THERAPEUTICS INC.
The Dermatology CRO

STATISTICAL ANALYSIS PLAN

VERSION: 1.0

DATE: 13-AUG-2023

SPONSOR:	Technoderma Medicines Inc.
PROTOCOL NUMBER:	239-11651-203
TI PROJECT NUMBER:	239-11651-203
PROTOCOL TITLE:	A Randomized, Double-Blind, Vehicle-Controlled, Parallel Group, Multi-Dose Study to Evaluate the Efficacy and Safety of TDM-105795 in Male Subjects with Androgenetic Alopecia
PROTOCOL DATE:	November 30, 2022

SAP APPROVAL

The following individuals approve version 1.0 of the SAP dated 13-Aug-2023. All changes to this version of the SAP must have written approval and require an amendment.

The **Project Statistician** is signing below to confirm he/she has developed the SAP to provide a comprehensive description of the methods of data analyses for the clinical study.

Name: [redacted]
Title:

Date: See eSignature Date **Signature:** [redacted]

The **Statistical Reviewer** is signing below to confirm he/she has reviewed and verified the SAP has been written with proper statistical methods to be used to analyze the results from the clinical study.

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Date: See eSignature Date **Signature:** [redacted]

The **Clinical Project Manager** is signing below to confirm he/she has reviewed and verified the SAP addresses the efficacy and safety endpoints identified in the clinical study protocol.

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The **Clinical Development Management Reviewer** is signing below to confirm he/she has reviewed and verified the SAP addresses the efficacy and safety endpoints identified in the clinical study protocol.

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Date: See eSignature Date **Signature:** [redacted]

The **Sponsor Representative** (if applicable) is signing below to confirm he/she has reviewed and verified the SAP.

Name: [redacted]
Title:

Date: See eSigature Date **Signature:** [redacted]

ABBREVIATIONS

AE	Adverse Event
AGA	Androgenetic Alopecia
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CK-MB	Creatine Kinase-MB
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
GGT	Gamma-Glutamyltransferase
HGA	Hair Growth Assessment
HGI	Hair Growth Index
ICE	Intercurrent Event
I/E	Inclusion/Exclusion
IGA	Investigator's Global Assessment
IND	Investigational New Drug
IP	Investigational Product
ITT	Intent-to-Treat
LDH	Lactate Dehydrogenase
LSM	Least Squares Means
LSR	Local Skin Reaction
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per-Protocol
PT	Preferred Term
RBC	Red Blood Cells
RDW	Red Blood Cell Distribution Width
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	System Organ Class
SOE	Schedule of Events
SSA	Subject Self-Assessment

T3	Triiodothyronine
T4	Thyroxine
TAHC	Target Area Hair Count
TAHD	Target Area Hair Darkness
TAHW	Target Area Hair Width
TI	Therapeutics, Inc.
TR	Thyroid Hormone Receptors
TSH	Thyroid Stimulating Hormone
WBC	White Blood Cells
WHO	World Health Organization

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1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analyses to be performed for data from Protocol 239-11653-203, A Randomized, Double-Blind, Vehicle-Controlled, Parallel Group, Multi-Dose Study to Evaluate the Efficacy and Safety of TDM-105795 in Male Subjects with Androgenetic Alopecia.

This SAP was created using Clinical Protocol 239-11651-203 Version 1.0 dated November 30, 2022, and the Electronic Case Report Forms (eCRF) Version 1.0 dated March 08, 2023.

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 239-11651-203. 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

1. To evaluate efficacy of TDM-105795 administered topically in male subjects with androgenetic alopecia (AGA).
2. To evaluate the safety and tolerability of TDM-105795 administered topically in male subjects with AGA.
3. To evaluate the pharmacokinetics (PK)/pharmacodynamics (PD) of TDM-105795.

3.2 Efficacy Endpoints

Primary Efficacy Endpoint(s):

1. Changes from Baseline in non-vellus Target Area Hair Counts (TAHC) using digital image analysis at Week 16.
2. The subject's evaluation of treatment benefit via the Hair Growth Assessment (HGA) questionnaire at Week 16.

Secondary Efficacy Endpoints:

1. Changes from Baseline in non-vellus Target Area Hair Width (TAHW) using digital image analysis at Week 16.
2. Changes from Baseline in non-vellus Target Area Hair Darkness (TAHD) using digital image analysis at Week 16.
3. The subject's evaluation of treatment benefit via the Hair Growth Index (HGI) questionnaire at Week 16.
4. Proportion of subjects with each Investigator's Global Assessment (IGA) grade at Week 16.

3.3 Safety Endpoints

1. Incidence (severity and causality) of any local and systemic adverse events (AEs).
2. Number of subjects with presence (and severity) of the following local skin reactions (LSRs): erythema, edema, erosion, scaling, pruritus, and burning/stinging at each time point.
3. Changes from Baseline in vital signs at each time point.
4. Changes from Baseline in clinical laboratory tests (chemistry [including lipid panel and thyroid function], hematology, and urinalysis, and cardiac biomarkers) at Week 4, Week 8, Week 12, and Week 16.
5. Changes from Baseline in electrocardiogram (ECG) parameters and overall ECG interpretation at Week 4, Week 8, Week 12, and Week 16.

3.4 Pharmacokinetic Endpoints

If plasma concentrations of TDM-105795 are quantifiable, the plasma concentrations will be summarized for active treatment groups.

4. STUDY DESIGN

This is a multi-center, randomized, double-blind, vehicle-controlled, parallel group, multi-dose study of TDM-105795 in male subjects, 18 to 55 years old, with AGA. Approximately 72 subjects with a clinical diagnosis of mild to moderate AGA in temple and vertex region, IIIv to V on the Modified Norwood-Hamilton Scale (i.e., IIIv, IV, and V) who fulfill the inclusion/exclusion (I/E) criteria will be enrolled at approximately 12 study sites in the United States. Subjects will be randomized (1:1:1) to 1 of the 3 investigational products (IPs) listed below. The assigned investigational product (IP) will be applied once daily (1 mL/dose of IP) for 16 weeks, with application to the scalp focusing on the regions that are bald and thinning.

1. TDM-105795 topical solution, 0.0025%
2. TDM-105795 topical solution, 0.02%
3. TDM-105795 topical vehicle solution (Placebo)

Subjects will have 10 study visits (8 in person and 2 via phone): Screening, Baseline/Day 1, and Follow-Up visits at Days 14 (Week 2), 28 (Week 4), 42 (Week 6 via phone), 56 (Week 8), 70 (Week 10 via phone), 84 (Week 12), 112 (Week 16/End of Treatment [EOT]), and 140 (Week 20/End of Study [EOS]). Efficacy will be assessed via IGA, quantitative hair measurements that include TAHC, TAHW, and TAHD, and subject self-assessment (SSA) questionnaires which include HGA and HGI. Safety will be assessed by physical examinations, vital signs, 12-lead ECG, clinical labs (chemistry [including lipid panel and thyroid function], hematology, urinalysis, and cardiac biomarkers), LSRs, and AEs.

4.1 Schedule of Events

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9[1]	Visit 10
	Screening	Baseline	Week 2	Week 4	Week 6 Phone	Week 8	Week 10 Phone	Week 12	Week 16 / EOT	Week 20 / EOS
Day	-45 to -3	1	14 ± 3	28 ± 3	42 ± 3	56 ± 3	70 ± 3	84 ± 3	112 ± 3	140 ± 5
Informed Consent	X									
Demographics	X									
Inclusion / Exclusion Assessment	Review	X								
Medical History	X	X								
Concomitant Medications / Concurrent Procedures/Therapies	X	X	X	X		X		X	X	X
Modified Norwood-Hamilton Scale	X									
Drug Screen	X	X								
Alcohol Screen	X	X								
Physical Examination[2]	X	X		X		X		X	X	X[3]
Height, Weight, and Body Mass Index	X								X	
Vital Signs[4]	X	X	X	X		X		X	X	X[3]
12-Lead ECG[5]	X	X		X		X		X	X	X[3]
Clinical Laboratory Tests[6] (chemistry [including lipid panel and thyroid function[7]], hematology, urinalysis, and cardiac biomarkers[8])	X	X		X		X		X	X	X[3]
Serology[9]	X									
Standardized Global Photography[10]	X	X[11]		X		X		X	X	
Subject Self-Assessment[12]				X		X		X	X	
Investigator Global Assessment[13]				X		X		X	X	
Local Skin Reactions		X[14]	X	X		X		X	X	X
Scalp Micro-Dot Tattoo		X		X[15]		X[15]		X[15]	X[15]	
Standardized Macro Photography[16]		X		X		X		X	X	
PK Blood Draw		X[17]		X[18]		X[18]		X[18]	X[18]	

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9[1]	Visit 10
	Screening	Baseline	Week 2	Week 4	Week 6 Phone	Week 8	Week 10 Phone	Week 12	Week 16 / EOT	Week 20 / EOS
Day	-45 to -3	1	14 ± 3	28 ± 3	42 ± 3	56 ± 3	70 ± 3	84 ± 3	112 ± 3	140 ± 5
Randomization[19]		X								
IP Accountability: Dispense (D) / Collect (C)		D	C + D	C + D		C + D		C + D	C	
Subject Diary: Dispense (D) / Collect (C) / Review (R)		D	C+R D	C+R D		C+R D		C+R D	C+R	
Apply IP in Clinic		X								
Adverse Events	X[20]	X	X	X	X	X	X	X	X	X

[1] Or early termination visit.
[2] Assessments will include examination of head and neck, dermatologic (except scalp hair loss), cardiovascular, respiratory, gastrointestinal (abdomen), and gross motor and gait. Clinically significant abnormalities at Visit 1/Screening and Visit 2/Baseline will be recorded as medical history. Any new or worsening clinically significant abnormalities after first dose of IP will be recorded as AEs.
[3] To be performed if: 1) there are new or worsening clinically significant abnormalities at the subject's most recent prior evaluation or 2) as warranted based on subject's current medical condition, in the opinion of the investigator. In addition, at the discretion of the investigator, most recent clinical labs or ECGs that are out of the normal range may also be repeated at this visit, if viewed as clinically significant by the investigator.
[4] Assessments will be made after the subject has rested in a seated position for at least 5 minutes.
[5] 12-lead ECGs will be performed after the subject has rested for at least 10 minutes in the supine position.
[6] The subject must have at least one fasting set of labs prior to treatment being administered at Visit 2/Baseline. It is preferred that subjects be fasting (approximately 8 hours) for both Visit 1/Screening and Visit 2/Baseline and, if possible, for all clinical laboratory testing; however, if a subject arrives at the clinic without fasting for at least 8 hours, laboratory specimens may be collected as non-fasting, at the discretion of the investigator, and with the appropriate fasting status documented on the lab requisition form.
[7] Free T4, Total T3, and TSH.
[8] CK-MB, Troponin T, and NT-proBNP.
[9] HIV, Hepatitis B and C screen.
[10] Global photography (for SSA and IGA) must occur prior to macro photography. At Screening, global reshoots must occur in time to ensure the global photos are of an acceptable quality for assessment, as verified by the vendor, prior to Visit 2/Baseline. No reshoots of global photos will occur for subsequent scheduled visits.
[11] If Screening photos are not adequate and re-shoot prior to Baseline was not performed, additional global photo(s) will be taken at Baseline.
[12] The subject must refer to their baseline and current visit global photos when completing the SSA.
[13] The evaluator must refer to the subject's 'baseline' global photos (taken at Screening) and compare them to the current visit's photos of subject's scalp hair growth.

[14] LSRs will be assessed prior to dosing.
[15] Check scalp micro-dot tattoo and re-apply if it has significantly faded at any visit during the study.
[16] Macro photography (for TAHC, TAHW, and TAHD) must occur after global photography. Macro photo reshoots must occur within 7 days after the visit.
[17] Baseline PK blood sample, in the clinic, will be collected pre-application and a second PK blood sample 1-4 hours post-application.
[18] PK blood samples will be collected in the clinic 1 to 4 hours after at home IP application by the subject.
[19] Subject will be randomized using the IWRS.
[20] During any wash out and screening periods, any changes in the health of subjects should be recorded as changes in medical history unless an event occurred as a result of a study-related procedure and is unanticipated; in such cases, the event should be recorded as an AE and reported to the Institutional Review Board (IRB) as an "unanticipated problem" in accordance with local procedures.

5. DEFINITIONS

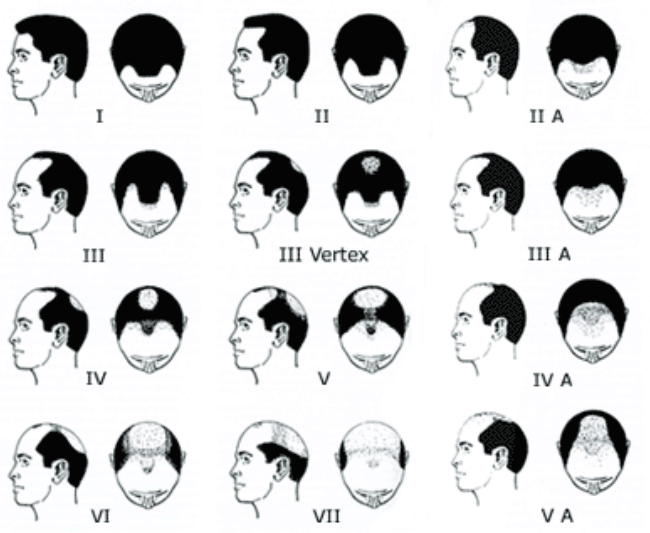
- The **Study Day** is the day of the study relative to the first dose (Baseline Visit / Treatment #1) of the IP. Study day is derived as:
  Assessment visit date – First dose date + 1.
- The **Baseline Assessment** is defined as the last non-missing measurement collected at Screening or Baseline (Day 1) visit prior to the first administration of the IP. For subjects without approved Baseline photos an appropriate imputation method may be considered for Baseline values.
- **Post-baseline** is defined as a measurement taken after the administration of the first dose of IP.
- **Change from baseline** will be calculated as:
  Post-baseline value – Baseline value
  Correspondingly, **percent change from baseline** will be calculated as:
  100 × (Post-baseline value – Baseline value) / Baseline value

6. CLINICAL EVALUATIONS

6.1 Modified Norwood-Hamilton Scale

The Modified Norwood-Hamilton Scale will be used at Visit 1/Screening to classify the pattern of hair loss and determine subject eligibility. Subjects must have mild to moderate AGA in the temple and vertex region, rating IIIv to V on the Modified Norwood-Hamilton Scale (i.e., IIIv, IV, and V), to be eligible for the study. The Modified Norwood-Hamilton Scale describes the most regular patterns for male pattern baldness.

Figure 6.1-1 Modified Norwood-Hamilton Scale Describing Male Pattern Baldness



- **Type I.** No recession or very minimal recession along the anterior border of the hairline in the frontotemporal region.
- **Type II.** The anterior border of the hair in the frontotemporal region has triangular areas of recession which tend to be symmetrical. These areas of denudation extend no further posteriorly than approximately 2 cm anterior to a line drawn in a coronal plane between the external auditory meatus. Hair also is lost, or sparse, along the midfrontal border of the scalp, but the depth of the affected area is much less than in the frontotemporal region.
- **Type III.** This represents the minimal extent of hair loss considered sufficient to represent baldness. Most type III scalps have deep frontotemporal recessions which are usually symmetrical and are either bare or very sparsely covered by hair. These recessions extend further posteriorly than a point which lies approximately 3 cm anterior to a coronal line drawn between the external auditory meatus.
- **Type IV.** The frontal and frontotemporal recession is more severe than in type III. Also, there is sparseness or absence of hair on the vertex area. These areas are extensive but separated from each other by a band of moderately dense hair that extends across the top. This band joins the fully haired fringe on each side of the head.
- **Type V.** The vertex region remains separated from the frontotemporal region. The separation is now not as distinct, because the band of hair across the crown has become narrower and sparser. Both the vertex and frontotemporal areas of hair loss have become larger.
- **Type VI.** The bridge of hair that crossed the crown in the previous type is now gone. The frontotemporal and vertex regions of hair loss have become confluent, and in addition the entire area of hair loss has increased laterally and posteriorly.
- **Type VII.** This is the most severe form of male pattern baldness. All that remains is a narrow horseshoe-shaped band of hair which begins laterally just anterior to the ear and extends posteriorly on the sides and quite low on the occiput. This hair is usually not dense and frequently is fine. The hair is also extremely sparse on the nape of the neck and in a

semicircle over both ears. It should be noted that the anterior border of this band on each side of the head has receded posteriorly to just in front of the ears.

6.2 Investigator's Global Assessment

The evaluator will use standardized global photos (i.e., a vertex view and a superior view) of the subject's scalp taken at Visit 1/Screening and will compare them to the current visit's photos of the subject's scalp hair growth using the Canfield Review application. The evaluator will assess the subject's scalp hair growth using the following 7-point scale: greatly decreased (-3), moderately decreased (-2), slightly decreased (-1), no change (0), slightly increased (1), moderately increased (2), and greatly increased (3).

6.3 Subject Self-Assessment

The subject will use the standardized global photos (i.e., a vertex view and a superior view) of the subject's scalp taken at Visit 1/Screening and will compare them to the current visit's photos of subject's scalp hair growth for HGA and HGI which comprise the SSA.

6.3.1 Hair Growth Assessment

Scalp hair growth will be compared from baseline using the following 7-point scale: greatly decreased (-3), moderately decreased (-2), slightly decreased (-1), no change (0), slightly increased (1), moderately increased (2), and greatly increased (3).

6.3.2 Hair Growth Index

Scalp hair growth will be compared from baseline using the following 7-point scale: much less (-3), moderately less (-2), slightly less (-1), the same amount (0), slightly more (1), moderately more (2), and much more (3) for the following 3 questions:

1. "Since the start of treatment, when I look at my thinning area, I can see … (scalp)";
2. "Since the start of treatment, my hair now covers … (scalp)"; and
3. "Since the start of treatment, the appearance (thickness/quality/ amount) of the thinning area on my head is …"

7. SAFETY EVALUATIONS

7.1 Physical Examination

Physical examinations will be performed per the Schedule of Events (SOE). Assessments will include examination of head and neck, dermatologic (except the indication being studied), cardiovascular, respiratory, gastrointestinal (abdomen), and gross motor and gait. Clinically significant abnormalities at Visit 1/Screening and Visit 2/Baseline will be recorded as medical history. Any new or worsening clinically significant abnormalities after first dose of IP will be recorded as AEs.

7.2 Vital Signs

Vital signs including temperature, systolic and diastolic blood pressure, heart rate, and respiration rate will be measured per the SOE. Assessments will be made after the subject has rested in a seated position for at least 5 minutes. Height, weight, and Body Mass Index (BMI) will also be measured at Visit 1/Screening and Visit 9/EOT.

7.3 Electrocardiogram

ECGs will be performed per the SOE. 12-lead ECGs will be performed after the subject has rested for at least 10 minutes in the supine position. ECG results will be recorded on the appropriate eCRF.

7.4 Local Skin Reactions

LSRs will be collected per the SOE. LSRs of erythema, edema, erosion, scaling, pruritus, and burning/stinging will be assessed using a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, and 4=severe). Only reactions that require medical intervention (e.g., prescription medication) will be documented as AEs. Any reactions to the IP that are not listed above will be recorded as AEs.

7.5 Pharmacokinetic Tests

Blood samples will be collected per the SOE. At Visit 2, subjects will be dosed in the clinic and a PK blood sample will be collected before the first dose as well as 1-4 hours post-dose. At Visits 4, 6, 8, and 9, PK blood samples will be collected. These visits should be scheduled so that PK sample collection will occur 1 to 4 hours after the subject has self-applied the IP application at home. Sampling date/times will be recorded on the appropriate eCRFs. Concentrations of TDM-105795 in plasma will be determined from these samples using validated analytical methods.

7.6 Laboratory Tests

Blood and urine specimens will be collected per the SOE for chemistry (including lipid panel and thyroid function), hematology, urinalysis, and cardiac biomarkers. It is preferred that subjects be fasting (approximately 8 hours) for all laboratory assessments; however, if a subject arrives at the clinic without fasting for at least 8 hours, laboratory specimens may be collected as non-fasting, at the discretion of the investigator, and with the appropriate fasting status documented on the lab requisition form. However, the subject must have at least one fasting set of labs prior to treatment being administered on Visit 2/Baseline. Any new or worsening abnormal test results that are identified as clinically significant after Baseline will be recorded as AEs.

The following clinical safety laboratory tests will be performed:

LABORATORY TESTS		
Chemistries	**Hematology**	**Urinalysis**
Albumin	Hemoglobin	Color
Alkaline phosphatase	Hematocrit	Appearance/Clarity
ALT (SGPT)	MCV	Bilirubin
AST (SGOT)	MCH	Blood
Bilirubin, total	MCHC	Glucose
Calcium	RBC (Erythrocytes)	Ketones
Carbon Dioxide §	WBC (Leucocytes)	Leukocyte Esterase
Chloride	RDW	Nitrite
Creatinine	Differential count	pH
GGT	Basophils	Protein
Glucose (fasting, preferred)	Eosinophils	Specific gravity
LDH	Lymphocytes	Urobilinogen
Phosphate	Monocytes	Microscopic analysis (if indicated)
Potassium	Neutrophils	
Protein, total	Platelets	
Sodium		
Urea (BUN)	**Cardiac Biomarkers**	
Uric acid	CK-MB	
Lipid Panel	Troponin T	
Cholesterol, total	NT-proBNP	
Triglycerides		
Thyroid Function		
TSH		
Total T3		
Free T4		

8. STATISTICAL METHODS

8.1 Estimands for Efficacy Endpoints

Treatment conditions of interest	Condition under study: AGA in males. Investigational Drugs: • TDM-105795 topical solution, 0.0025% • TDM-105795 topical solution, 0.02% Comparator Drug: • TDM-105795 topical vehicle solution (Placebo)
Population	Male subjects 18-55 years of age with mild to moderate AGA
Endpoints	**Primary Efficacy Endpoint(s):** 1. Changes from Baseline in non-vellus TAHC using digital image analysis at Week 16. 2. The subject's evaluation of treatment benefit via the HGA questionnaire at Week 16. **Secondary Efficacy Endpoint(s):** 1. Changes from Baseline in non-vellus TAHW using digital image analysis at Week 16. 2. Changes from Baseline in non-vellus TAHD using digital image analysis at Week 16. 3. The subject's evaluation of treatment benefit via the HGI questionnaire at Week 16. 4. Proportion of subjects with each IGA grade at Week 16.
Population level summary	**Primary endpoints**: The changes from Baseline at Week 16 in the non-vellus TAHC will be evaluated by analysis of covariance (ANCOVA) where the model includes treatment and site as factors and the baseline TAHC as the covariate. Least squares means (LSM) will be presented for pairwise comparisons of treatment groups. Descriptive statistics will be also provided by treatment group for each time point for non-vellus quantitative hair measurements. The HGA will be evaluated at Week 16 descriptively (frequencies and percentages) for each assessment category by treatment group. **Secondary endpoints:** The changes from Baseline at Week 16 with respect to non-vellus TAHW and TAHD will be evaluated by ANCOVA with treatment group and site as fixed factors, and the corresponding baseline value as the covariate. LSM will be presented for pairwise comparisons of treatment groups.

	Each of the 3 subject-rated questions that comprise the HGI will be summarized by frequency and individual response category at Week 16 by treatment group. The IGA will be summarized by frequency and individual response category at Week 16 by treatment group.
ICEs and strategies to handle ICEs	A treatment policy strategy will be employed where no ICEs will be defined. No imputation for missing data will be performed.

8.2 General Considerations

All statistical processing will be performed using SAS®. Summary tables (descriptive statistics and/or frequency tables) will be provided for screening and/or baseline variables, efficacy variables, and safety variables. Continuous variables will be summarized by descriptive statistics including the number of subjects with non-missing data (n), mean, median, standard deviation, minimum, and maximum values by treatment group. Means will be presented to one additional decimal place and the associated standard deviation will be presented to 2 additional decimal places than the presentation level of the respective subject data. Minimum and maximum values will be presented using the same number of decimal places as the subject data. Frequency counts and percentage of subjects within each category will be provided for categorical data. Summaries will be provided for each treatment group. No formal tests of hypotheses will be performed. If present, p-values, will be provided for descriptive purposes only and will be reported to 3 decimal places.

In general, all summary tables will be supported by relevant subject data listings which will be sorted by treatment, study site, subject identification, and visit, as applicable. Figures may be created to aid in the interpretation of results.

8.3 Analysis Populations

8.3.1 Safety Population

The Safety population will include all randomized subjects who received and applied the IP.

8.3.2 Intent-to-Treat Population

The intent-to-treat (ITT) population will include all randomized subjects who were dispensed the IP.

8.3.3 Per-Protocol Population

The per-protocol (PP) population will include a subset of the ITT population who completed the Visit 9 (Week 16/EOT) efficacy assessments without significant protocol deviations.

8.3.4 PK Population

The PK population will include those subjects in the ITT population with at least 1 measurable concentration value.

8.4 Final Analyses and Reporting

Final database lock will occur after all subjects have completed the study assessment period (or withdrew from the study prematurely) and all subject data have been monitored and all queries resolved.

Further exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses performed and not described in this SAP will be clearly identified as such in the CSR.

8.5 Sample Size

The sample size for this study is based on clinical considerations only. No formal sample size calculation was performed.

8.6 Subject Disposition

The number and percent of subjects who were enrolled in the study, in each analysis population, who completed the study, who withdrew from the study, and their reasons for withdrawal will be summarized by treatment groups.

The number of subjects enrolled by site and by visit will be summarized for all analysis populations (safety, ITT, PP and PK).

Informed consent information and subject eligibility status will be provided in a subject listing.

Subjects who were screen failures, along with their reason for screen failure will be listed.

8.7 Screening and Baseline Assessments

8.7.1 Demographics

Demographic characteristics including sex, age, race, and ethnicity will be summarized descriptively by treatment group for the safety, ITT. PP, PK populations. Demographic data for screen failures will be summarized separately.

8.7.2 Physical Examination

Physical examination abnormalities will not be provided separately, but will be included with medical history listing.

8.7.3 Baseline Modified Norwood-Hamilton Scale

Modified Norwood-Hamilton Scale grade recorded at screening will be tabulated by treatment group for the safety, ITT, and PP populations.

8.7.4 Baseline Standardized Macro Photography Measurements

Baseline quantitative hair measurements will include TAHC, TAHW, and TAHD, which will be calculated using digital image analysis from standardized macro photos. TAHC, TAHW, and TAHD for non-vellus and vellus/vellus-like (miniaturized) hair will be descriptively summarized by treatment group for the safety, ITT, and PP populations.

8.8 Efficacy Evaluation

The efficacy analyses will be conducted on the ITT and PP populations.

8.8.1 Analysis of Efficacy

8.8.1.1 Primary Efficacy Analysis

The changes from Baseline at Week 16 in the non-vellus TAHC will be evaluated by ANCOVA where the model includes treatment and site as factors and the baseline TAHC as the covariate. LSM and the associated 95% CI will be presented for pairwise comparisons of treatment groups.

The HGA will be evaluated at Week 4, 8, 12, and 16 descriptively (frequencies and percentages) for each assessment category by treatment group.

Descriptive statistics will be provided by treatment group for each time point for non-vellus TAHC.

8.8.1.2 Secondary Efficacy Analysis

The changes from Baseline at Week 16 with respect to non-vellus TAHW and TAHD will be evaluated by ANCOVA with treatment group and site as fixed factors, and the corresponding baseline value as the covariate. LSM and the associated 95% CI will be presented for pairwise comparisons of treatment groups.

Each of the 3 subject-rated questions that comprise the HGI will be summarized by frequency and individual response category at Week 16 by treatment group.

The IGA will be summarized by frequency and individual response category at Week 4, 8, 12, and 16 by treatment group.

Descriptive statistics by treatment group will be provided for each time point for non-vellus TAHW and TAHD quantitative hair measurements.

8.8.1.3 Dosing Compliance

Descriptive statistics will be used to summarize the total number of applications for the ITT, PP and PK populations. Subjects who apply at least 80% of the expected total number of applications and have no other evidence of material dosing non-compliance will be considered to be compliant with IP dosing.

8.8.2 Statistical / Analytical Issues

8.8.2.1 Analysis Visit Windows for Assigning Observed Data

Efficacy data will be assigned to analysis visits based on its nominal scheduled visit.

An early termination visit will be assigned to analysis visits as defined in the visit window tables below. If 2 or more visits occur within the same analysis window, the value under nominal scheduled visit will be used; otherwise, the value closest to the target day will be used. If the assessments are the same distance from the target day, the latest one will be used. After applying visit window, each analysis visit should contain no more than one record and is considered observed data.

Efficacy assessments include TAHC, TAHW, TAHD, HGA, HGI and IGA.

Table 8.8.2.1.1 Analysis Visit Windows for Efficacy Assessments

Visit	*Target Day*	*Study Days*
Visit 4	Day 28	Days [2, 42]
Visit 6	Day 56	Days [43, 70]
Visit 8	Day 84	Days [71, 98]
Visit 9	Day 112	Days ≥ 99

Study Days are relative to the day of first study treatment.

8.8.2.2 Handling of Dropouts or Missing Data

No imputation for missing values of any efficacy endpoints will be performed.

Missing Dates for Medical History, Concomitant Medications, and Concurrent Therapies/ Procedures

For the purpose of calculating the Study Day, the following algorithms will be applied to missing and incomplete start and stop dates:

Missing Date	Imputation for Start Date
Day missing	If the day portion of the start date is missing, then the start date will be estimated to be the first of the month in which the event occurred, "01."
Month Missing	If the month portion of the start date is missing, then the start date will be estimated to be the first of the month of the year, (e.g., "JAN").
Completely Missing	If the start date is completely missing the study day will be estimated to be "UNKNOWN".
Missing Date	**Imputation for Stop Date**
Day missing	If the day portion of the stop date is missing, the day will be estimated to be the last day of the month (e.g., UN-JAN-2013 will be treated as 31-JAN-2013).
Day and Month Missing	If the Month portion of the stop date is missing, the month will be assumed to be the last month of the year (e.g., "DEC")
Completely Missing	If the stop date is completely missing the study day will be estimated to be "UNKNOWN".

8.8.2.3 Interim Analyses

No interim analyses are planned.

8.8.2.4 Multicenter Studies

Approximately 12 sites will participate in the study.

8.8.2.5 Multiple Comparisons / Multiplicity

No adjustments for multiplicity are planned in this study.

8.8.2.6 Examination of Subgroups

No subgroups analyses are planned.

8.9 Safety Evaluation

Summaries of the safety parameters will be provided as described below for the Safety population. No inferential analyses are planned.

8.9.1 Extent of Exposure

Descriptive statistics will be used to summarize the extent of exposure in the Safety population.

The duration of treatment for a subject will be calculated as the date of final application minus date of first application plus 1.

The total amount of IP used for a subject will be calculated as the difference between the weight of the IP dispensed and weight of IP returned. For the calculation of total amount of IP used, if test article is not returned at a given collection period, the amount of IP used for that period will be unknown and treated as missing.

The mean daily amount of IP applied for a subject will be calculated as the total amount of IP applied divided by the duration of treatment will be calculated.

8.9.2 Vital Signs

Descriptive statistics will be provided for the observed and change from Baseline values for temperature, systolic and diastolic blood pressure, heart rate, respiration rate, height, weight, and BMI for each treatment group.

8.9.3 Local Skin Reactions

LSRs (erythema, edema, erosion, scaling, pruritus, and burning/stinging) will be summarized by frequency and severity of each individual LSR for each treatment group.

8.9.4 Electrocardiograms

Descriptive statistics will be provided for the observed and change from Baseline values for ECG parameters by treatment group. Changes in overall interpretation of the ECG from Baseline to Weeks 4, 8, 12, and 16 will be examined by shift table.

8.9.5 Clinical Laboratory Tests

Clinical laboratory tests will be evaluated for any material changes during the study period. All laboratory data (chemistry [including lipid panel and thyroid function], hematology, urinalysis, and cardiac biomarkers [CK-MB, Troponin T, and NT-proBNP]) will be listed and reported in the units received from the laboratory. Shift tables by analyte and by out of range flag will be presented to facilitate the evaluation of change from Baseline to Weeks 4, 8, 12, and 16.

8.9.6 Adverse Events

All AEs reported during the study will be listed, documenting course, severity, investigator assessment of the relationship to the IP, and outcome. Verbatim terms will be coded to preferred terms (PTs) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) mapping system (version 26.0). The PTs and SOC will then be tabulated.

All reported AEs will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to IP by treatment group. For all AE summaries, if a subject has more than one

AE within a PT, the subject is counted once in that PT. If a subject has more than one AE within a SOC, the subject is similarly counted once in that SOC.

The number and percentage of unique subjects reporting each treatment emergent AE (TEAE, events with an onset on or after the first treatment) will be summarized by SOC and PT. The number and percent of unique subjects reporting each TEAE will also be summarized by SOC, PT, and maximum severity (mild, moderate, severe) and closest relationship to IP (not related, unlikely, possibly, probably, definitely).

Serious AEs, if any, will be summarized by SOC, PT, and treatment group.

8.9.7 Concomitant Medications and Concurrent Therapies/Procedures

A subject listing of the concomitant medications will be provided. Concomitant medications will be coded using the current version of World Health Organization (WHO) Drug Global Dictionary (version 01March2023). A separate listing of concurrent procedures and therapies will also be provided as applicable.

8.10 Pharmacokinetic Analyses

A PK analysis will be conducted on the PK population. If plasma concentrations of TDM-105795 are quantifiable, the plasma concentrations will be summarized for active treatment groups.

8.11 Methods for Handling Missing Data

This section is not applicable.

8.12 Subgroup Analyses

No subgroup analyses are planned.

8.13 Interim Analysis

No interim analyses are planned.

9. CHANGES TO PLANNED PROTOCOL ANALYSIS

None.