deviations will be reviewed and assessed by the study team prior to database release. In general, all data will be summarized using descriptive statistics. No imputation will be made for missing data.*

4.3. Safety Analysis Set

The Safety Analysis Set *will include any subject receiving ≥ 1 dose of investigational product.*

4.4. Other Analysis Sets

N/A.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

One of the primary analyses will be a superiority test to demonstrate crisaborole ointment 2% is more efficacious than vehicle in the target lesion in subjects with mild to moderate AD as measured by the change from baseline in target lesion severity score (TSS) between crisaborole treated lesion and vehicle treated lesion. The null hypothesis is that there is no difference between crisaborole ointment 2% and vehicle, and the alternative hypothesis is that crisaborole ointment 2% is superior to vehicle as measured by change from baseline in TSS at Day 15. The difference between crisaborole and vehicle in TSS change from baseline at Day 15 is significant if $p\text{-value} < 0.05$.

Another primary analysis is for the change in the key skin biomarkers S100A12, CCL17, CCL18, CCL22, elafin/PI3, K16, or IL-13 in the target lesion treated with crisaborole 2% ointment or vehicle. The null hypothesis is that there is no difference between crisaborole ointment 2% and vehicle in the change from baseline to Day 15 in these biomarkers, and the alternative hypothesis is that there is a difference between crisaborole ointment 2% and vehicle in the expression level of biomarkers. Mixed effect model will be used and p-values will be adjusted by Benjamini-Hochberg procedure.

5.2. General Methods

In general, number and percent will be presented for categorical variables. Number, mean, standard deviation, minimum, 1st, 2nd and 3rd quartiles and maximum will be presented for continuous variables.

5.2.1. Analyses for Binary Data

Lesion ISGA response of clear or almost clear and at least a 2 grade improvement from Baseline to Day 8 and Day 15 will be descriptively summarized using number, percentage and 95% confidence interval (CI) of percentage, and compared using McNemar's test for the comparison of crisaborole vs vehicle at each time point.

CCI

5.2.2. Analyses for Continuous Efficacy Data

For the lesion TSS, the linear mixed model will be used to model the intra-subject change from baseline in TSS between the crisaborole ointment 2% treated lesion and vehicle treated lesion. The model includes the fixed effect of visit as factor, and an unstructured variance and covariance matrix will be used to model the dependence among the same subjects across different visits up to Day 15. If there is convergence issue for unstructured variance-covariance matrix, first order autoregressive (AR(1)) variance-covariance matrix will be used. The least square (LS) mean of difference and the associated 95% CI will be presented.

CCI

Continuous secondary endpoints in the double blind period:

- Change from baseline in lesion ISGA up to day 15;

CCI

- Change from baseline in lesion pruritus numerical rating scale up to Day 15.

will be analyzed using similar methods as lesion TSS.

CCI

will be descriptively summarized using number, mean, standard deviation, minimum, 1st, 2nd and 3rd quartiles and maximum.

5.2.3. Analyses for Biomarkers

The skin biopsy samples will be analyzed using immunohistochemistry (IHC), gene arrays and gene expression of specific genes to elucidate the mechanism of action of Crisaborole, which will be done using Taqman Low Density Array (TLDA) PCR for 48 genes including housekeeping genes as well as single gene PCR for few genes that are below detection level on TLDA. TLDA PCR expression values are estimated by $-\Delta Ct$ that is computed relative to RPLPO housekeeping gene. Measurements under the limit of detections are imputed as 20% of the minimum value observed for that gene.

The gene expression data is modeled using a mixed effect model with Time, Tissue, and Treatment as a fixed effect and a random intercept for each patient. This formulation intrinsically models the patient correlation structure as in the case of a paired t-test, having the advantage that estimation of the main effects is possible even in the presence of missing values. This allows to use all available data at each time point rather than using only complete observations. This approach introduces less bias than restricting the analysis for those patients who completed the study. Contrasts are used to estimate the fold changes with treatment within each treatment group and conduct hypothesis testing. Changes with treatment will be estimated and per gene improvement will be defined as $-100 * (XW12,LS - XW0,LS) / (XW0,LS - XW0,NL)$, $XW12,LS - XW0,LS$ represents the least square means for the treatment change and $XW0,LS - XW0,NL$ represents the least square means for the baseline differences.

The microarray data is processed using standard QC metrics and R packages. Expression measures are obtained using GCRMA algorithm. Adjustments by batch effect and clinical variables are carried out using ComBat. Probe-sets with at least 15 samples with expression

values larger than 3 are kept for further analysis. Expression values are modeled using mixed-effect models with fixed factors Time, Tissue and Treatment and a random effect for each patient. Fold changes for the comparisons of interest are estimated and hypothesis testing was conducted on such comparisons using contrasts under the general framework for linear models. P-values from the moderated (paired) t-test were adjusted for multiple hypotheses using the Benjamini–Hochberg procedure which controls the False Discovery Rate (FDR).

Additionally, extensive bioinformatics tools will be employed to gain insights into the mechanism of action of crisaborole.

Correlation analysis will be performed to assess if change from baseline in biomarkers correlates with change in the lesion TSS. Pearson correlation coefficient will be provided.

5.2.4. Analyses for Categorical Data

Categorical endpoints will be summarized using number and percentage. Shift table from baseline to Day 8 and Day 15 will be provided for lesion ISGA.

5.3. Methods to Manage Missing Data

Missing will not be imputed for efficacy descriptive summary. For continuous endpoints analyzed using mixed model in the double blinded period, the missing values post-randomization will be handled in a linear mixed-effect model with repeated measures for this continuous variable, where the values are assumed to be missing at random.

Non responder imputation (NRI) will be used for missing values of lesion ISGA response of clear or almost clear and at least a 2 grade improvement from baseline at Day 8 and Day 15. No imputation for missing values of ISGA response of clear or almost clear and at least a 2 grade improvement from Day 15 to Day 43.

In addition, missing values for safety endpoints will not be imputed.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Change In Lesion TSS From Baseline To Day 15

6.1.1.1. Primary Analysis

- Analysis time points: Day 15.
- Analysis population: FAS.
- Analysis methodology: the intra-subject difference of change from baseline in lesion TSS between crisaborole and vehicle up to Day 15 will be analyzed using the model specified in [Section 5.2.2](#).

- Imputation for missing values: observed data will be included in the model, the missing values will be handled in the model, where the values are assumed to be missing at random.
- Supporting objective and Decision rule: Primary Objective, the lesion TSS change is superior for crisaborole treated area if $p\text{value} < 0.05$.

Reporting results:

- Raw data: The sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum at baseline and post-baseline visits will be presented for each treatment.
- Change from baseline: The sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum will be presented for each treatment. The LS means of difference and the corresponding standard error, 95% CI, p-value will be presented.

Figures

- Line plots of the means change from baseline at Day 15 and 8 for two treatments.

6.1.1.2. Sensitivity/Robustness Analyses

To support the interpretation of the primary analysis the following analyses will be performed:

6.1.1.2.1. Analysis for PPAS

- Analysis time points: up to Day 15.
- Analysis population: PPAS.
- Analysis methodology: the intra-subject difference of change from baseline in lesion TSS between crisaborole and vehicle will be analyzed using the model specified in [Section 5.2.2](#).
- Imputation for missing values: observed data will be included in the model, the missing values will be handled in the model, where the values are assumed to be missing at random.
- Supporting objective and Decision rule: Primary Objective, the lesion TSS change is superior for crisaborole treated area if $p\text{value} < 0.05$.

Reporting results:

- Raw data: The sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum at baseline and post-baseline visits will be presented for each treatment.

- Change from baseline: The sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum will be presented for each treatment. The LS means of difference and the corresponding standard error, 95% CI, p-value will be presented.

6.1.2. Change in Key Skin Biomarkers (S100A12, CCL17, CCL18, CCL22, K16, elafin/PI3 and IL-13 expression level) From Baseline to Day 15

6.1.2.1. Primary Analysis

- Analysis time points: Day 15.
- Analysis population: PPAS.
- Analysis methodology: the change from baseline in lesion biomarkers will be analyzed using the model specified in [Section 5.2.3](#).
- Imputation for missing values: observed data will be included in the model, the missing values will be handled in the model, where the values are assumed to be missing at random.
- Supporting objective and Decision rule: Primary Objective, the lesion biomarker change is superior for crisaborole treated area if adjusted pvalue<0.05.

Reporting results:

- Raw data: The sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum at baseline and post-baseline visits will be presented for each treatment.
- Change from baseline: The sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum will be presented for each treatment. The LS means of difference and the corresponding standard error, 95% CI, p-value will be presented.

6.2. Secondary Endpoint(s)

6.2.1. Change in The Lesion TSS From Baseline to Day 8

Day 8 is a time point in the mixed model for the primary analysis for lesion TSS change from baseline at Day 15. The analysis for lesion TSS change at Day 8 is from the same model, and data reporting is same as for Day 15. See [Section 6.1.1](#).

6.2.2. Changes in Key Skin Biomarkers From Baseline to Day 8

Day 8 is a time point in the mixed model for the primary analysis for biomarkers change from baseline at Day 15. The analysis for biomarkers change at Day 8 is from the same model, and data reporting is same as for Day 15. See [Section 6.1.2](#).

6.2.3. Correlation Between Biomarkers Change And Lesion TSS Change

The analysis for correlation between change from baseline to Day 15 in key biomarkers and change from baseline to day 15 in lesion TSS will be performed by treatment. Pearson correlation coefficient will be presented.

6.2.4. Change From Baseline to Day 8 and Day 15 in ISGA

6.2.4.1. Primary Analysis

- Analysis time points: Day 8 and Day 15.
- Analysis population: FAS.
- Analysis methodology: the intra-subject difference of change from baseline in lesion ISGA between crisaborole and vehicle will be analyzed using the model specified in [Section 5.2.2](#).
- Imputation for missing values: observed data will be included in the model, the missing values will be handled in the model, where the values are assumed to be missing at random.

Reporting results:

- Raw data: The sample size, number and percentage for each category at baseline and post-baseline visits will be presented for each treatment.
- Change from baseline: The sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum will be presented for each treatment. The LS means of difference and the corresponding standard error, 95% CI, p-value will be presented.
- Shift table: number and percentage from each category at baseline to each category at Day 8 and Day 15 will be presented.

6.2.5. Change From Baseline To Visits Up To Day 15 In Pruritus Numerical Scale

- Analysis time points: Day 2 to Day 15
- Analysis population: FAS
- Analysis methodology: the intra-subject difference of change from baseline in lesion pruritus between crisaborole and vehicle will be analyzed using the model specified in [Section 5.2.2](#).
- Imputation for missing values: observed data will be included in the model, the missing values will be handled in the model, where the values are assumed to be missing at random.

Reporting results:

- Raw data: The sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum at baseline and post-baseline visits will be presented for each treatment.

CCI



CCI



6.4. Subset Analyses

N/A

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographic and baseline characteristics will be summarized for safety analysis set according to Pfizer data standards. Lesion baseline data will be summarized by treatment.

6.5.2. Study Conduct and Subject Disposition

Subjects evaluation, disposition, discontinuation will be summarized for safety analysis set according to Pfizer data standards.

6.5.3. Study Treatment Exposure and Compliance

The exposure to study drug in each treatment group in double blind period will be summarized by total number of applications, the total number of days of dosing, and number and percentage of subjects who are compliant with the dosing regimen. The exposure to crisaborole in open label period will be summarized as well.

For double blind period, a subject is considered compliant with the dosing regimen if the subjects:

- *not miss more than 6 IP applications during the double-blind treatment period;*
- *and have no missed IP applications the 2 days before Day 15 biopsy collection;*
- *and not miss more than 3 IP applications in total before Day 8;*
- *and have no missed IP applications the 2 days before Day 8 biopsy collection (if collected).*

For open label period, a total of 56 doses are expected to be applied. A subject will be considered compliant with the dosing regimen if they receive at least 45 but no more than 67 investigational product doses (ie, 80 – 120%, inclusive, of the expected number of doses) administered in accordance with the protocol.

6.5.4. Concomitant Medications and Non-Drug Treatments

Prior drug and non-drug treatment, concomitant drug and non-drug treatment will be summarized according to Pfizer data standards.

6.6. Safety Summaries and Analyses

6.6.1. Adverse Events

Adverse events will be summarized according to Pfizer data standards for each phase.

- TEAEs.
- Serious AEs.

AEs will not be double counted across phases. Counting of AEs will be based on start date of AE. If the start date of an AE is in the double blind period, the end date of the AE in the open label period and severity of AE remained the same in both phases or became lower, then the AE will be counted in double blind period, not in the open label period. However, if the same AE started in the double blind period, and get worse in severity in the open label period, then the AE will be counted in both phases.

Lesion TEAEs and SAEs in double blind phase will be summarized by treatment. General TEAEs and SAEs will be summarized for overall safety analysis set.

TEAEs will be summarized by the number of subjects reporting any TEAE, system organ class (SOC), preferred term, severity, relationship to investigational product, and seriousness.

Serious adverse events (SAEs) will be summarized by SOC and PT, and individual SAEs will be listed by subject. A list of subjects who prematurely discontinue from the study due to an AE will be provided. (If no SAE or few SAEs, SAE summary table may not be needed. Listing would be enough).

6.6.2. Laboratory Data

Safety laboratory data will be summarized according to Pfizer standards.

6.6.3. Vital Signs

Descriptive summary tables for vital signs at screening will be provided.

6.6.4. Physical Examination

Descriptive summary tables will be provided in accordance with Pfizer reporting standards.

7. INTERIM ANALYSES

N/A.

8. REFERENCES

1. Pfizer Protocol C3291001.

9. APPENDICES

9.1. Definition and Use of Visit Windows in Reporting

Visit windows will be used for efficacy biomarker variables.

If more than one observation from the same subject falls into the same visit window, the value closest to the targeted day will be used as the observation for that week. All observations will, however, be included in the listings.

Double Blind Phase		
Visit Label	Targeted Day	Analysis window for data sets
Baseline (Screening (Day -30) to up to first dosing date)	Day 1	Last observation up to and including first dosing date
Day 8	Day 8	Day 2 – Day 11
Day 15	Day 15	Day 12 – First day of open label phase/day of early terminate (early one)
Day 15*	Day 15	Day 2 – First day of open label phase/day of early terminate (early one)
Open Label Phase		
Day 15	Day 15	Last observation up to and including first dosing date of open label phase
Day 43	Day 43	Second day of first dosing date of open label phase - end of study

* For ISGA (global), CCI and pruritus NRS (global). There is no Day 8 assessment for these endpoints.

CCI

