TOPICAL DERMATOLOGIC CORTICOSTEROIDS IN VIVO BIOEQUIVALENCE STUDY SUMMARY TABLES AND SAS TRANSPORT FORMATTED TABLES FOR DATASET SUBMISSION

I. Pre-Study Method Validation

Table 1. Chromameter Validation

Operator ID/Subject ID/Site #				
Reading	**Chromameter 1**	**Chromameter 2**	**Chromameter 3**	**Chromameter n**
Date of Testing				
Replicate 1				
Replicate 2				
Replicate 3				
Replicate 4				
Intra-chromameter, mean				
Intra-chromameter, %CV (<15%)				
Inter-chromameter, %CV (<15%)				

(The chromameter qualification should be repeated with at least four study subjects, using at least four skin sites in each study subject)

Table 2. Operator Validation

Chromameter ID/Subject ID/Site #				
Reading	**Operator 1**	**Operator 2**	**Operator 3**	**Operator n**
Date of Testing				
Replicate 1				
Replicate 2				
Replicate 3				
Replicate 4				
Intra-operator, mean				
Intra-operator, % CV (<15%)				
Inter-operator, CV%				

(<15%)	

(The operator qualification should be repeated with at least four study subjects, using at least four skin sites in each study subject)

II. Summary of Studies

Table 3. Summary of the Pilot Dose Duration-Response Study

Study Ref. No.	Study Objective	Study Design	Treatment(s) (Dose, Dosage Form, Route) [Product ID]	Subject No. (M/F) Type Age: Mean (Range)	Mean Parameters		Study Report Location
					Emax	ED_{50} (minutes)	

Table 4. Summary of the Pivotal Bioequivalence Study

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: Mean (Range)	Mean Parameter	Study Report Location
					Negative AUEC (no. of subjects[1])	
					Test:	
					Reference:	

Table 5. Summary of the Pivotal Bioequivalence Study

Treatment Dose: XX per site: Occlusion/Non-Occlusion Pharmacodynamic Parameters, Area Under the Effect Curve, Point Estimates and 90% Confidence Intervals					
Pivotal (Vasoconstrictor Study), Study No.					
Locke's Method	Number of Subjects[2]	$AUEC_{(0\text{-}24hr)}$		Point Estimate	90% C.I.
		Test	Reference		
Calculated by Applicant					

Table 6. Listing of Relevant Standard Operating Procedures for Pre-Study Method Validation and Pilot Dose Duration-Response and Pivotal BE Studies

SOP No.	Effective Date of SOP	SOP Title

[1] Number of subjects who meet the criterion of (AUEC at D2)/(AUEC at D1) ≥ 1.25
[2] Number of subjects who meet the criterion of (AUEC at D2)/(AUEC at D1) ≥ 1.25

III. Pilot Dose Duration-Response Study

Table 7. Study Information

Study Number	
Study Title	
Clinical Site (Name & Address)	
Principal Investigator	
Dosing Dates	
Were the subjects dosed in more than group?	Yes/No
If yes, specify the screening dates for each group	
If yes, specify the dosing dates for each group	
If yes, specify whether the same clinical sites were used for each group	

Table 8. Product Information

Product	**Reference**
Treatment ID	
Product Name	
Manufacturer	
Batch/Lot No.	
Expiration Date	
Strength	
Dosage Form	
Potency	
Homogeneity	If applicable
Dose Administered	(e.g. 5.0 μL/cm^2 (20μL total/4-cm^2 site))(e.g.)
Route of Administration	

Table 9. Demographic Profile of Subjects Completing the Pilot Dose Duration-Response Study

Study No.		
		Treatment Group
		Reference Product N =
Age (years)	**Mean ± SD** **Range**	
Age Groups	**< 18** **18 – 40** **41 – 64** **65 – 75** **> 75**	
Sex	**Male** **Female**	
Race	**American Indian or Alaska Native** **Asian** **Black or African American** **Native Hawaiian or Other Pacific Islander** **White**	
Ethnicity	**Hispanic or Latino** **Not Hispanic or Latino**	
BMI	**Mean ± SD Range**	
Other Factors		

Table 10. Dropout Information, Pilot Dose Duration-Response Study

Study No.				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**

Table 11. Study Adverse Events, Pilot Dose Duration-Response Study

Body System/Adverse Event	**Study No.** **Reference Product** **N=**
Total	N (%)

Table 12. Protocol Deviations, Pilot Dose Duration-Response Study

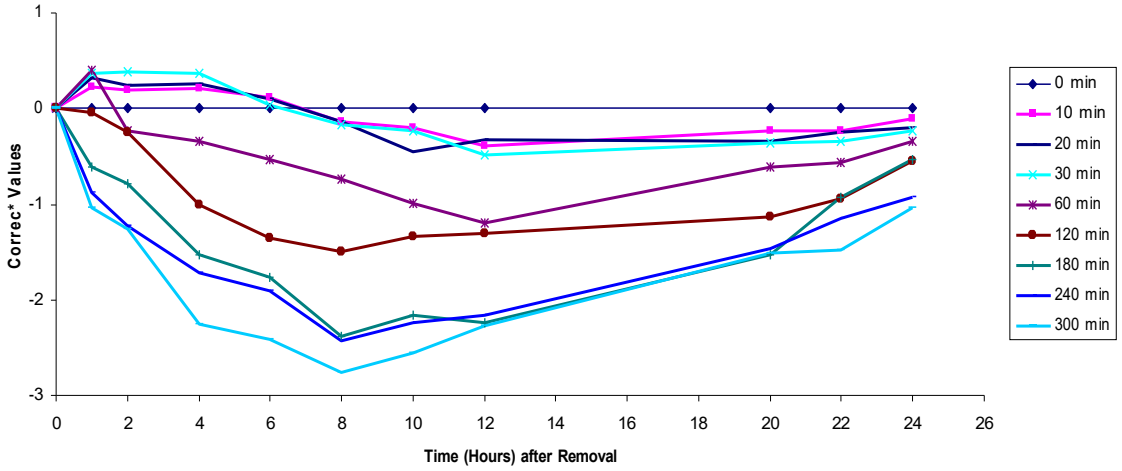
Study No.	
Type	**Subject #s**

Table 13. ED_{50} and Emax Values Calculated

Model	Software Used	Assumption of Distribution (ED_{50}) (Normal/Log Normal)			
Initial Population Parameter Estimates		**Final Population Parameter (Model Derived) Estimates**			
ED_{50}	**Emax**	**ED_{50}**	**Emax**	**Maximum Likelihood**	**Akaike Criteria Value**

Figure 1. Graphical Representation of Time After Drug Removal versus Mean Corrected Values

Example:



IV. Pivotal Bioequivalence Study

Table 14. Study Information

Study Number	
Study Title	
Clinical Site (Name & Address)	
Principal Investigator	
Dosing Dates	
Were the subjects dosed in more than group?	Yes/No
If yes, specify the screening dates for each group	
If yes, specify the dosing dates for each group	
If yes, specify whether the same clinical site was used for each group	

Table 15. Product Information

Product	**Test**	**Reference**
Treatment ID		
Product Name		
Manufacturer		
Batch/Lot No.		
Manufacture Date		N/A
Expiration Date	N/A	
Strength		
Dosage Form		
Bio-batch Size		N/A
Production Batch Size		N/A
Potency		
Homogeneity	If applicable	If applicable
Dose Administered	(e.g. 5.0 µL/cm^2 (20µL total/4-cm^2 site))(e.g.)	(e.g. 5.0 µL/cm^2 (20µL total/4-cm^2 site))(e.g.)
Route of Administration		

Table 16. Demographic Profile of Subjects Completing the Pivotal Bioequivalence Study

Study No.			
		Treatment Groups	
		Test Product N =	Reference Product N =
Age (years)	Mean ± SD Range		
Age Groups	< 18 18 – 40 41 – 64 65 – 75 > 75		
Sex	Male Female		
Race	American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander White		
Ethnicity	Hispanic or Latino Not Hispanic or Latino		
BMI	Mean ± SD Range		
Other Factors			

Table 17. Dropout Information, Pivotal Bioequivalence Study

Study No.				
Subject No.	Reason for dropout/replacement	Period	Replaced?	Replaced with

Table 18. Study Adverse Events, Pivotal Bioequivalence Study

Body System/Adverse Event	Reported Incidence by Treatment Groups		
	Study No.		
	Test Product A: N=	Reference Product B: N=	Not Assignable N=
Total	N (%)	N (%)	N (%)

Table 19. Protocol Deviations, Pivotal Bioequivalence Study

Study No.		
Type	Subject #s (Test)	Subject #s (Ref.)

Table 20. Area Under the Effect Curve and 90% Confidence Intervals

Name of Drug Product Dose: [XXX µL per site – Non Occluded/Occluded, X minutes] Pharmacodynamic Parameters, Area Under the Effective-Dose Curve, Point Estimates and 90% Confidence Intervals (Locke's Method)				
Pivotal (Vasoconstrictor Assay) Study (Study No.)				
Number of Subjects[3]	AUEC(0-24h)		Point Estimate	90% CI
	Test	Reference		

Table 21. Test Product Formulation

Ingredient	Function	% w/w

[3] Number of subjects who meet the criterion of (AUEC at D2)/(AUEC at D1)≥ 1.25

V. SAS Transport Formatted Tables for Data Submission for Pilot Dose Duration-Response Study and Pivotal Bioequivalence Study

Definitions:

Variable Name	Variable Label	Variable Type	Notes
DD	Dose Duration	Numeric (minutes)	A dose measured as the duration of exposure of the drug to the skin over a specified time period
ED50	Half-Maximal Effect Dose	Numeric (minutes)	The dose duration at which half-maximal skin blanching effect occurs
D1	Shorter Dose Duration Calibrator	Numeric (minutes)	The dose duration equal to one-half of the ED50
D2	Longer Dose Duration Calibrator	Numeric (minutes)	The dose duration equal to two times the ED50

V.1 Pilot Dose Duration-Response Study Data Submission Format

Table 22. Chromameter Raw Data

Subject	Time after drug removal (hours)	DD0 (Untreated sites)	DD1	DD2	DD3	DDn
1	Baseline (pre-dose)*					
1	0					
1	0.5					
1	1					
1	n					
2	Baseline (pre-dose)					
2	0					
2	0.5					
2	1					
2	n					
n	Baseline (pre-dose)					
n	0					
n	0.5					

n	1					
n	n					

*Baseline reading is within one hour prior to drug application

Example:

Subject	Time after drug removal (hours)	DD0 (Untreated sites)	DD1	DD2	DD3	DDn
1	Baseline (pre-dose)	9.86	10.36	9.59	9.34	9.43
1	0	9.99	9.89	8.77	8.66	9.6
1	0.5	10.10	10.38	9.35	8.53	9.99
1	1	9.52	10.32	9.27	8.04	9.93
1	n	9.65	10.04	9.82	9.82	10.23
2	Baseline (pre-dose)	10.12	8.89	9.18	9.24	9.15
2	0	10.28	8.28	9.61	9.54	9.24
2	0.5	10.25	8.36	9.30	10.24	10.52
2	1	10.68	7.89	8.92	10.34	10.78
2	n	11.21	8.03	10.61	11.40	10.89

Table 23. Baseline-Adjusted Data

Subject	Time after drug removal (hours)	DD0 (Untreated sites)	DD1	DD2	DD3	DDn
1	0					
1	0.5					
1	1					
1	n					
2	0					
2	0.5					
2	1					
2	n					
n	0					
n	0.5					
n	1					
n	n					

Table 24. Baseline-Adjusted, Untreated Control Site-Corrected Data

Subject	Time after drug removal (hours)	DD1	DD2	DD3	DDn
1	0				
1	0.5				
1	1				
1	n				
2	0				
2	0.5				
2	1				
2	n				
n	0				
n	0.5				
n	1				
n	n				

Table 25. Area Under Effect Curve Data, All Subjects at Each Dose Duration

Subject	DD1	DD2	DD3	DDn
1				
2				
n				

V.2 Pivotal Bioequivalence Study Data Submission Format

Table 26. Chroma Meter Raw Data

Subject	Time after drug removal (hours)	DD0 (Untreated sites)	D1	D2	ED50 (T)	ED50 (R)
1	Baseline (pre-dose)					
1	0					
1	0.5					
1	1					
1	n					
2	Baseline (pre-dose)					
2	0					
2	0.5					
2	1					
2	n					

n	Baseline(pre-dose)					
n	0					
n	0.5					
n	1					
n	n					

Table 27. Baseline-Adjusted Data

Subject	Time after drug removal (hours)	DD0 (Untreated sites)	D1	D2	ED50 (T)	ED50 (R)
1	0					
1	0.5					
1	1					
1	n					
2	0					
2	0.5					
2	1					
2	n					
n	0					
n	0.5					
n	1					
n	n					

Table 28. Baseline-Adjusted, Untreated Control Site-Corrected Data

Subject	Time after drug removal (hours)	D1	D2	ED50 (T)	ED50 (R)
1	0				
1	0.5				
1	1				
1	n				
2	0				
2	0.5				
2	1				
2	n				
n	0				
n	0.5				
n	1				
n	n				

Table 29. Area Under Effect Curve Data, All Subjects at Each Dose Duration

Subject	D1	D2	ED50 (T)	ED50 (R)
1				
2				
n				