Protocol B7931004

A PHASE 2A, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE SAFETY AND EFFICACY OF PF-06700841 IN SUBJECTS WITH MODERATE TO SEVERE PLAQUE PSORIASIS

Statistical Analysis Plan (SAP)

Version: 3

Author: PPD, PPD (PPD, PPD, MA)

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

This is the first version 1.0

Table 1 Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	No Changes	
2	Added additional Safety analyses	Added to match displays requested by IRC
	Changed sensitivity analyses	Changed to produce population average estimates
	Added detail to multiplicity adjustment procedure	Detail needed for implementation in SAS
	Corrected example SAS code to have consistent alpha levels	Changed all alpha levels to 0.1
	CCI [redacted]	[redacted]
3	Added appendix with C-SSRS mapping algorithm	Not defined before
	Updated appendices 10 and 11 SAS model code from Dose to Trt	Added consistency with other appendices
	Updated section 8.1.1 to specify additional estimates and contrasts from existing MMRM model	Added model output needed for EQDD plan
	Added SAS code to Appendix 8 to extract new estimates and contrasts defined in section 8.1.1	Custom code needed byprogramming

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	Removed requirement for Tier 1 display in sections 8.1.3 and 8.2.4	There are no Tier 1 events defined for this program
	Section 8.2.4, changed Tier 2 events to "…5% in any treatment group"	Aligns displays with reports for other JAK compounds
	Section 8.2.4 changed 90%CI to 95% CI	Aligned SAP with protocol text
	CCI [redacted]	CCI [redacted]
	Added additional detail on windowing algorithm when there are multiple observations within a visit window	Documents programming algorithm

2. INTRODUCTION

Note: in this document any text taken directly from the protocol is *italicized*.

PF-06700841 is a potent TYK2/JAK1 inhibitor with an excellent selectivity profile over the other human kinases. Thus, PF-06700841 is targeted for clinical development for the treatment of patients with psoriasis.

The Janus kinase (JAK) family, including JAK1, JAK2, JAK3 and TYK2, is a group of cytoplasmic tyrosine kinases that mediate signal transduction via interactions with Type 1 and Type 2 cytokine receptors critical for immune cell function, survival, activation, and proliferation. JAK2 homodimers are critical for the signaling of hematopoietic cytokines and hormones including erythropoietin (EPO), IL-3, granulocyte-macrophage colony-stimulating factor (GM-CSF) and prolactin.

JAK1-dependent cytokines include IFN-alpha, IFN-gamma, IL-6, IL-21, and IL-22. IL-6 and IL-21 play a critical role in the development of Th17 cells and production of IL-17, which is a target of several efficacious biologic therapies. JAK1-selective inhibitors spare dose-limiting effects of pan-JAK inhibition by preserving JAK2 homodimer signaling and thus provide the potential for more efficacious oral treatments for several inflammatory

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diseases including psoriasis. The previous positive psoriasis studies with two JAK1 selective inhibitors, INCB39110 and GSK2586184, have provided clinical support for JAK1 inhibition as a novel approach to treat plaque psoriasis.

PF-06700841 is a dual TYK2/JAK1 inhibitor with good selectivity profile over other human kinases. Based on its cytokine inhibition profile, PF-06700841 is expected to target the TH17 pathway directly by inhibiting TYK2 and indirectly by inhibiting JAK1, and to provide therapeutic benefit in the treatment of plaque psoriasis. In the first in human clinical trial of PF-06700841 (Study B7931001), psoriasis subjects receiving active treatment with PF-06700841 (30 mg or 100 mg once daily for 28 days) had clinically meaningful decreases in disease activity as measured by PASI. Preliminary safety, efficacy and pharmacodynamic results from Study B7931001 support further development of PF-06700841 in plaque psoriasis.

The current trial B7931004 is a Phase 2 study that will assess the safety and efficacy of several dose levels of PF-06700841, and will include daily and weekly dosing regimens in subjects with moderate to severe chronic plaque psoriasis.

(Source: Protocol Section 1)

2.1. Study Design

2.1.1. Initial Design

This is a Phase 2a, randomized, double-blind, placebo-controlled, parallel group, multicenter study in subjects with moderate to severe plaque psoriasis. The first part of the study, following a screening period (up to 6 weeks), is a 4 week induction period with double blind daily treatment. At the end of Week 4, all subjects switch to their predefined double blind maintenance treatment regimen for Week 5 through Week 12.

Approximately 200 subjects are planned to be randomized into the study, to allow for approximately 160 evaluable subjects (20 completers per arm). The randomization ratio will be 7:1, active: placebo. During the first 4 week treatment period, 2 oral daily dose levels (30 mg and 60 mg) of PF-06700841, plus matching placebo, will be investigated. During the 8 week maintenance treatment period (Weeks 5 through 12), subjects will receive either 10 mg or 30 mg PF-06700841 once daily, or a 100 mg once weekly regimen of PF-06700841, or matching placebo. Maintenance dose level and regimen will be assigned at the initial time of randomization into the study. All subjects, regardless of assigned regimen (ie, QD or QW) will receive blinded QD dosing throughout the study treatment period to maintain the study blind.

The duration of study subject participation will be approximately 26 weeks, including screening, 12 week treatment period, and 8 week follow up period.

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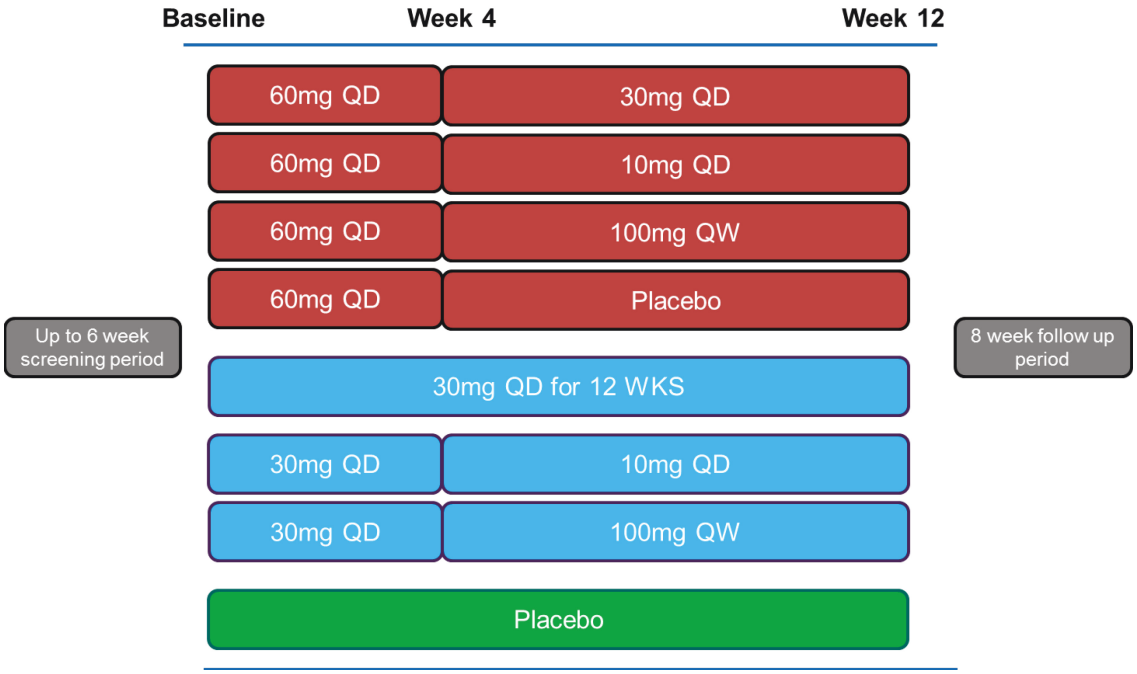
Figure 1. Study Schematic



2.2. Study Objectives

2.2.1. Primary Objective

- *P1: To evaluate the efficacy of PF-06700841 in moderate to severe plaque psoriasis.*

2.2.2. Secondary Objectives

- *S1: To explore the efficacy of PF-06700841 induction and maintenance dosing regimens in moderate to severe plaque psoriasis.*
- *S2: To assess the safety and tolerability of PF-06700841 induction and maintenance dosing regimens.*

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(Source of *italicized* text: Protocol Section 2)

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4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

Statistical inference will be made on the primary endpoint: change from baseline in PASI score at Week 12. The null hypothesis is that there is no difference between any arm of PF-06700841 (60mg QD-30mg QD, 60mg QD-10mg QD, 60mg QD-100mg QW, 60mg QD-Placebo, 30mg QD for 12 Weeks, 30mg QD-10mg QD, 30mg QD-100mg QW) and placebo on the primary endpoint. The alternative hypothesis is that one of *PF*-06700841 arms being tested is superior to placebo on the primary endpoint.

4.2. Statistical Decision Rules

4.2.1. Multiplicity Adjustment

Multiplicity adjustments are considered for the primary endpoint. The overall Type I family wise error rate (FWER) is controlled at 0.05 (one sided). Hochberg method (Hochberg, 1988) is used to maintain appropriate alpha control for rejection of the null hypothesis if a significant treatment effect is detected at Week 12.

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5. ANALYSIS SETS

The data sets to be used for analyses are defined below.

5.1. Full Analysis Set

As specified in the protocol, the analysis of the efficacy, health outcome and CCI [redacted] endpoints will be performed for the modified intent-to-treat (mITT) population, defined as all randomized subjects who receive at least 1 dose of investigational product (PF-06700841 or placebo). This population is also called the Full Analysis Set (FAS).

5.2. Safety Analysis Set

The safety analysis set (SAS) will be all subjects who receive at least 1 dose of investigational product. The safety analysis set will include the follow up period. The final safety database will include all reported safety data at the time of database release.

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5.4. Treatment Misallocations

If a subject was:

- Randomized but not treated: the subject will appear on the subject evaluation table as randomized but not treated; this is the extent of how much the subject will be reported;

- Treated but not randomized: the subject will be reported under the treatment they actually received for all safety analyses, but will not be included in the efficacy analyses;

- Randomized but took incorrect treatment: If a subject received the incorrect treatment for the whole duration of the study, then the subject will not be reported for any efficacy analysis, but will be summarized under the treatment they actually received for all safety analyses; if a subject received the incorrect treatment at only some dosing occasions then the subject will be reported under their randomized treatment group for both efficacy and safety analyses. If sufficient doses were incorrect and therefore deemed a major protocol deviation, the subjects may be excluded as sensitivity analysis.

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5.5. Protocol Deviations

The following sections describe any protocol deviations that relate to the statistical analyses. It is possible that unexpected deviations will arise, becoming known only after the study has been active for a long period of time; hence more deviations may be added. A full list of protocol deviations for the study report will be compiled prior to database release.

5.5.1. Deviations Assessed Prior to Randomization

At screening phase prior to randomization, the investigator will assess and document subjects against the inclusion and exclusion criteria as set out in sections 4.1 and 4.2 of the protocol.

5.5.2. Deviations Assessed Post-Randomization

Post-randomization deviations include:

- Subjects who receive excluded concomitant medications or rescue medications during the treatment period as described in Section 5.8 of the Protocol;
- Subjects who were randomized but took incorrect treatment;
- Subjects not satisfying the eligibility criteria, although, not identified until after randomization occurred.

Any significant deviation or violations from the protocol will be reviewed by the clinical team during the course of the study and prior to database release and a decision taken regarding evaluation for each analysis set.

6. ENDPOINTS AND COVARIATES

For all clinically planned measures, visits should occur within a window of the scheduled visit, which can be found in Appendix 1.

6.1. Efficacy Endpoint(s)

6.1.1. Primary Endpoint

- *Change from baseline in Psoriasis Area and Severity Index (PASI) score at Week 12.*

6.1.2. Key Secondary Endpoint

- *Proportion of subjects achieving a PASI 75 response at Week 12.*

6.1.3. Secondary Endpoints

- *Proportion of subjects achieving 50%, 75% and 90% reduction from baseline PASI at time-points specified in the SoA* of the protocol.
- *Change from baseline in PASI scores at time-points specified in the SoA* of the protocol.
- *Percent change from baseline in PASI scores at time-points specified in the SoA* of the protocol.

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- *Change from baseline in PASI score at Week 4.*

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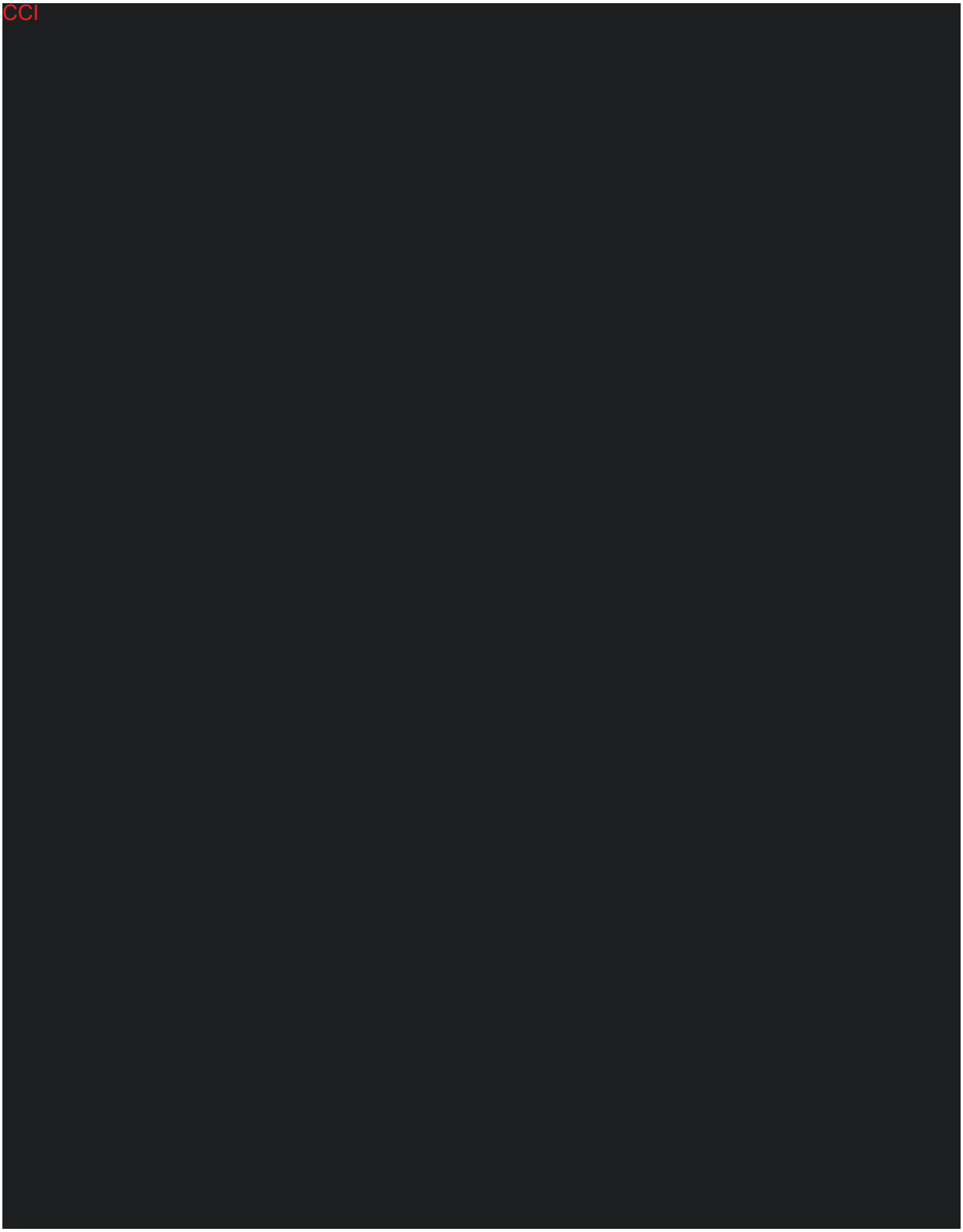

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6.2. Safety Endpoints

- *Incidence and severity of adverse events, serious adverse events and withdrawals due to adverse events.*
- *Change from baseline in clinical laboratory values (chemistry and hematology, lipids).*
- *Change from baseline in vital signs (blood pressure, pulse rate, oral or tympanic temperature measurements).*
- *Change from baseline in ECG parameters (heart rate, QT, QTc, PR and QRS intervals).*

6.3. Covariates

For variables expressed as change from baseline or percent change from baseline, the baseline value will also be included in the analysis model as a covariate.

7. HANDLING OF MISSING VALUES

In general missing values will not be imputed for descriptive statistics.

7.1. Efficacy Data

For the continues efficacy data such as change from baseline in PASI score at Week 12, the observed case (OC) approach will be used.

For the binary efficacy data such as PASI75 response, non-responder imputation (NRI) will be considered, in which case subjects who receive at least one investigational product and discontinue from the study will be considered as non-responders, in addition any subjects with missing data but included in the FAS will have data imputed using NRI.

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7.3. Safety Endpoints

Missing data for safety endpoints will not be imputed and will be left as missing. The follow-up period will be included for the safety endpoint. A sensitivity analysis maybe carried out excluding the follow-up period.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

All efficacy analyses described in this section will only apply to the data in the treatment period to the end of week 20 (Week 0 to 20).

Percentages will be presented to one decimal place in all summaries. Minimum and maximum values will be presented to the same number of decimal places as collected on the CRF or within the laboratory screening panel; mean and median will be presented to one further decimal place; standard deviation will be presented to two further places.

Whilst every effort has been made to pre-specify all analyses in this statistical analysis plan, should any additional exploratory analyses be found to be required after unblinding, the analyses and the reasons for them will be fully detailed in the clinical study report.

In all data presentations, results will be sorted in same order as the study schematic in section 2.1.

8.1. Statistical Methods

The following sub-sections contain the descriptions of the methods that will be used in the analysis of the various endpoints in this study. The choice of analysis method will be dependent on the endpoint of interest (eg whether the endpoint is a primary, key secondary or CCI endpoint or whether the endpoint is efficacy or safety). The analysis methods to be used for each endpoint will be covered in Section 8.2.

8.1.1. Statistical Methods for Continuous Variables

Unless stated otherwise, descriptive summary statistics for all continuous variables will be presented on FAS with OC by treatment group and will include the following: n, mean, median, standard deviation, minimum and maximum

For longitudinal continuous variables, such as the changes from baseline of PASI score, the primary analysis will be conducted using a mixed model repeated measures (MMRM) analysis on the FAS using all available data (no imputation). Each analysis will be performed with a restricted maximum likelihood (REML) MMRM approach. Baseline measurement such as baseline score will be used as a covariate. The model will include treatment and visit as fixed factors, along with the interactions of treatment by visit and baseline score by visit. An unstructured covariance structure will be used to model the within-subject variability. In the event there are difficulties with initially fitting an unstructured covariance matrix, a variety of methods such as heterogeneous CS, heterogeneous AR(1) and antedependence will be used to facilitate the computations. Method that gives rise to the smallest AIC will be used in the final model. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The model will be fit using SAS PROC MIXED. Least squares (LS) means of the treatment groups at each available visit along with 90% CIs will be presented. LS mean difference between treatment and placebo for each visit will be presented along with 90% confidence intervals. LS means and confidence intervals will be back transformed to an appropriate scale when necessary. In

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the case of convergence issues, analysis of covariance (ANCOVA) may be performed at each time point on the FAS.

In addition to the above summaries from the MMRM model, the following will also be calculated and displayed for PASI, Change from Baseline PASI and Percent Change from Baseline PASI:

- Contrasts of Week 4 versus Week 12 LSmeans (i.e., Week 12 – Week 4) by treatment arm.

- Contrasts at Week 12 of LSmeans with same maintenance dose but different induction doses (eg. 60 mg -> 30 mg versus 30 mg -> 30 mg etc.).

- LSmeans at Weeks 1 2 and 4 by induction dose (i.e., placebo, 30 mg and 60 mg)

    - Contrasts at Weeks 1, 2 and 4 comparing 10 mg induction versus placebo induction and 30 mg induction versus placebo induction.

- LSmeans at Week 12 by combined maintenance dose (e.g. 30 mg, 10 mg, 100 mg QW and placebo.

    - Contrasts at Week 12 of the different combined maintenance arms versus the combined placebo arm.

Secondary analyses for continuous variables will be performed with ANCOVA on the FAS at each time point with OC data..

8.1.2. Statistical Methods for Binary Variables

For all binary endpoints, a summary of the number of subjects in each category based on OC in each treatment arm at each time point will be produced and the response rate will also be plotted against time, by treatment group. In addition, similar summary tables will be generated for PASI50/75/90 for each visit with NRI.

Analysis of binary variables over time such as PASI75 response at Week 12 may be analyzed using a marginal logistic regression model fit by pseudo-likelihood in PROC GLIMMIX. The model will include fixed effects for treatment, time , and treatment by time interaction, the model will not contain any random effects. The model will be fit using restricted pseudo-likelihood with an expansion about the marginal solution (method=RMPL in PROC GLIMMIX). The residual covariance (R-side matrix) will be modeled as an unstructured covariance matrix. If convergence fails with the unstructured covariance structure, the following covariance structures will be attempted in order: eg, ANTE(1), CSH, ARH(1), AR(1) and CS, the first structure that allows convergence will be used. Upper and lower 2-sided 90% Wald CIs for the proportions will be calculated using the LSMEANS statement with the ILINK option. The denominator degrees of freedom will be approximated using the Satterthwaite method. Odds ratios for treatment contrasts along with 90% CIs will also be

reported. Two-sided p-value for the test of the 0 difference between PF-06700841 and placebo will be provided.

If there are convergence issues for marginal logistic regression due to zero responses at a visit, then that visit may be dropped from the analysis. If the model still does not converge or if there are issues in interpretability then a logistic regression analysis at each time point may be performed on the FAS with NRI.

8.1.3. Statistical Methods for Safety Data

Test-based methods of constructing exact confidence intervals for the difference in two binomial proportions proposed by Chan and Zhang (1999) will be used when needed to compare incidence rate of safety strata between active groups and placebo, 95% confidence intervals will be formed for tier 2 events.
The exposure adjusted summaries for Tier 2 events will also be conducted. See Section 8.2.1 for the calculation of exposure.

8.1.4. Analyses for Time-to-Event Endpoints

For time to event endpoint (Time to first PASI50 and first PASI75 response), Kaplan-Meier analyses will be used to account for any right censoring, i.e., event not observed. Kaplan-Meier survival estimates from proc LIFETEST and the number and percentage of subjects experiencing the relevant event or being censored will be summarized by treatment group.

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8.2. Statistical Analyses

8.2.1. Standard Analyses

Study conduct and subject disposition

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The number of subjects randomized, treated, completed and discontinued from the study, as well as the number of subjects in each analysis population will be summarized by treatment group. For subjects who did not complete the study, the reasons for withdrawal from the study will be presented.

Demography and baseline characteristics

Demographic and baseline characteristics will be summarized by randomized treatment group for all randomized and treated subjects. Continuous variables will be summarized using mean and standard deviation. Categorical variables will be summarized using relative frequency. Key demographic and baseline variables to be summarized include: geographic region, age, gender, race, ethnicity, height, weight, body mass index, disease duration, baseline PASI score, baseline PGA, baseline BSA score etc.

Exposure and compliance

Exposure to the study therapy is defined as the number of days the subject is known to be on study drug. The exposure is roughly calculated as the date of the last visit (including the follow up visits) of the subject in this study minus the date of the first administration of the study therapy plus one. Summary statistics will be provided for exposure by treatment group.

For each subject, percent will then be calculated using the following formula:

Percent Compliance = # doses actually administrated / # doses planned * 100%.

The number of doses planned or actually administrated is counted up to the conclusion date of the treatment period. Summary statistics will be provided to percent compliance by treatment group.

Descriptive Statistics

Descriptive statistics for all primary, secondary and CCI [redacted] endpoints presented in Section 6 will be tabulated.

8.2.2. Statistical Analyses for Efficacy, Health Outcomes and CCI [redacted]

Unless stated otherwise, the analyses for efficacy, health outcomes and CCI [redacted] will be based on the FAS, as defined in Section 5.1. A summary table of the analysis strategy for all the efficacy and health outcome is shown in Section 8.2.6.

8.2.2.1. Analysis for the Primary Endpoint

The primary efficacy endpoint is the change from baseline in PASI score at Week 12. The primary analysis data will be based on the FAS using MMRM as described in Section 8.1.1. Baseline is defined as the score for each assessment on Day 1 pre-dose.

As secondary analyses, ANCOVA will be employed on FAS population with observed cases (OC).

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8.2.2.2. Analyses for the Secondary Endpoints

8.2.2.2.1. Analyses for the Continuous Secondary endpoints

The analyses for continuous second endpoints are based on the FAS population. Baseline is defined as the score for each assessment on Day 1 pre-dose. These endpoints include:

- *Change from baseline in PASI scores at time-points specified in the SoA* of the protocol.
- *Percent change from baseline in PASI scores at time-points specified in the SoA* of the protocol.
- *Change from baseline in PASI score at Week 4.*

All continuous secondary endpoints including all time points will be analyzed using MMRM with OC as described in Section 8.1.1. LS means at each time point will be computed. P values and 90% confidence intervals will also be computed for placebo adjusted effect (LS mean difference between treatment and placebo) at each time point. Sensitivity analysis will be provided using ANCOVA In case of convergence issues, ANCOVA may be performed at each time point with observed cases.

8.2.2.2.2. Analyses for the Categorical Secondary Endpoints

Unless otherwise stated, all primary analyses for the binary secondary endpoints are based on the FAS population. Baseline is defined as the score for each assessment on Day 1 pre-dose. These endpoints include:

Key secondary endpoint:

- *Proportion of subjects achieving a PASI 75 response at Week 12.*

Secondary endpoint:

- *Proportion of subjects achieving 50%, 75% and 90% reduction from baseline PASI at time-points specified in the SoA* of the protocol.

Marginal logistic regression will be employed on FAS with OC as described in section 8.1.2. Additional analysis will be performed by logistic regression at each time point with NRI. In the case of convergence issues of the marginal logistic regression logistic regression analysis with NRI will be applied.

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8.2.3. Analyses for Time-to-Event Endpoints

For time to event endpoints (Time to first PASI50 and first PASI75 response), Kaplan-Meier analyses will be used to account for any right censoring, i.e., event not observed. Kaplan-Meier survival estimates and the number and percentage of subjects experiencing the relevant event or being censored will be summarized by treatment group.

8.2.4. Statistical Analyses for Safety

The analysis population for safety is described in Section 5.2. Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs) and laboratory tests. A complete list of laboratory parameters can be obtained in Section 7.3 of the protocol.

All the tables, listings and graphs for adverse events, lab parameters and vital sign and ECG will follow Pfizer standards. The binary safety endpoints including the incidences of on-treatment AEs, withdrawals due to AEs and serious AEs will be analyzed using the exact test described in Section 8.1.3. A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers.

Tier-1 events: These are pre-specified events of clinical importance and are maintained in a list in the product's Safety Review Plan. There are no Tier 1 events for this study. Tier 1 displays will not be created.

Tier-2 events: These are events that are not tier-1 but are "common". A MedDRA Preferred Term (PT) is defined as a tier-2 event if there is a 5% incidence in in any treatment group.

Tier-3 events: These are events that are neither tier-1 nor tier-2 events.

There will be no adjustment for multiple comparisons or stratification factors in the analyses unless specified. For tier-1 and tier-2 events, the proportion of AEs observed in each treatment groups will be presented along with the point estimates and associated 95% confidence intervals of the risk difference for each active treatment compared with placebo using the exact methods described in Section 8.1.3. For tier-1 events p-values may be included in the presentations. AEs will be arranged in the output sorted in descending point

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estimate of the risk difference within system organ class. Footnotes in the outputs will include the methods used to derive any p-values and confidence intervals as per Pfizer standards. The exposure adjusted summaries for the Tier 1 and Tier 2 events will also be conducted.

Additionally,

1) For AST, ALT, WBC, neutrophils, lymphocytes, platelets, reticulocytes, Hemoglobin, CK, hsCRP, TBNK, IP-10, immunoglobulins, creatinine, Cystatin C, creatinine eGFR, cystatin C eGFR, HDL, LDL, LDL:HDL ratio, total cholesterol and triglycerides:
    a. Descriptive statistics for observed values, change from baseline and percent change from baseline summarized as follows:
        i. At all time point by the 8 randomized treatment groups
        ii. At Week 4 by three groups defined by induction dose; everyone who had 30 mg Induction (30 mg, 30 mg -> 10 mg, 30 mg -> 100 mg QW) , everyone with 60 mg induction (60 mg -> placebo, 60 mg -> 100 mg QW, 60 mg -> 10 mg, 60 mg -> 30 mg) and placebo
        iii. At Week 12 by four groups defined by maintenance dose; 100 mg QW maintenance (30 mg -> 100 mg QW and 60 mg -> 100 mg QW), 10 mg QD maintenance (30 mg -> 10 mg, 60 mg -> 10 mg), 30 mg maintenance (30 mg, 60 mg -> 30 mg) and placebo (placebo, 60 -> placebo
    b. Figures for each lab endpoint over time showing the mean +/- 90% confidence interval, figures and median figures without confidence intervals. For each lab these figures will be repeated three times displaying, observed values, change from baseline and percent change from baseline.
2) Safety AE incidence through week 4 by induction dose; everyone who had 30 mg Induction (30 mg, 30 mg -> 10 mg, 30 mg -> 100 mg QW) , everyone with 60 mg induction (60 mg -> placebo, 60 mg -> 100 mg QW, 60 mg -> 10 mg, 60 mg -> 30 mg) and placebo.
3) Safety AE incidence from week 4 through week 12 by maintenance dose; 100 mg QW maintenance (30 mg -> 100 mg QW and 60 mg -> 100 mg QW), 10 mg QD maintenance (30 mg -> 10 mg, 60 mg -> 10 mg), 30 mg maintenance (30 mg, 60 mg -> 30 mg) and placebo (placebo, 60 -> placebo)
4) Modified Hy's Law plots with 2.5 times ULN for AST and ALT and 1.5 times ULN for bilirubin.

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8.2.6. Summary of Major Efficacy Analyses

Endpoints	Primary, Secondary, or CCI Endpoint	Analysis	Including Follow-UP	Missing Data Imputation	Primary or Sensitivity Approach
Change of PASI	Primary	MMRM	Yes	OC	Primary
Change of PASI by Visit	Primary	ANCOVA	Yes	OC	Sensitivity
PASI50/75/90 Response	Secondary	Marginal Logistic Regression	Yes	OC	Primary
PASI50/75/90 Response	Secondary	Logistic regression	Yes	NRI	Sensitivity
Percent change of PASI	Secondary	MMRM	Yes	OC	Primary
Percent change of PASI by Visit	Secondary	ANCOVA	Yes	OC	Sensitivity

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9. REFERENCES

1. Pfizer Clinical Protocol B7931014: a Phase 2a, Randomized, Double-Blind, Placebo-controlled Study to Evaluate Safety and Efficacy of PF-06700841 in Subjects with Moderate to Severe Plaque Psoriasis.

2. Hochberg, Y, A sharpened Bonferroni procedure for multiple tests of significance, Biometrica, 1988, 75, 4: 800-802.

[redacted]

3. Chan, I. S. F. and Zhang, Z. (1999), "Test-Based Exact Confidence Intervals for the Difference of Two Binomial Proportions," Biometrics, 55, 1202–1209.

10. APPENDICES

Appendix 1. Definition And Use Of Visit Windows In Reporting

Note Day 1 in the table below is taken as the first day of dosing with study drug. It may not be the same as the first study date which is the randomization date. Also note that Day 0 does not exist, therefore Day -1 is the day before Day 1. In addition, the relative days (rel_day) from Day 1 are defined as the visit date minus the first dosing date plus one. Visit windows will be used for efficacy variables, and for any safety displays that display by week. When multiple observations fall in the same analysis visit window, the observation closest to the targeted day will be used. If the observations are with equal distant from the targeted day in absolute value, the one before the targeted day will be used.

Table 2. Visit Window Definition for Analysis

Visit No.	Visit Label	Target Day	Visit Window
1	Screening	N/A	-42 ≤ rel_day ≤ -1
2	Baseline*	1	Rel_day = 1
3	Week 1	8	2≤rel_day≤11
4	Week 2	15	12≤rel_day≤22
5	Week 4	29	23≤rel_day≤36
6	Week 6	43	37≤rel_day≤50
7	Week 8	57	51≤rel_day≤64
8	Week 10	71	65≤rel_day≤78
9	Week 12	85	79≤rel_day≤92
10	Week 14	99	93≤rel_day≤106
11	Week 16	113	107≤rel_day≤127
12	Week 20	141	128≤rel_day≤148
* Baseline analysis visit window may be considered as Rel_day≤1 in some analyses (eg, those involving change from baseline). That is, in case that Day 1 observation is missing, the last observation by the first dosing date may be considered as the baseline. The baseline measurements for demography, height, pre-study medical history and medications will be collected at the "Screening" visit.			

Appendix 2. Psoriasis Area and Severity Index (PASI)

The Psoriasis Area and Severity Index quantifies the severity of a subject's psoriasis based on both lesion severity and the percentage of body surface area affected. Lesion severity: the basic characteristics of psoriatic lesions - erythema, induration and scaling - provide a means

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for assessing the severity of lesions. Assessment of these three main signs is performed separately for four areas of the body: head, upper limbs, trunk, and lower limbs. Average erythema, induration and scaling are rated for each body area according to a 5-point scale: 0, no involvement; 1, slight; 2, moderate; 3, marked; 4, very marked.

Body surface area (BSA) involvement: the extent (%) to which each of the four areas of the body is affected by psoriasis is assigned a numerical score according to the following area scoring criteria: 0, no involvement; 1, >0 to 9%; 2, 10 to 29%; 3, 30 to 49%; 4, 50 to 69%; 5, 70 to 89%; 6, 90 to 100%. Details see Appendix 3.

Derivation of PASI score

In each area, the sum of the severity rating scores for erythema, induration and scaling is multiplied by the score representing the percentage of this area involved by psoriasis, multiplied by a weighting factor (head 0.1; upper limbs 0.2; trunk 0.3; lower limbs 0.4). The sum of the numbers obtained for each of the four body areas is the PASI.

PASI = 0.1Ah(Eh + Ih + Sh) + 0.2Au(Eu + Iu + Su) + 0.3At(Et + It + St) + 0.4Al(El + Il + Sl)

where A = area of involvement score; E = erythema; I =induration; S = scaling; h = head; u = upper limbs; t = trunk; l = lower limbs

The PASI score can vary in increments of 0.1 units from 0.0 to 72.0, with higher scores representing increasing severity of psoriasis.

PASI 50/75/90 response

At least 50/75/90% reduction in PASI relative to baseline PASI Score.

Appendix 3. Body Surface Area (BSA)

Assessment of body surface area involved in psoriasis is performed separately for four areas of the body: head, upper limbs, trunk, and lower limbs. The percentage surface area affected by psoriasis is estimated by means of the "handprint method", where the full hand of the subject (i.e., the subject's flat hand, thumb and fingers) represents approximately 1% of the total BSA2 and a set percentage of each of the four areas of the body:

- 1 handprint corresponds to approximately 10% of the head/neck;
- 1 handprint corresponds to approximately 5% of the arm/upper limbs;
- 1 handprint corresponds to approximately 3.3% of the trunk;
- 1 handprint corresponds to approximately 2.5% of the lower limbs.

[redacted]

The extent (%) to which each of the four areas of the body is affected is captured on the CRF (to 2 decimal places, as necessary). A weighting factor is applied to each of the four areas in calculation of the total body surface area affected: head x0.1; upper limbs x0.2; trunk x0.3; lower limbs x0.4, as the four areas correspond to approximately 10%, 20%, 30% and 40% of the total BSA, respectively. The sum of the weighted percent involvement obtained for each of the four body areas is the overall psoriatic BSA.

Table 2. Handprint Determination of Body Region Surface Area (BSA)

Body Region	Total Number of Handprints in Body Region*	Surface Area of Body Region Equivalent of One Handprint*
Head and Neck	10	10%
Upper Limbs	20	5%
Trunk (including axillae and groin/genitals)	30	3.33%
Lower Limbs (including buttocks)	40	2.5%

Handprint refers to the hand size of each individual subject.

* The number of handprints will be for the entire body region; these values will not be adjusted for exclusion of scalp, palms, and soles from the BSA assessment.

Appendix 4. Physician Global Assessment (PGA)

The Physician Global Assessment of psoriasis is scored on a 5-point scale, reflecting a global consideration of the erythema, induration and scaling across all psoriatic lesions. Average erythema, induration and scaling are rated separately over the whole body according to a 5-point severity scale, scored from 0 to 4, with appropriate morphologic descriptors. The severity rating scores are summed and the average taken - the total average is rounded to the nearest whole number score to determine the PGA. The 5-point scale for PGA is: 0, "clear"; 1, "almost clear"; 2, "mild"; 3, "moderate"; 4 "severe".

CCI

CCI

[redacted]

CCI

[redacted]

Appendix 8. Examples of SAS Code for Statistical Analyses – MMRM

Table 3. Input Parameters for MMRM Analyses

ID	Subject's ID
CFB	Change from baseline
VISIT	Visit of interest (stored as a categorical variable). Only the post-baseline visits are included.
TRT	Treatment group (stored as a categorical variable)
Baseline	Baseline observation of the outcome

Create data set ds as described in the 3 and sort it by visit. The analysis will be implemented as follows

[redacted]

```
proc mixed data=ds;
        class    id trt visit;
        model cfb = trt visit trt*visit baseline /alpha=0.10  ddfm=kr;
        repeated visit /subject= id type= un;
        lsmeans trt*visit /alpha=0.10 cl pdiff;
        ods output diffs= dmmrm;
run;
```

Examples of Estimates and Contrasts of Combined Induction doses at Week 4(please extend similar code to Weeks 1 and 2 as per analysis section) and Combined maintenance dose. Code below assumes that:

- Visits in data start at Week 1 and continue through week 16 in the following order (Week 1, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 14, and Week 16).

- Treatment is coded by treatment arm in the following order (60 -> 30, 60 -> 10, 60 -> 100 QW, 60 ->plb, 30 ->30, 30 ->10, 30 -> 100 QW, Placebo->Placebo).

- Furthermore it is assumed that the treatment by visit contrast is order first by treatment and then by visit, that is (60->30 week 1, 60->30 week 2, … 60 ->30 week 16, 60->10 week 1, …Placebo Week 16).

- &basemean is a macro variable with the overall mean baseline value for the dataset being analyzed. It should match the mean used internally by the LSMeans statement which can be verified using the ‘e’ option in the LSmeans.

NB: The ‘e’ option can be added to the estimate statements for quality control to verify that the correct linear estimate is specified. They are not necessary for the correct calculation of the estimates and contrasts. The ‘singular’ option with a number close to 1, instead of the default value, may be used in the estimate statement if the output indicates that a particular estimate is ‘non-estimable’. However, it will then be necessary to check that the estimate appears numerically reasonable and the standard error is similar to other estimates, or contrasts.

```
estimate "60 week 4"  intercept 1   avisitn 0 0 1  trtan .25 .25 .25 .25
      trtan*avisitn 0 0 .25 0 0 0 0 0 0
                    0 0 .25 0 0 0 0 0 0
                    0 0 .25 0 0 0 0 0 0
                    0 0 .25 0 0 0 0 0 0
     base  &basemean/cl alpha = .1   ;
estimate "30 week 4"  intercept 1   avisitn 0 0 1  trtan 0 0 0 0  .3333 .3333 .3333
      trtan*avisitn 0 0 0 0 0 0 0 0 0
                    0 0 0 0 0 0 0 0 0
```


[redacted]

```
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 .3333 0 0 0 0 0 0
                0 0 .3333 0 0 0 0 0 0
                0 0 .3333 0 0 0 0 0 0
     base  &basemean/ cl  alpha=.1  ;
estimate "Placebo week  4"  intercept 1   avisitn 0 0 1  trtan 0 0 0 0  0 0 0 1
      trtan*avisitn 0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 1 0 0 0 0 0 0
     base  &basemean/ cl alpha =.1   ;



estimate "60 vs Plb week 4"  intercept 0   avisitn 0 0 0
               trtan .25 .25 .25 .25 0 0 0 -1
      trtan*avisitn 0 0 .25 0 0 0 0 0 0
                0 0 .25 0 0 0 0 0 0
                0 0 .25 0 0 0 0 0 0
                0 0 .25 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 - 1 0 0 0 0 0 0

     base  0/cl  alpha=.1  ;

estimate "30 vs Plb week 4"  intercept 0   avisitn 0 0 0
      trtan 0 0 0 0  .3333 .3333 .3333 -1
      trtan*avisitn 0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 .3333 0 0 0 0 0 0
                0 0 .3333 0 0 0 0 0 0
                0 0 .3333 0 0 0 0 0 0
                0 0 -1    0 0 0 0 0 0
     base  0/ cl alpha=.1

estimate "30 week 12"  intercept 1   avisitn 0 0 0 0 0 0 1  trtan .5 0 0 0 .5
      trtan*avisitn 0 0 0 0 0 0 .5 0 0
```


[redacted]

```
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 .5 0 0
      base  &basemean/cl alpha = .1   ;


estimate "10 week 12"  intercept 1   avisitn 0 0 0 0 0 0 1  trtan 0 .5 0 0 0 .5
      trtan*avisitn 0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 .5 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 .5 0 0
      base  &basemean/cl alpha = .1   ;

estimate "100 week 12"  intercept 1   avisitn 0 0 0 0 0 0 1  trtan 0 0 .5 0 0 0 .5
      trtan*avisitn 0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 .5 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 .5 0 0
      base  &basemean/cl alpha = .1    singular=1;
estimate "Placebo week 12"  intercept 1   avisitn 0 0 0 0 0 0 1  trtan 0 0 0 .5 0 0 0 .5
      trtan*avisitn 0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 .5 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 .5 0 0
      base  &basemean/cl alpha = .1    singular=1;


estimate "30 vs Plb week 12"  intercept 0    avisitn  0 0 0 0 0 0 0  trtan .5 0 0 -.5 .5 0 0 -.5
      trtan*avisitn 0 0 0 0 0 0 .5 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 -.5 0 0
                0 0 0 0 0 0 .5 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 0 0 0
                0 0 0 0 0 0 -.5 0 0
```


[redacted]

```
      base 0/cl alpha = .1  e  ;

estimate "10 vs Plb week 12"  intercept 0   avisitn 0 0 0 0 0 0 0   trtan  0 .5 0 -.5  0 .5 0 -.5
       trtan*avisitn 0 0 0 0 0 0 0 0 0
                     0 0 0 0 0 0 .5 0 0
                     0 0 0 0 0 0 0 0 0
                     0 0 0 0 0 0 -.5 0 0
                     0 0 0 0 0 0 0 0 0
                     0 0 0 0 0 0 .5 0 0
                     0 0 0 0 0 0 0 0 0
                     0 0 0 0 0 0 -.5 0 0
      base  0 /cl alpha = .1   ;
 estimate "100 vs Plb week 12"  intercept 0   avisitn 0 0 0 0 0 0 0   trtan  0 0 .5 -.5  0 0 .5 -.5
       trtan*avisitn 0 0 0 0 0 0 0 0 0
                      0 0 0 0 0 0 0 0 0
                     0 0 0 0 0 0 .5 0 0
                     0 0 0 0 0 0 -.5 0 0
                     0 0 0 0 0 0 0 0 0
                     0 0 0 0 0 0 0 0 0
                     0 0 0 0 0 0 .5 0 0
                     0 0 0 0 0 0 -.5 0 0
      base  0 /cl alpha = .1   ;
```

Appendix 9. Examples of SAS Code for Statistical Analyses – ANCOVA

Using the same input parameters in Table 3, the analysis will be implemented as follows

```
proc mixed data=dataset ;
        by visit;
        class    id trt visit;
        model cfb = trt baseline /alpha=0.10 ddfm=kr;
        lsmeans trt  /alpha=0.10 cl pdiff;
        ods output diffs=dancova;
run;
```

Appendix 10. Example SAS Code for Generalized Mixed Model for Binary Data (GMMRM)

```
PROC GLIMMIX DATA=xxx NOCLPRINT method=rmpl;
CLASS ID Visit trt;
MODEL efrslt(event='1') = trt Visit trt*Visit/ SOLUTION DIST=BINARY LINK=LOGIT
htype=3  ddfm=sat;
random Visit / type=un subject=ID  residual;
lsmeans Dose*Visit / slicediff=Visit or alpha=.1 ilink cl e; ods output lsmeans=lsmout
slicediffs=diffsout;
```


[redacted]

Run;

Appendix 11. Logistic Regression Code

```
PROC GENMOD data=<dataset>  descending;
  Class trt;
MODEL efrslt =trt/   dist=bin  link=logit  alpha=0.1  lrci ;
Run;
```

Appendix 12. Hochberg Testing Procedure

Consider testing null hypotheses H01, …H07 and let pi, i=1,…,7 denote the corresponding 1-sided p-values from the individual pairwise comparisons against the placebo arm prior to multiplicity adjustment. Furthermore, let [1], ….[7] denote the order of the p-values so that p[1] ≤ p[2] ≤ …. P[7]. The procedure starts with the largest p-value p[7] as follows:

1. If p[7] < α reject all null hypotheses, otherwise go to next step
2. If p[6] <α/2 reject hypotheses H0[1] through H0[6], otherwise go to next step

   ……
3. If p[k] < α/(7-k +1), reject hypotheses H0[1] through H0[k]

   ….
4. If p[1] < α/7, reject H0[1], otherwise stop and do not reject any hypotheses

Alternatively, the unadjusted raw p-values can be read into Proc Multtest and adjusted using the HOC option.

```
data pvals;
  Input Test$ Raw_P;
Datalines;
Test1 .xxxxx
Test2 .xxxxx
…..
Test6 .xxxxx
;
Proc multtest pdata=pvals hoc out=new;
run;
```

Appendix 13. Details on C-SSRS Mapping

Columbia-Classification Algorithm of Suicide Assessment (C-CASA)

[redacted]

Table 1. C-CASA Suicidality Events and Codes

Event Code	Event
1	Completed suicide
2	Suicide attempt
3	Preparatory acts towards imminent suicidal behavior
4	Suicidal ideation
5	Self-injurious behavior, intent unknown
6	Not enough information, fatal
7	Self-injurious behavior, no suicidal intent
8	Other, accident, psychiatric; mental
9	Not enough information, non fatal

* Note: Event Codes 5, 6, 8 and 9 are not applicable to prospectively collected data

Table 2. C-SSRS Mapped to C-CASA - Suicidality Events and Codes

C-CASA Event Code	C-CASA Event	C-SSRS Response
1	Completed suicide	As captured in the safety database
2	Suicide attempt	"Yes" on "Actual Attempt"
3	Preparatory acts towards imminent suicidal behavior	"Yes" on any of the following: • "Aborted attempt", or • "Interrupted attempt", or • "Preparatory Acts or Behavior"
4	Suicidal ideation	"Yes" on any of the following: • "Wish to be dead", or • "Non-Specific Active Suicidal Thoughts", or • "Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act", or • "Active Suicidal Ideation with Some Intent to Act, without Specific Plan", or • "Active Suicidal Ideation with Specific Plan and Intent"
7	Self-injurious behavior, no suicidal intent	"Yes" on "Has subject engaged in Non-suicidal Self-Injurious Behavior?"

[redacted]