A Randomized, Evaluator-Blinded, Bilateral Comparison Study of Two Topicals in the Treatment of Subjects with Acne Vulgaris

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Appendix 16.1.9 Documentation of Statistical Methods

STATISTICAL ANALYSIS PLAN

VERSION:1.0

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SPONSOR:	Foamix Pharmaceuticals
PROTOCOL NUMBER:	FX2018-23
TI PROJECT NUMBER:	152-11051-401
PROTOCOL TITLE:	A Randomized, Evaluator-Blinded, Bilateral Comparison Study of Two Topicals in the Treatment of Subjects with Acne Vulgaris
PROTOCOL DATE:	Version 2.0, 13-Nov-2018

PREPARED BY: PPD
Therapeutics, Inc.

ABBREVIATIONS

AE	Adverse Event
CRF	Case Report Form
CSR	Clinical Study Report
EOT	End of Treatment
IGA	Investigator's Global Assessment
LSR	Local Skin Reaction
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
PP	Per-Protocol
PT	Preferred Term
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TEWL	Transepidermal Water Loss
TI	Therapeutics, Inc.
UPT	Urine Pregnancy Test

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1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analyses to be performed for data from Protocol FX2018-23, "A Randomized, Evaluator-Blinded, Bilateral Comparison Study of Two Topicals in the Treatment of Subjects with Acne Vulgaris".

This SAP was created using Clinical Protocol FX2018, Version 2.0 dated 13-Nov-2018, and the Case Report Forms (CRF) Version 1.0, dated 12-Nov-2018.

2. PURPOSE OF THE ANALYSES

The purpose of this SAP is to outline the planned analyses to be completed to support the Clinical Study Report (CSR) for Protocol FX2018-23. Any post-hoc or unplanned analyses not identified in this SAP will be clearly identified in the CSR.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The objective of this study is to evaluate the safety and efficacy of the two topical formulations in acne vulgaris subjects. More specifically, the above formulations will be compared for their effect on facial sebum.

3.2 Efficacy Endpoints

- Investigator's Global Assessment (IGA) at Week 6
- IGA "success" at Week 6
- Absolute and Percent Change from Baseline to Week 6 in inflammatory lesion count
- Absolute and Percent Change from Baseline to Week 6 in non-inflammatory lesion count
- Sebum and Transepidermal Water Loss (TEWL) assessments relative to Baseline at Weeks 2, 4, 6 and 7
- VISIA Digital Photographs for analysis of clinical changes relative to Baseline may undergo an independent separate analysis

3.3 Safety Endpoints

- Incidence (severity and causality) of any reported or observed treatment emergent adverse events (TEAEs)
- LSR severity status [improved/same versus worsened] compared to Baseline at each time point

4. STUDY DESIGN

This is a randomized, evaluator-blinded, bilateral comparison study of FMX101 hydrophobic oil based vehicle (Test Article A) and hydro-alcohol solution based vehicle (Test Article B) in healthy male or female subjects 9 years of age or older with facial acne vulgaris. Eligible subjects must

have a clinical diagnosis of symmetric moderate facial acne vulgaris (IGA of Grade 3) and ≥16 inflammatory lesions (i.e., papules and pustules) on the face. Approximately 12 subjects will be enrolled to obtain about 10 evaluable subjects at one to two study sites. Subjects will be randomized (1:1) to treatment with Test Article A to one side of the face versus Test Article B on the contralateral side.

Test Articles:

1. FMX101 hydrophobic oil based vehicle (Test Article A)
2. Hydro-alcohol solution based vehicle (Test Article B)

Test articles will be applied once daily in the evenings for six weeks to the appropriate side of the face.

The study schedule of visits and assessments is provided in Table 1. Further details regarding the study may be found in the study protocol.

Table 1: Schedule of Events

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Unscheduled Visit
	Screening/ Baseline	Week 1 / Follow – up 1	Week 2 / Follow – up 2	Week 4 / Follow – up 3	Week 6 / EOT[1]	Week 7 / EOS	
Days	1	8 ± 2	15 ± 3	29 ± 3	43 ± 3	50 ± 3	
Informed Consent/Assent[2]	X						
Demographics	X						
Eligibility	X						
Medical History	X						
Concomitant Medications and Procedures/Therapies	X	X	X	X	X	X	X
Dermatological Exam	X						
UPT[3] for WOCBP[4]	X				X		
Clinical Evaluations (IGA and lesion counts, R vs L) [5]	X	X	X	X	X	X	
LSR Assessment, R vs L	X[6]	X	X	X	X	X	X
VISIA Photography	X		X	X	X		
TEWL/Sebum, R vs L	X		X	X	X	X	
Randomization	X						
Test Article Accountability, R vs L	X	X	X	X	X		X
Demonstrate how to apply test articles[7]	X	X	X	X			
Apply test articles	X						
Subject Diary and Compliance Review[8]: Dispense (D), Review (R), and/or Collect (C)	D	C+R+D	C+R+D	C+R+D	C+R		C+R+D, as necessary
Adverse Events	X[9]	X	X	X	X	X	X

[1]Or early termination from the study.
[2] Consent/assent may be performed up to 45 days prior to Baseline. Subjects who require "washout" for longer than 45 days will be re-consented.
[3] UPTs must have a minimum sensitivity of 25 mIU ß-hCG/mL.
[4] WOCBP include any female who has experienced menarche or is 10 years of age or older and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).
[5] Clinical grading to be done by the same Blinded Evaluator.
[6] LSRs will be assessed both before and 15 minutes following test article application.
[7] Study staff will provide a Subject Instruction Sheet to the subject and parent/guardian (if applicable) and test article application will be demonstrated using the test article samples provided to the site.
[8] Review Subject Diary and amount of test article used since last visit to determine subject compliance. Re-educate subject on use of the test article with particular attention to inappropriate prior use of test article – be it amount of product applied and/or frequency of use.
[9] Recorded under Medical History.

5. DEFINITIONS

Study Day: The Study Day is the day of the study relative to the first dose of test article, therefore, the Baseline Visit is Study Day 1.
Study Day = Follow-up Visit Date – Baseline Date + 1.

6. CLINICAL EVALUATIONS

6.1 Investigator's Global Assessment

The IGA score is a static evaluation of the overall severity or "average" degree of severity of a subject's disease by the Blinded Evaluator, taking into account all of the subject's facial acne lesions as the subject appears on the day of the evaluation. Overall severity of acne will be assessed using a five-point scale from 0-Clear to 4-Severe. Subjects must have an identical IGA score of moderate severity (IGA Grade 3) on both the right and left side of the face at Baseline.

Table 2: IGA Severity Grades

Grade	Description
0	**Clear**; Normal, clear skin with no evidence of acne vulgaris
1	**Almost clear**; Rare non-inflammatory lesions may be present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink- red)
2	**Mild**; Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	**Moderate**; Many non-inflammatory lesions. Multiple inflammatory lesions evident with several to many papules/pustules, and there may be one small nodulocystic lesion
4	**Severe**; Inflammatory lesions are more apparent, many comedones and papules/pustules, there may be a few nodulocystic lesions

6.2 Acne Lesion Counts

The number of non-inflammatory lesions (open and closed comedones), inflammatory lesions (papules and pustules), and nodulocystic lesions (nodules and cysts) on the face (including those present on the nose) will be counted by the Blinded Evaluator. Subjects must have a minimum of 16 inflammatory lesions AND ≤ 2 nodulocystic lesions on the face in total (with no more than one nodule/cyst per the right or left side of the face) at Visit 1/Baseline. The inflammatory lesion count on the right and left side of the face should be similar (defined as within ~ 50% of each other) at the Baseline visit.

Lesions will be counted separately for the right and left side of the subject's face. Lesions are defined as follows:

Non-inflammatory lesions:

- Comedones: open (blackheads) and closed (whiteheads).

Inflammatory lesions:

- Papules: raised inflammatory lesions with no visible purulent material.
- Pustules: raised inflammatory lesions with visible purulent material.

Nodulocystic lesions:

- Nodules and cysts: any circumscribed, inflammatory masses greater or equal to 5 mm in diameter with or without cystic changes.

6.3 VISIA Photography

Digital photographs will be taken of the face with the VISIA (Canfield Scientific) to document the progress of the subject (right vs left sides) in the study at Visit 1/Baseline, Visit 3, Visit 4, and Visit 5.

6.4 Bioinstrumentation Assessments

TEWL ($g/m^2/h$) and sebum (%) measurements will be conducted on the right and left side of the face. The sebum measurement represents the sebum score of saturation of the film and has a range of 0 to 99, where 99 equates to very oily skin.

7. SAFETY EVALUATIONS

7.1 Adverse Events

All reported or observed AEs will be recorded. At each visit, subjects will also be questioned specifically about the status of any ongoing AEs. Untoward events that occur prior to the first dose of test article will be captured in the Medical History section of the CRF unless they are related to a study-specific procedure. AEs in the face will be segmented to the right and/or left sides of the face.

7.2 Local Skin Reactions

At each visit, local skin reactions (LSRs) (erythema, edema, scaling/dryness, burning/stinging, pruritus, erosion, and pain) will be assessed. Erythema, edema, scaling/dryness, and erosion will be assessed by the investigator and burning/stinging, pain, and pruritus will be assessed by the subject. Assessments will be made using a 4-point ordinal scale where 0-absent, 1-mild (slight, barely perceptible), 2-moderate (distinct presence), and 3-severe (marked, intense). Only LSRs that require medical intervention (e.g., prescription medication), require withholding or discontinuation of the application of the test article, or extend 2 cm beyond the Treatment Area will be documented as AEs. LSRs will be segmented to the right and/or left sides of the face.

8. STATISTICAL METHODS

8.1 General Considerations

SAS® 9.4 will be used to provide all tables, figures, and listings. This section presents the statistical approaches that are anticipated for the analysis of the study data. These approaches may at time require modifications due to unanticipated features of the data. Deviations from the analyses summarized below will be noted in the CSR.

In general, continuous variables will be summarized by descriptive statistics including the number of subjects with non-missing data (n), mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized by frequency and percentage of subjects within each category. Subject data listings sorted by study site and subject number will be presented.

8.2 Analysis Populations

8.2.1 Safety Population

The Safety population will include all randomized subjects who received test article and applied at least one application.

8.2.2 Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population will include all randomized subjects who met all I/E criteria, applied at least one dose of test article, and returned for at least one post-Baseline evaluation visit.

8.2.3 Per-Protocol Population

The per-protocol (PP) population will be a subset of the mITT population and will include subjects who meet the following criteria:

- Applied at least CCI and no more than CCI of the expected test article applications
- Did not miss the schedule test article applications for more than three consecutive days
- No other evidence of material dosing noncompliance

- Completed the primary endpoint evaluation at Week 6 within the visit window (± 3 days)
- No protocol deviations or prohibited medications that would affect the treatment evaluation.

8.3 Final Analyses and Reporting

Final database lock will occur after all subjects have completed the study assessment period (or discontinued early) and all subject data has been monitored. Analysis may not occur until after database lock, this SAP is approved, and analysis populations have been identified.

8.4 Sample Size

This is a pilot proof of principle study, as such no specific power calculations were used to establish the sizing of this study.

8.5 Subject Disposition

The number and percentage of subjects who enrolled in the study, who completed the study, who withdrew from the study and their reasons for discontinuation will be tabulated.

Subject data listings of protocol deviations, if any, and analysis population identification will be provided.

8.6 Screening and Baseline Assessments

8.6.1 Demographics

Sex, age (computed from date of birth and Baseline visit date), ethnicity and race will be summarized. If a subject has more than one self-reported race, then he/she will be summarized in the "multiple" category.

8.6.2 Dermatologic Examination

Any abnormalities noted during the dermatologic examination at the Baseline Visit will be captured in the Medical History.

8.6.3 Baseline Clinical Evaluations

The frequency distribution of IGA scores will be tabulated as Test Article A versus Test Article B to reflect the paired data. Descriptive statistics for the acne lesion counts, TEWL and sebum measurements will be presented for each test article.

8.6.4 Baseline Local Skin Reactions

The frequency distribution of each of the pre-application LSR severity scores will be tabulated as Test Article A versus Test Article B to reflect the paired data.

8.7 Dosing Compliance

Descriptive statistics will be used to summarize dosing duration and test article compliance for each analysis population. Dosing duration (days) will be calculated as [date of last dose] – [date of first dose] + 1. Subjects will be instructed to apply each test article once daily for six weeks, therefore, the expected number of applications is 42. Dosing compliance will be calculated as [reported number of applications] divided by [expected number of applications] multiplied by 100. Compliant subjects are defined as those who apply at least [redacted] and no more than [redacted] of the expected test article applications (Right and Left face), and did not miss scheduled applications for more than three consecutive days. The percentage of compliant subjects will also be presented.

8.8 Efficacy Evaluation

As appropriate, outcomes relative to Test Article A versus Test Article B will be tabulated for all visits. The efficacy analyses will be conducted on the mITT and PP populations and will be compiled using descriptive statistics only for all efficacy variables.

8.8.1 Analysis of Efficacy

8.8.1.1 Investigator's Global Assessment

IGA scores will be recorded for each side of the face at every visit with Visit 5 / Week 6 being the primary time point of interest. IGA scores will be dichotomized to "success" or "failure" where "success" is defined as at least a two-point improvement in IGA score relative to Baseline.

The following tabulations of IGA scores will be provided at each post-Baseline visit:

- Frequency distribution of IGA scores for Test Article A versus Test Article B.
- Proportions of subjects where Test Article A score > Test Article B score, Test Article A score = Test Article B score, and Test Article A score < Test Article B score.
- Proportions of subjects with IGA "success" for Test Article A versus Test Article B.

8.8.1.2 Acne Lesion Counts

Inflammatory and non-inflammatory lesion counts will be assessed at each visit with Visit 5 / Week 6 being the primary time point of interest. Descriptive statistics will be provided for the observed and absolute and percent change from Baseline for each post-Baseline visit for each test article. In addition, descriptive statistics for the within subject differences (Test Article A – Test Article B) of the absolute and percent change values will be presented.

8.8.1.3 TEWL and Sebum Assessments

Descriptive statistics will be provided for the observed and absolute and percent change from Baseline at Weeks 2, 4, 6 and 7 for the sebum (sebumetric value) and TEWL values.

8.8.2 Statistical / Analytical Issues

8.8.2.1 Handling of Dropouts or Missing Data

There will be no imputation of missing data.

8.8.2.2 Interim Analyses

There are no interim analyses planned for this study.

8.8.2.3 Multicenter Studies

Not applicable to this study.

8.8.2.4 Multiple Comparisons / Multiplicity

Not applicable to this study.

8.8.2.5 Examination of Subgroups

There are no subgroup analyses planned for this study.

8.9 Safety Evaluation

As appropriate, outcomes relative to Test Article A vs Test Article B will be tabulated. All safety analyses will be performed in the Safety population unless otherwise stated.

8.9.1 Extent of Exposure

The total amount of test article used (grams of test article applied) will be determined from the weights of the returned test articles. The average daily amount of test article used will be determined as [total amount used (grams)] divided by [dosing duration (days)]. Descriptive statistics will be provided by test article for the total amount of test article used by each subject and the average daily amount of test article used.

8.9.2 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The number and percent of unique subjects reporting each TEAE will be summarized by MedDRA system organ class (SOC), MedDRA preferred term (PT). AEs will also be similarly summarized by SOC, PT, maximum severity, as well as, by SOC, PT, and closest relationship to test article. Application site AEs will be summarized separately by test article. All AEs reported during the study will be listed.

8.9.3 Local Skin Reactions

The frequency distributions of the severity scores of the LSRs (erythema, edema, scaling/dryness, burning/stinging, pruritus, erosion, and pain) will be tabulated as Test Article A versus Test Article B at each visit. The frequency distribution of change from Baseline, categorized as improved/same versus worsened will also be presented.

8.9.4 Urine Pregnancy Tests

Results from the UPT at Baseline and EOT will be presented in a listing.

8.9.5 Concomitant Medications and Concurrent Therapies/Procedures

Concomitant medications and concurrent therapies/procedures will be provided in a subject listing.

9. CHANGES TO PROTOCOL

The statistical analyses presented here are consistent with the protocol with more details provided.