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

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PROTOCOL APPROVAL

The following individuals approve version 1.0 of the 239-11651-203 protocol dated November 30, 2022. All changes to this version of the protocol must have prior written approval and require an amendment or administrative letter.

Therapeutics, Inc. Representative(s):

[redacted]
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STUDY ACKNOWLEDGEMENT

I understand this protocol contains information that is confidential and proprietary to Technoderma, the Sponsor.

I have read this protocol, agree that it contains all the details necessary to conduct the study as described, and will conduct this study following this protocol.

I will provide the contents of this protocol to study staff under my direct supervision that need to know the contents to conduct the study. I will discuss this information with the study staff to ensure they are fully informed about the study and the investigational products. I will provide the contents of the protocol to the responsible Institutional Review Board(s). These disclosures may be made; provided the contents are not used in any other clinical study and they are not disclosed to any other person or entity without prior written consent from Technoderma. This condition does not apply to disclosure required by government regulations or laws; however, I agree to give prompt notice to Technoderma of any such disclosure.

I understand the study may be terminated or enrollment suspended at any time by Technoderma, with or without cause, or by me if it becomes necessary to protect the interests of the study subjects.

Any additional information added to this protocol is also confidential and proprietary to Technoderma and must be treated in the same manner as the contents of this protocol.

_____
Printed Name of Principal Investigator

_____ _____
Signature of Principal Investigator Date

Protocol: 239-11651-203 Site number: _____

PROTOCOL SYNOPSIS

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
Study Type	Phase 2
Investigational Product	The study includes the following investigational product (IP) or treatment groups: 1. TDM-105795 topical solution, 0.0025% 2. TDM-105795 topical solution, 0.02% 3. TDM-105795 topical vehicle solution (Placebo)
Study Objective	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.
Study Design	Multi-center, randomized, double-blinded, vehicle-controlled, parallel group, multi-dose comparison of two active formulation strengths against placebo.
Treatment Groups	After enrollment in the study, each subject will be randomized (1:1:1) to 1 of the 3 IPs listed above. The assigned 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.
Duration of Treatment	16 weeks
Duration of Study	Approximately 26 weeks for an individual subject (6 weeks [45days] for screening, 16 weeks for treatment, and 4 weeks for follow-up).
Study Population	Male subjects 18-55 years of age with mild to moderate AGA
Total Number of Subjects	Approximately 72 subjects will be enrolled (24 per treatment group)
Number of Sites	Approximately 12 sites will participate in the study
Inclusion Criteria	To enter the study, a subject must meet the following criteria: 1. Subject is male, 18-55 years old. 2. Subject has provided written informed consent. 3. Subject has a clinical diagnosis of mild to moderate AGA in temple and vertex region with a score of IIIv, IV, or V on the Modified Norwood-Hamilton Scale. 4. Subject, in the investigator's opinion, is in good general health and free of any disease state or physical condition that might impair evaluation of AGA or exposes the subject to an unacceptable risk by study participation.

	5. Subject has normal renal, thyroid, and hepatic function as determined by the Visit 1/Screening laboratory results in the opinion of the investigator. 6. Subject is a non-smoker, defined as not having smoked or used any form of tobacco or non-tobacco products containing nicotine in more than 4 months before Visit 2/Baseline. 7. Subject is willing to maintain the same hairstyle, hair length, and hair color throughout the study. 8. Subject agrees to continue his other general hair care products and regimen for at least 2 weeks prior to Visit 2/Baseline, and through the entire study. 9. Subject is willing and able to apply the IP as directed, comply with study instructions, and commit to all follow-up visits for the duration of the study. 10. Subjects who are sexually active with a female partner and are not surgically sterile (vasectomy performed at least 6 months prior to treatment) must agree to refrain from sperm donation for at least 90 days after administration of their last dose of IP and inform their non-pregnant female sexual partner to use a highly effective form of birth control[1] as described in the informed consent form. Note: Female partner must be confirmed according to subject to be non-pregnant at Visit 1/Screening and Visit 2/Baseline or at the visit when a subject identifies a new sexual partner.
Exclusion Criteria	A subject is ineligible to enter the study if he meets 1 or more of the following criteria: 1. Subject has any dermatological disorders of the scalp on the regions that are bald and thinning with the possibility of interfering with the application of the IP or examination method, such as fungal or bacterial infections, seborrheic dermatitis, psoriasis, eczema, folliculitis, scars, or scalp atrophy. 2. Subject has history or active hair loss due to diffuse telogen effluvium, alopecia areata, scarring alopecia, trichotillomania, or conditions/diseases other than AGA. 3. Subject has any skin pathology or condition (e.g., uncontrolled thyroid disease, certain genetic disorders that involve hair growth or patterns) that, in the investigator's opinion, could interfere with the evaluation of the IP or requires use of interfering topical, systemic, or surgical therapy.

[1] For females, highly effective forms of birth control include 1) intrauterine device (IUD; copper or hormonal); 2) implantable hormonal contraception; 3) surgical sterilization (i.e., hysterectomy, tubal ligation, or bilateral oophorectomy) performed at least 6 months prior to the subject's study entry; 4) total abstinence; or 5) using one of each of the following a) hormonal contraceptives [other than IUD or implantable, e.g., oral, transdermal, injectable, or vaginal ring] and b) double barrier methods [i.e., male or female condom, diaphragm with spermicidal foam/gel/film/cream/vaginal suppository, cervical cap with spermicides, or contraceptive sponge]. Male subjects who become sexually active or begin to have relations with a female partner who is not sterile during the trial must have a female partner who is not pregnant and agrees to use a highly effective form of birth control for 90 days after administration of their last dose of IP. Female partner taking hormonal therapy must be on treatment prior to the subject's entry into the study, continued per label, and must not change their dosing regimen during the trial; highly effective birth control forms must be for (1) oral: at least 1 complete cycle (e.g., 4 to 8 weeks); (2) transdermal, injectable (e.g., Depo-Provera), implantable, vaginal ring (e.g., NuvaRing), IUD: at least 1 week; or (3) total abstinence: at least 1 complete cycle (e.g., 4 to 8 weeks) prior to initiation of IP. For males, adequate forms of contraception include condom and spermicide in combination with other forms of female contraception.

	4. Subject has any visible inflammatory skin disease, injury, or condition of their scalp that could compromise subject safety and/or interfere with the evaluation of local or systemic assessments performed during the study. 5. Subject has history (within 6 months of Visit 1/Screening) of severe dietary or weight changes or history of eating disorder(s), which has resulted in hair loss, in the opinion of the investigator. 6. Subject has a history of scalp reduction or notable trauma with related scarring, hair transplants, and/or hair weaves. 7. Subject has a known or suspected malignancy excluding cutaneous basal cell carcinoma or cutaneous squamous cell carcinoma not located within the treatment area. 8. Subject has a positive blood screen for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C antibody. 9. Subject has any condition, which, in the investigator's opinion, would make it unsafe for the subject to participate in this study, including clinically significant abnormal laboratory, or 12-lead electrocardiogram (ECG) findings during the screening period or Visit 2/Baseline prior to dosing of the IP. 10. Subject has used any topical scalp treatments for hair growth including minoxidil, hormone therapy, anti-androgen, or other agents known to affect hair growth within 12 weeks of Visit 2/Baseline. 11. Subject has used any topical scalp over-the-counter (OTC) or cosmetic treatments known or reasonably believed to affect hair growth (e.g., brands such as Aminexil, Maxilene, Nioxin, Foltene) or hair growth products with saw palmetto, copper, etc. within 4 weeks of Visit 2/Baseline. 12. Subject has used any topical scalp treatments that may have ancillary effects on hair growth including, but not limited to, corticosteroids, pimecrolimus, tacrolimus, and retinoids within 4 weeks of Visit 2/Baseline. 13. Subject has had any scalp procedures, including surgical, laser, light or energy treatments, micro-needling, etc. within 6 months of Visit 2/Baseline. 14. Subject has had platelet rich plasma (PRP) procedures on the scalp at any time. 15. Subject has used systemic beta blockers, cimetidine, ketoconazole, diazoxide, or corticosteroids (including intramuscular and intralesional injections) within 12 weeks of Visit 2/Baseline. Inhaled, intranasal, or ocular corticosteroids are allowed if use is stable. Stable is defined as doses and frequency unchanged for at least 4 weeks prior to Visit 2/Baseline. 16. Subject has used systemic retinoids, isotretinoin, vitamin A intake above 10,000 IU per day, or cyclosporine therapy within 6 months of Visit 2/Baseline. 17. Subject has used finasteride (e.g., Propecia®), dutasteride, minoxidil (oral), or similar products within 6 months of Visit 2/Baseline. 18. Subject has used chemotherapy or cytotoxic agents within 12 months of Visit 2/Baseline. 19. Subject has had radiation of the scalp at any point. 20. Subject has used any other systemic therapy, which in the opinion of the investigator, may materially affect the subject's hair growth, including, but not limited to, vitamin or homeopathy supplement hair growth or hair health products or other steroid hormones (in any form), including anabolic steroids. 21. Subject is currently enrolled in an investigational drug, biologic, or device study.

	22. Subject has used an investigational drug, investigational biologic, or investigational device treatment within 30 days or 5 half-lives, whichever is longer, prior to Visit 2/Baseline. 23. Subject has previously been treated with the IP. 24. Subject has a history of prescription drug abuse, or illicit drug use within 6 months prior to Visit 1/Screening. 25. Subject has a history of alcohol abuse according to medical history within 6 months prior to Visit 1/Screening. 26. Subject has a positive screen for alcohol or drugs of abuse at Visit 1/Screening or Visit 2/Baseline. 27. Subject has signs or symptoms consistent with COVID-19 at Visit 1/Screening or Visit 2/Baseline or has been diagnosed with COVID-19 within 4 weeks of Visit 1/Screening. 28. Subject has a history of sensitivity to any of the ingredients in the IP or tattoo ink. 29. Subject is known to be noncompliant or is unlikely to comply with the requirements of the study protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator.
Study Procedures	Each subject will have 10 clinic visits. Visit 1 (Day -45 to -3): Screening. Subjects can be screened up to 45 days prior to Baseline. If applicable, qualified subjects can washout from prohibited medications and/or procedures/therapies prior to Baseline (after obtaining informed consent). Subjects who require washout for longer than 45 days will be reconsented. General hair care products and regimen must be continued for at least 2 weeks prior to Visit 2/Baseline and for the entire study. The study requirements and procedures will be reviewed and written informed consent must be obtained prior to the initiation of any study-related procedures. Demographics, inclusion/exclusion (I/E) criteria, medical history, and concomitant medications and concurrent procedures/therapies will be reviewed to determine eligibility. The subject's pattern of hair loss using the Modified Norwood-Hamilton Scale will be classified. The subject will complete a drug and alcohol screen. Subject must have a negative drug screen and alcohol screen to participate in the study. A physical examination, vital signs with height, weight, and body mass index (BMI), 12-lead ECG, and clinical laboratory testing (chemistry [with lipid panel and thyroid function], hematology, urinalysis, cardiac biomarkers, and serology) will be performed. Note: If a subject fails one or more screening laboratory and/or other assessment criteria, the assessment(s) may be repeated once within the Screening Period (Day -45 to -3), at the discretion of the investigator. The subject may be enrolled if criteria are then met upon the second assessment; only qualifying screening assessments will be recorded in the electronic case report forms (eCRFs). Standardized global photos[2] will be taken. Adverse events (AEs) will be recorded, as applicable. Subjects who continue to meet eligibility criteria after review of clinical labs and final interpreted ECG will be scheduled for Visit 2/Baseline and instructed to come to the visit with clean hair and scalp.

[2] Prior to Visit 2/Baseline, photo acceptability must be confirmed by the vendor. Global reshoots must occur in time to ensure the global photo is of an acceptable quality for assessment prior to Visit 2.

	Visit 2 (Day 1): Baseline. The subject will return to the clinic and be queried for any changes in health status since the previous visit, including medical history, concomitant medications, and concurrent procedures/therapies. The subject will complete and must have a negative drug screen and alcohol screen to be enrolled in the study. A physical examination, vital signs, and 12-lead ECG will be performed. I/E criteria will be reviewed and confirmed for eligibility. Blood and urine will be collected for clinical laboratory testing (chemistry [with lipid panel and thyroid function], hematology, urinalysis, and cardiac biomarkers) and a baseline PK blood sample will be collected prior to IP application. Local skin reactions (LSRs) will be assessed prior to the first dose. If screening photos are not adequate and a re-shoot prior to Baseline was not performed, additional global photo(s) will be taken. A micro-dot tattoo will be done on the scalp to identify the Target Area for macro photography. Macro photographs will be taken.[3] The subject will be randomized to an IP by allocation of a unique 5-digit randomization number via an interactive web response system (IWRS) and dispensed the IP kit numbers assigned by the IWRS. Subject Diary and Subject Instruction Sheet will be dispensed. Subject will be instructed on how to apply the IP and to record applications in the Subject Diary. IP accountability will be documented. The first dose will be applied at the site under supervision of study staff. A second PK blood sample 1 to 4 hours after IP application will be collected. AEs will be recorded. The subject will be scheduled for follow-up. Visit 3 (Day 14 ± 3): Week 2. The subject will return to the clinic and be queried for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies. Vital signs will be measured. LSRs will be assessed. Any AEs will be recorded. IP accountability will be documented; all containers of IP and Subject Diaries will be collected and reviewed. Additional IP and a new Subject Diary will be dispensed as needed. The subject will be scheduled for follow-up. Visits 4 and 6 (Days 28 ± 3 and 56 ± 3): Week 4 and Week 8. Note: 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. The subject will return to the clinic and be queried for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies. A physical examination, vital signs, and 12-lead ECG will be performed. Blood and urine will be collected for clinical laboratory testing (chemistry [with lipid panel and thyroid function], hematology, urinalysis, and cardiac biomarkers) and a PK blood sample will be collected 1 to 4 hours after IP application. Global photos will be taken. Subject Self-Assessments (SSAs) will be performed. Investigator's Global Assessment (IGA) and LSRs will be assessed. The scalp micro-dot tattoo will be checked and re-applied if needed; then, macro photographs will be taken. IP accountability will be documented; all containers of IP and Subject Diaries will be collected and reviewed. Additional IP and a new Subject Diary will be dispensed as needed. Any AEs will be recorded. The subject will be scheduled for follow-up.

[3] Macro photo shoots must occur within 7 days after the Baseline visit if a re-shoot is required.

	Visits 5 and 7 (Days 42 ± 3 and 70 ± 3): Week 6 and Week 10 Phone Calls. The site staff will contact the subject by telephone and query the subject for any changes in health status. The site staff will remind the subject to continue to apply the IP every morning until the next clinic visit and to record all applications in the Subject Diary. Any AEs will be discussed with the investigator to determine if the subject should return to the study site for an unscheduled visit. The next visit will be confirmed. Visits 8 and 9 (Days 84 ± 3 and 112 ± 3): Week 12 and Week 16/End of Treatment (EOT) or Early Termination. Note: 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. The subject will return to the clinic and be queried for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies. A physical examination, vital signs (with height and weight at Visit 9 only), and 12-lead ECG will be performed. Blood and urine will be collected for clinical laboratory testing (chemistry [with lipid panel and thyroid function], hematology, urinalysis, and cardiac biomarkers) and a PK blood sample will be collected 1 to 4 hours after IP application. Global photos will be taken. SSAs will be performed. IGA and LSRs will be assessed. The scalp micro-dot tattoo will be checked and re-applied if needed; then, macro photographs will be taken. IP accountability will be documented; all containers of IP and Subject Diaries will be collected and reviewed. **At Visit 8 only**, additional IP and a new Subject Diary will be dispensed. Any AEs will be recorded. The next visit will be confirmed. Visit 10 (Day 140 ± 5): Week 20/End of Study (EOS). The subject will return to the clinic and be queried for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies. If any new or worsening clinically significant abnormalities were present at EOT, or as warranted based on the subject's current medical condition, any of the following assessments may be performed: a physical examination, vital signs, 12-lead ECG, and clinical laboratory testing (chemistry [with lipid panel and thyroid function], hematology, urinalysis, and cardiac biomarkers). LSRs will be assessed. AEs will be recorded. The subject will exit the study.
Study Measurements	**Hair Loss Classification:** The Modified Norwood-Hamilton Scale will be used to assess the eligibility of the subjects at Visit 1/Screening. Subjects must have mild to moderate AGA in the temple and vertex region, rating IIIv, IV, or V on the Modified Norwood-Hamilton Scale to be eligible for the study. **Efficacy:** Photography Standardized global photos (i.e., a vertex view and a superior view) for SSA and IGA and standardized macro photos for assessment of Target Area Hair Counts (TAHC), Target Area Hair Width (TAHW), and Target Area Hair Darkness (TAHD) will be performed per the Schedule of Events (SOE). 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). Quantitative Hair Measurements TAHC, TAHW, and TAHD will be calculated using digital image analysis from standardized macro photos. TAHC, TAHW, and TAHD will be calculated for non-vellus and vellus/vellus-like (miniaturized) hair, separately. Subject Self-Assessment Questionnaires 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 the following 2 assessments, which comprise the SSA: • *Hair Growth Assessment (HGA)* [1]. 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) • *Hair Growth Index (HGI)* [2]. 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 …" **Safety:** Physical examinations, vital signs, 12-lead ECGs, clinical labs (chemistry [including lipid panel and thyroid function], hematology, urinalysis, and cardiac biomarkers), LSRs, and AEs will be recorded 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. **Pharmacokinetics:** 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.
Study 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 Endpoints: 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. Safety Endpoint(s): 1. Incidence (severity and causality) of any local and systemic AEs. 2. Number of subjects with presence (and severity) of the following 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 ECG parameters and overall ECG interpretation at Week 4, Week 8, Week 12, and Week 16. Pharmacokinetics Endpoint(s): If plasma concentrations of TDM-105795 are quantifiable, the plasma concentrations will be summarized for active treatment groups.
Sample Size Calculations	The sample size for this study is based on clinical considerations only. No formal sample size calculation was performed.
Statistical Methods	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. **Estimands for Efficacy Endpoints:** **Treatment conditions of interest**: Condition under study: AGA in males. IPs: • 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	The **primary endpoints** will be changes from Baseline in non-vellus TAHC using digital image analysis at Week 16, and the subject's evaluation of treatment benefit via the HGA questionnaire at Week 16. The **secondary endpoints** will be: 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.
Intercurrent Events (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.

	Study Populations: The Safety population will include all randomized subjects who received and applied the IP. The intent-to-treat (ITT) population will include all randomized subjects who were dispensed the IP. 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. The PK population will include those subjects in the ITT population with at least 1 measurable concentration value. **Efficacy Analyses:** The efficacy analyses will be conducted on the ITT and PP populations. <u>Primary Efficacy Analysis</u> 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 will be presented for pairwise comparisons of treatment groups. The HGA will be evaluated at Week 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 both non-vellus and vellus quantitative hair measurements. <u>Secondary Efficacy Analysis</u> 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. Descriptive statistics by treatment group will be provided for each time point for both non-vellus and vellus quantitative hair measurements. <u>Dosing Compliance</u> Descriptive statistics will be used to summarize the total number of applications for the ITT and PP 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. **Safety Analyses:** The safety analyses will be conducted on the Safety population. <u>Extent of Exposure</u> Descriptive statistics will be used to summarize the extent of exposure in the Safety population. The duration of treatment (date of final application minus date of first application plus 1), the total amount of IP used (difference between the weight of the

	IP dispensed and weight of IP returned), and the mean daily amount of IP applied (total amount of IP applied divided by the duration of treatment) will be calculated. Physical Examinations Findings from physical examinations will be recorded in medical history (from assessment at Screening and Baseline) or as AEs (from assessments after first dose). Vital Signs Descriptive statistics of vital signs (temperature, systolic and diastolic blood pressure, heart rate, and respiration rate), including height, weight, and BMI will be provided by treatment group. Electrocardiograms ECGs will be evaluated for any material changes during the study period. Descriptive statistics of ECG parameters will be provided by treatment group. Changes in overall interpretation of the ECG from Baseline to Weeks 4, 8, 12, and 16 will be examined using shift tables. 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. 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. Adverse Events All AEs reported during the study will be listed, documenting course, severity, investigator assessment of the relationship to the IPs, and outcome. Verbatim terms on the eCRFs will be linked to preferred terms (PTs) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) mapping system. 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. **Pharmacokinetics Analyses:** A PK analysis will be conducted on the PK population. PK results will be summarized using descriptive statistics for each active treatment group.

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.

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
CFR	Code of Federal Regulations
CK-MB	Creatine Kinase-MB
COVID	Coronavirus Disease
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
GGT	Gamma-Glutamyltransferase
HBsAg	Hepatitis B surface Antigen
HGA	Hair Growth Assessment
HGI	Hair Growth Index
HIV	Human Immunodeficiency Virus
Hr	Hairless
IB	Investigator's Brochure
ICE	Intercurrent Event
I/E	Inclusion/Exclusion
IGA	Investigator's Global Assessment
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
IWRS	Interactive Web Response System
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
OTC	Over-the-Counter

PD	Pharmacodynamics
pg	Picogram
PK	Pharmacokinetics
PP	Per-Protocol
PRP	Platelet Rich Plasma
PT	Preferred Term
RBC	Red Blood Cells
RDW	Red Blood Cell Distribution Width
SAE	Serious Adverse Event
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, Incorporated
TR	Thyroid Hormone Receptors
TSH	Thyroid Stimulating Hormone
WBC	White Blood Cells
WHO	World Health Organization

TABLE OF CONTENTS

1. BACKGROUND

The skin, the largest body organ, is well recognized as a target for thyroid hormones. The biological activities of thyroid hormone (T3) are mediated through nuclear thyroid hormone receptors (TR). These effects are in part mediated through ligand-specific interactions of TR with its partner retinoid X receptor and binding of these transcription factors to specific promoter regions of thyroid hormone response element genes. Two highly homologous TRs, designated as TRα and TRβ, are present in the skin. Expression of TRα and TRβ has been localized to nuclei of outer root sheath and dermal papilla cells in human hair follicles, suggesting a role(s) of thyroid hormones in hair growth [3, 4].

Immunohistochemistry staining of TR in human scalp hair follicles shows TRβ1 protein is predominantly present in scalp hair follicles [3]. Thyroid hormone also stimulates extracellular matrix production such as proteoglycan and glycosaminoglycan synthesis by dermal fibroblasts [5]. In humans, changes in the texture of the hair, as well as alopecia of the scalp, the eyebrow, and other body hair are some characteristic clinical signs of myxedema. Hypothyroidism causes alopecia characterized by dull, brittle hair and an increase in the percentage of follicles in telogen. In addition, treatment of thyrotoxicosis (Graves' disease) led to reversible alopecia [6].

The hair cycle is a highly regulated process, consisting of four distinct phases: anagen (growing phase), catagen (regressing phase), telogen (resting phase), and exogen (shedding phase). In the initiation of each cycle, stem cells in the bulge divide and migrate downward to enter anagen phase of hair cycle directed by the dermal papilla. Hormones including T3 are important modulators of this process through their interactions with complex, genetically determined biological pathways [7]. Canonical Wnt signaling pathway has been implicated to play a central role in hair follicle development and morphogenesis. Genetic analysis has also identified mutation at Hairless (Hr) gene and this genetic change is associated with congenial hair loss disorders [8]. Thyroid receptors interact with hairless gene product (Hr), a transcription factor required for hair growth [9, 10]. However, precise roles of TR in the regulation of hair growth and associated co-regulators are largely unknown.

Thyroid hormone receptor agonists (thyromimetics) are closely associated with hair growth [11]. In animals, thyroid hormones have been shown to stimulate epidermal proliferation and hair growth. Topical triiodothyronine (T3) stimulates epidermal proliferation, dermal thickening, and hair growth in both mice and rats. Some human subjects given thyroxine (T4) to treat thyroid hormone deficiency reported hair growth as a side effect [11]. Thyroid hormones are also found to directly alter human hair follicle functions including anagen prolongation and stimulation of both hair matrix keratinocyte proliferation and hair pigmentation [11]. In 2009, Li et al reported a TR-β subtype-selective thyromimetic PF-00277343 that is efficacious in both mouse and monkey hair growth models after topical applications [12]. They reported that the serum drug level of PF-00277343 is below the limit of quantification during tests in the bald stump-tailed macaques (*M. arctoides*) after successive application of the drug for 3 months in the monkeys [12]. Recently, Contreras-Jurado et al showed that deletion in mice of the thyroid hormone nuclear receptors TRα1

and TRβ (the main thyroid hormone–binding isoforms) results in impaired epidermal proliferation, hair growth, and wound healing [13]. Stem cells located at the bulge of the hair follicles are responsible for hair cycling and contribute to the regeneration of the new epidermis after wounding. They also demonstrated that thyroid hormone signaling is an important determinant of the mobilization of stem cells out of their niche in the hair bulge [13]. In 2016, a thyromimetic compound KB2115 was shown to significantly increase the percentage of anagen hair follicles compared with vehicle controls in *in vitro* cultured human scalp hair follicles [14]. KB2115 significantly increased the percentage of proliferating Ki67-labeling cells in the hair matrix, whereas the percentage of apoptotic (TUNEL) hair matrix cells remained unchanged, suggesting prolongation of anagen phase by KB2115. KB2115 effectively countered the tendency of organ-cultured hair follicles to spontaneously enter into catagen [14]. Altogether, these studies indicated that thyromimetics may prevent or reduce premature catagen entry leading to telogen effluvium *in vivo*, and promote anagen entry and hair growth. However, due to systemic toxicity concerns of thyromimetics, no thyromimetics have been tested in the clinic for treating androgenetic alopecia (AGA).

To date, only two drugs, minoxidil (Rogaine, a potassium channel opener) and finasteride (Propecia, a 5a-reductase inhibitor), have been approved for treating AGA by the FDA. Current treatments such as minoxidil and finasteride are only efficacious in a small percentage of subjects, apart from drug-related undesirable side effects. Therefore, significant unmet medical need exists in developing more efficacious drugs with less drug-related unwanted side effects for treating AGA, and other forms of hair loss. Drugs with novel mechanisms may lead to robust efficacy and superior safety for the treatment of AGA.

The Sponsor is exploring the use of thyromimetics for treating AGA with a suitable topical drug candidate for potential clinical application. The Sponsor has developed TDM-105795 topical solution for the potential treatment of AGA. TDM-105795 is a thyroid hormone receptor-beta agonist being developed as a topical drug to promote hair growth. Preclinical assessment of TDM-105795 indicated that TDM-105795 has poor systemic absorption following topical application and short elimination half-life to avoid unwanted systemic effects. Moreover, an *in vivo* efficacy study in C3H mice suggests that TDM-105795 was able to potently stimulate hair growth in telogen follicles in a dose-dependent manner when applied topically. This is likely because TDM-105795 is able to induce a premature initiation of anagen in telogen hair follicles when binding to thyroid receptors in hair follicle cells. No overt abnormality was observed associated with the treatment. TDM-105795 therefore has a potential to be a novel, potent, and safe therapy to promote hair growth in AGA.

One first-in-man, single ascending dose pharmacokinetic (PK) study was conducted with TDM-105795 (Study 239-11651-101). In this study, 30 male subjects with moderate to severe AGA were studied; subjects received a single dose of 0.025 mg (N=8), 0.05 mg (N=8), 0.1 mg (N=8), or placebo (N=6) applied to the scalp in the hair loss area (e.g., top of head and temple regions) and had PK blood draws at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, and 48 hours after the dose. No measurable plasma drug levels were detected in any samples for any subjects (below the limit of quantification of 5 pg/mL). There were no adverse events (AEs) and no local skin reactions

(LSRs) of erythema, edema, erosion, scaling, pruritus, and burning/stinging for all subjects across all visits. There were no materially clinically significant changes in vital signs, clinical laboratory tests (including thyroid function), and electrocardiograms (ECGs).

A multi-dose PK study with TDM-105795 (Study 239-11651-102) was recently completed. In this study, 32 male subjects with moderate to severe AGA were enrolled. Subjects received 1 mL of TDM-105795 topical solutions (0.0025%, 0.005%, 0.01%, or 0.02%) or placebo for once daily application for 4 weeks. Results showed that the doses tested were well tolerated. There were no material clinically significant changes in vital signs, clinical laboratory tests (including thyroid function), ECGs, echocardiograms, and cardiac biomarkers. In addition, there were no consistently measurable plasma drug levels above the lower limit of quantification (5 pg/mL). Based upon these findings, TDM-105795 formulation strengths of 0.0025% and 0.02% were chosen for further evaluation in the current Proof-of-Concept study.

2. RATIONALE

TDM-105795 could offer advantages over existing products in the treatment of AGA due to its potential efficacy and lack of systemic absorption. It would be desirable as a topical formulation to treat AGA because it affords targeted delivery at the local site of application; thus, minimizing systemic exposure and the potential for associated side effects. The pharmacological action of TDM-105795 appears to be limited to the local site of application.

The doses chosen in this study were supported by the nonclinical program for this drug product, the first-in-man single dose PK study, and the multi-dose PK study. The dosages selected for this study (0.0025% and 0.02%) span the anticipated range of potential therapeutic doses in order to evaluate the efficacy and safety of TDM-105795 topical solution in male human subjects with AGA. Moreover, doses tested in Study 239-11651-101 (0.0025%, 0.005%, and 0.01%) and Study 239-11651-102 (0.0025%, 0.005%, 0.01%, and 0.02%) were well tolerated. As such, the selected daily doses, 0.025 mg and 0.2 mg of TDM-105795, are expected to be safe and well tolerated; thus, no clinically relevant safety issues are anticipated.

3. OBJECTIVE

The objectives of the study are:

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

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 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 Investigator's Global Assessment (IGA), quantitative hair measurements that include Target Area Hair Counts (TAHC), Target Area Hair Width (TAHW), and Target Area Hair Darkness (TAHD), and subject self-assessment (SSA) questionnaires which include Hair Growth Assessment (HGA) and Hair Growth Index (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.

5. STUDY POPULATION

5.1 Subject Eligibility

To be included in the study, subjects must meet the following inclusion and none of the exclusion criteria.

5.1.1 Inclusion Criteria

1. Subject is male, 18-55 years old.
2. Subject has provided written informed consent.
3. Subject has a clinical diagnosis of mild to moderate AGA in temple and vertex region with a score of IIIv, IV, or V on the Modified Norwood-Hamilton Scale.
4. Subject, in the investigator's opinion, is in good general health and free of any disease state or physical condition that might impair evaluation of AGA or exposes the subject to an unacceptable risk by study participation.
5. Subject has normal renal, thyroid, and hepatic function as determined by the Visit 1/Screening laboratory results in the opinion of the investigator.
6. Subject is a non-smoker, defined as not having smoked or used any form of tobacco or non-tobacco products containing nicotine in more than 4 months before Visit 2/Baseline.
7. Subject is willing to maintain the same hairstyle, hair length, and hair color throughout the study.
8. Subject agrees to continue his other general hair care products and regimen for at least 2 weeks prior to Visit 2/Baseline, and through the entire study.

9. Subject is willing and able to apply the IP as directed, comply with study instructions, and commit to all follow-up visits for the duration of the study.
10. Subjects who are sexually active with a female partner and are not surgically sterile (vasectomy performed at least 6 months prior to treatment) must agree to refrain from sperm donation for at least 90 days after administration of their last dose of IP and inform their non-pregnant female sexual partner to use a highly effective form of birth control[4] as described in the informed consent form. Note: Female partner must be confirmed according to subject to be non-pregnant at Visit 1/Screening and Visit 2/Baseline or at the visit when a subject identifies a new sexual partner.

5.1.2 Exclusion Criteria

1. Subject has any dermatological disorders of the scalp on the regions that are bald and thinning with the possibility of interfering with the application of the IP or examination method, such as fungal or bacterial infections, seborrheic dermatitis, psoriasis, eczema, folliculitis, scars, or scalp atrophy.
2. Subject has history or active hair loss due to diffuse telogen effluvium, alopecia areata, scarring alopecia, trichotillomania, or conditions/diseases other than AGA.
3. Subject has any skin pathology or condition (e.g., uncontrolled thyroid disease, certain genetic disorders that involve hair growth or patterns) that, in the investigator's opinion, could interfere with the evaluation of the IP or requires use of interfering topical, systemic, or surgical therapy.
4. Subject has any visible inflammatory skin disease, injury, or condition of their scalp that could compromise subject safety and/or interfere with the evaluation of local or systemic assessments performed during the study.
5. Subject has history (within 6 months of Visit 1/Screening) of severe dietary or weight changes or history of eating disorder(s), which has resulted in hair loss, in the opinion of the investigator.
6. Subject has a history of scalp reduction or notable trauma with related scarring, hair transplants, and/or hair weaves.

[4] For females, highly effective forms of birth control include 1) intrauterine device (IUD; copper or hormonal); 2) implantable hormonal contraception; 3) surgical sterilization (i.e., hysterectomy, tubal ligation, or bilateral oophorectomy) performed at least 6 months prior to the subject's study entry; 4) total abstinence; or 5) using one of each of the following a) hormonal contraceptives [other than IUD or implantable, e.g., oral, transdermal, injectable, or vaginal ring] and b) double barrier methods [i.e., male or female condom, diaphragm with spermicidal foam/gel/film/cream/vaginal suppository, cervical cap with spermicides, or contraceptive sponge]. Male subjects who become sexually active or begin to have relations with a female partner who is not sterile during the trial must have a female partner who is not pregnant and agrees to use a highly effective form of birth control for 90 days after administration of their last dose of IP. Female partner taking hormonal therapy must be on treatment prior to the subject's entry into the study, continued per label, and must not change their dosing regimen during the trial; highly effective birth control forms must be for (1) oral: at least 1 complete cycle (e.g., 4 to 8 weeks); (2) transdermal, injectable (e.g., Depo-Provera), implantable, vaginal ring (e.g., NuvaRing), IUD: at least 1 week; or (3) total abstinence: at least 1 complete cycle (e.g., 4 to 8 weeks) prior to initiation of IP. For males, adequate forms of contraception include condom and spermicide in combination with other forms of female contraception.

7. Subject has a known or suspected malignancy excluding cutaneous basal cell carcinoma or cutaneous squamous cell carcinoma not located within the treatment area.
8. Subject has a positive blood screen for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C antibody.
9. Subject has any condition, which, in the investigator's opinion, would make it unsafe for the subject to participate in this study, including clinically significant abnormal laboratory, or 12-lead ECG findings during the screening period or Visit 2/Baseline prior to dosing of the IP.
10. Subject has used any topical scalp treatments for hair growth including minoxidil, hormone therapy, anti-androgen, or other agents known to affect hair growth within 12 weeks of Visit 2/Baseline.
11. Subject has used any topical scalp over-the-counter (OTC) or cosmetic treatments known or reasonably believed to affect hair growth (e.g., brands such as Aminexil, Maxilene, Nioxin, Foltene) or hair growth products with saw palmetto, copper, etc. within 4 weeks of Visit 2/Baseline.
12. Subject has used any topical scalp treatments that may have ancillary effects on hair growth including, but not limited to, corticosteroids, pimecrolimus, tacrolimus, and retinoids within 4 weeks of Visit 2/Baseline.
13. Subject has had any scalp procedures, including surgical, laser, light or energy treatments, micro-needling, etc. within 6 months of Visit 2/Baseline.
14. Subject has had platelet rich plasma (PRP) procedures on the scalp at any time.
15. Subject has used systemic beta blockers, cimetidine, ketoconazole, diazoxide, or corticosteroids (including intramuscular and intralesional injections) within 12 weeks of Visit 2/Baseline. Inhaled, intranasal, or ocular corticosteroids are allowed if use is stable. Stable is defined as doses and frequency unchanged for at least 4 weeks prior to Visit 2/Baseline.
16. Subject has used systemic retinoids, isotretinoin, vitamin A intake above 10,000 IU per day, or cyclosporine therapy within 6 months of Visit 2/Baseline.
17. Subject has used finasteride (e.g., Propecia®), dutasteride, minoxidil (oral), or similar products within 6 months of Visit 2/Baseline.
18. Subject has used chemotherapy or cytotoxic agents within 12 months of Visit 2/Baseline.
19. Subject has had radiation of the scalp at any point.
20. Subject has used any other systemic therapy, which in the opinion of the investigator, may materially affect the subject's hair growth, including, but not limited to, vitamin or homeopathy supplement hair growth or hair health products or other steroid hormones (in any form), including anabolic steroids.
21. Subject is currently enrolled in an investigational drug, biologic, or device study.
22. Subject has used an investigational drug, investigational biologic, or investigational device treatment within 30 days or 5 half-lives, whichever is longer, prior to Visit 2/Baseline.
23. Subject has previously been treated with the IP.
24. Subject has a history of prescription drug abuse, or illicit drug use within 6 months prior to Visit 1/Screening.
25. Subject has a history of alcohol abuse according to medical history within 6 months prior to Visit 1/Screening.

26. Subject has a positive screen for alcohol or drugs of abuse at Visit 1/Screening or Visit 2/Baseline.
27. Subject has signs or symptoms consistent with COVID-19 at Visit 1/Screening or Visit 2/Baseline or has been diagnosed with COVID-19 within 4 weeks of Visit 1/Screening.
28. Subject has a history of sensitivity to any of the ingredients in the IP or tattoo ink.
29. Subject is known to be noncompliant or is unlikely to comply with the requirements of the study protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator.

5.1.3 Subject Withdrawal Criteria

Procedures for handling subjects who are discontinued from the study are described in Section 13.2. Subjects who are discontinued may be replaced at the discretion of the Sponsor.

6. INVESTIGATIONAL PRODUCTS AND REGIMEN

6.1 Description

TDM-105795 topical solution is an organic solution containing common excipients for topical use.

Drug name:	TDM-105795 topical solution, 0.0025%
Active ingredient:	N1-(3,5-dichloro-4-(3-(4-fluorobenzyl)-4-hydroxyphenoxy)phenyl)-N2-hydroxyoxalamide
Other ingredients:	Absolute Ethanol, Propylene Glycol, Polyethylene Glycol 400 (PEG-400)

Drug name:	TDM-105795 topical solution, 0.02%
Active ingredient:	N1-(3,5-dichloro-4-(3-(4-fluorobenzyl)-4-hydroxyphenoxy)phenyl)-N2-hydroxyoxalamide
Other ingredients:	Absolute Ethanol, Propylene Glycol, Polyethylene Glycol 400 (PEG-400)

Drug name:	TDM-105795 topical vehicle solution (Placebo)
Other ingredients:	Absolute Ethanol, Propylene Glycol, Polyethylene Glycol 400 (PEG-400)

6.2 Instructions for Use and Application

Subjects will be instructed on how to apply the IP at Visit 2/Baseline. For each dose, 1 mL will be applied in a thin layer to the scalp focusing on the regions that are bald and thinning. Subjects will be instructed to apply the IP to the balding and thinning areas of the scalp once in the morning at approximately the same time as the dose on Day 1.

Subjects will be provided with a Subject Instruction Sheet detailing how to apply the IP (see Appendix 1) and a Subject Diary (see Appendix 2) to record dates and times of applications and if the full dose was applied. Subjects will be instructed to bring all IP containers (used and unused) and the Subject Diary to each study visit. At each visit, IP containers will be weighed and the

Subject Diary will be collected, reviewed, and a new one will be dispensed to the subject (as needed).

The investigator will provide the subject with a sample Subject Instruction Sheet as detailed in Appendix 1, which may include the following recommendations:

- Wash the scalp with your typical shampoo and dry the hair each morning prior to the daily dose of IP.
- For those days when you have a clinic visit, remember to bring your IP supplies with you to the clinic.
- Wash and dry hands thoroughly then apply 1 mL of IP to the balding and thinning areas of your scalp using the provided dropper and using a few drops at a time or a sparingly thin line to avoid having the IP drip off of the scalp.
- Spread the solution evenly over the hair loss area and gently massage the solution into the scalp with an emphasis over the entire balding area and adjacent regions with thinning hair.
- After application, wash and dry hands thoroughly.
- Do not wash the treated area, bathe, shower, swim, or have exposure to water on the head for at least approximately 4 hours following IP application.
- Avoid rigorous exercise within at least approximately 4 hours following IP application.
- Avoid wearing a cap or hat for at least approximately 30 minutes following IP application.
- Apply the dose at approximately the same time every morning.
- Record date and time of all applications in the Subject Diary.
- Bring all containers of the IP (used and unused) and the completed Subject Diary to every visit.

6.3 Warnings, Precautions, and Contraindications

The IPs are for topical use on the scalp only and for use by men only. The IP should not be applied to other parts of the body. Care should be taken to minimize inadvertent transfer of the IP to close contacts.

Care should be taken to avoid contact with eyes and all mucous membranes. If contact with eyes occurs, rinse thoroughly with water. If inadvertent transfer of the IP occurs with a close contact, such area of contact should be washed with soap and water as soon as possible.

Subjects with a known sensitivity to any of the ingredients in the IPs should not participate in this study.

Should skin irritation or rash develop, the subject should be instructed to contact the site immediately.

7. RANDOMIZATION ASSIGNMENT

Subjects will be randomized (1:1:1) to 1 of the 3 IPs listed below.

1. TDM-105795 topical solution, 0.0025%

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

The randomization will be blocked by investigational site. Subjects will be randomized to an IP by allocation of a unique 5-digit randomization number via an interactive web response system (IWRS).

8. PRIOR AND CONCOMITANT THERAPIES

Current medications/therapies, any medications/therapies taken in the 30 days prior to the start of the study (Visit 1/Baseline), and medications/therapies that require washout for more than 30 days will be recorded as concomitant medications or concurrent procedures, respectively, with the dose (for medications only) and corresponding indication. The medications to be recorded include prescription and OTC medications; vitamins, minerals, and herbal, holistic, and dietary supplements will only be recorded as concomitant medications if being taken for a therapeutic indication. All medications taken on a regular basis must be recorded on the electronic case report forms (eCRFs). All concomitant medications will be coded with the current version of the WHO Drug Dictionary at the start of the study. Therapies to be recorded include any non-drug therapy used to treat a medical condition. General hair care products will not be recorded in the eCRFs. Procedures which occurred prior to Baseline will be recorded as Medical History.

Any changes in concomitant medications and/or therapies during the study must be recorded. The reason for any changes in concomitant medications and/or therapies is needed and will typically reflect either a baseline medical condition documented in the medical history or in conjunction with an AE.

8.1 Prohibited Medications or Therapies

Prior to entry into the study, subjects must not use the medications or procedures/therapies as specified in Section 5.1.2.

The medications or treatments that are prohibited during the study include:

- Any topical scalp treatments for hair growth including minoxidil, hormone therapy, anti-androgen, or other agents known to affect hair growth
- Any topical scalp OTC or cosmetic treatments known or reasonably believed to affect hair growth (e.g., brands such as Aminexil, Maxilene, Nioxin, Foltene) or hair growth products with saw palmetto, copper, etc.
- Any topical scalp treatments that may have ancillary effects on hair growth including, but not limited to, corticosteroids, pimecrolimus, tacrolimus, and retinoids
- Any scalp procedures, including surgical, laser, light or energy treatments, micro-needling, etc.
- PRP procedures on the scalp
- Systemic beta blockers, cimetidine, ketoconazole, diazoxide, or corticosteroids (including intramuscular and intralesional injections)

- Systemic retinoids, isotretinoin, vitamin A intake above 10,000 IU per day, or cyclosporine therapy
- Finasteride (e.g., Propecia®), dutasteride, minoxidil (oral), or similar products
- Chemotherapy or cytotoxic agents
- Radiation of the scalp
- Any other systemic therapy, which in the opinion of the investigator, may materially affect the subject's hair growth, including, but not limited to, vitamin or homeopathy supplement hair growth or hair health products or other steroid hormones (in any form), including anabolic steroids
- An investigational drug, investigational biologic, or investigational device treatment

8.2 Allowed Medications or Therapies

Vitamins and mineral supplements are permitted at dosages considered by the investigator as reasonable for maintaining good health and will not be recorded in the eCRFs. Therapies (medication and non-medication therapies) not restricted by the protocol may be used during the study for the treatment or prevention of disease or to maintain good health. Non-prohibited chronic therapies being used at Visit 1/Baseline may be continued, but must be recorded.

Inhaled, intranasal, or ocular corticosteroids are allowed if use is stable. Stable is defined as doses and frequency unchanged for at least 4 weeks prior to Visit 2/Baseline.

9. STUDY PROCEDURES

Specific activities for each study visit are listed below.

9.1 Visit 1 (Day -45 to -3): Screening

Subjects can be screened up to 45 days prior to Baseline. If applicable, qualified subjects can washout from prohibited medications and/or procedures/therapies prior to Baseline (after obtaining informed consent). Subjects who require washout for longer than 45 days will be reconsented. General hair care products and regimen must be continued for at least 2 weeks prior to Visit 2/Baseline and for the entire study.

At Screening, the investigator or designee will:

- Obtain a signed, written informed consent.
- Record demographics.
- Review I/E criteria.
- Record medical history.
- Record prior and/or concomitant medications and concurrent procedures/therapies. Note: general hair care products and regimen must be continued for at least 2 weeks prior to Visit 2/Baseline and for the entire study, but do not need to be recorded in the eCRFs.
- Classify the pattern of subject's hair loss using the Modified Norwood-Hamilton Scale (Section 10.1).

- Perform drug (Section 12.3) and alcohol screens (Section 12.4).
- Perform a physical examination (Section 10.4.1). Record any clinically significant abnormalities in medical history.
- Measure vital signs (including height, weight, and BMI). See Section 10.4.2.
- Perform 12-lead ECG (Section 10.4.3).
- Collect urine and blood samples for clinical labs (chemistry [including lipid panel and thyroid function], hematology, urinalysis, and cardiac biomarkers; Section 12.1) and serology (HIV, Hepatitis B and C screen; Section 12.2).
    - It is preferred that subjects be fasting (approximately 8 hours); 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.
    - If a subject fails one or more screening laboratory and/or other assessment criteria, the assessment(s) may be repeated once during Screening, at the discretion of the investigator. The subject may be enrolled if criteria are then met upon the second assessment.
- Perform standardized global photography (Section 11.1). If repeat 'baseline' global photos are required, they must be taken prior to standardized macro photos at Baseline.
- Review I/E criteria and confirm preliminary eligibility including review of the Visit 1/Screening ECG such that the subject may advance to Visit 2/Baseline.
- Record any AEs[5].
- Instruct subject to come to the Visit 2/Baseline clinic visit with clean hair and scalp.
- Schedule Visit 2/Baseline.

9.2 Visit 2 (Day 1): Baseline

Prior to this visit, the investigator or designee will:

- Review laboratory results and cardiologist review of the ECG to determine if subject is eligible to enroll in the study.

At this visit, the investigator or designee will:

- Query the subject for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies and medical history, and document the findings.
- Perform drug (Section 12.3) and alcohol screens (Section 12.4).

[5] 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 IRB as an "unanticipated problem" in accordance with local procedures.

- Perform a physical examination (Section 10.4.1). Record any clinically significant abnormalities in medical history.
- Measure vital signs. See Section 10.4.2.
- Perform 12-lead ECG (Section 10.4.3).
- Review I/E criteria and confirm eligibility including review of the Visit 1/Screening safety laboratory results to determine normal renal, thyroid, and hepatic function, drug and alcohol screen, and ECG from Visit 1/Screening and Visit 2/Baseline, in the opinion of the investigator.
- Collect urine and blood samples for clinical labs (chemistry [including lipid panel and thyroid function], hematology, urinalysis, and cardiac biomarkers; Section 12.1).
    - It is preferred that subjects be fasting (approximately 8 hours); 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 at Visit 2/Baseline.
- Collect PK blood sample pre-application for Baseline TDM-105795 in plasma (Section 12.5).
- Perform standardized global photography (Section 11.1) prior to scalp micro-dot tattoo and standardized macro photography if Screening photos are not adequate and re-shoot prior to Baseline was not performed.
- Perform the scalp micro-dot tattoo procedure (Section 11.2).
- Perform standardized macro photography (Section 11.2). Note: If repeat macro photos are required, they must be taken within 7 days after the scheduled visit.
- Record LSRs pre-application (Section 10.4.4).
- Randomize the subject using the IWRS. Dispense the IP kit numbers assigned by the IWRS.
- Record IP Accountability.
- Dispense Subject Instruction Sheet and instruct the subject where and how to apply the IP and dispense the Subject Diary and provide completion instructions.
- Supervise the application of the IP and instruct the subject to record the date and time in the Subject Diary.
- Collect PK blood sample 1-4 hours post application (Section 12.5).
- Document any AEs.
- Schedule the next visit.

9.3 Visit 3 (Day 14 ± 3): Week 2

At this visit, the investigator or designee will:

- Query the subject for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies, and document the findings.
- Measure vital signs. See Section 10.4.2.
- Record LSRs (Section 10.4.4).

- Record IP Accountability.
- Collect, review, and dispense a new Subject Diary, as needed.
- Document any AEs.
- Schedule the next visit.

9.4 Visit 4 (Day 28 ± 3) and Visit 6 (Day 56 ± 3): Weeks 4 and 8

Note: 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.

At this visit, the investigator or designee will:

- Query the subject for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies, and document the findings.
- Perform a physical examination (Section 10.4.1).
- Measure vital signs (Section 10.4.2).
- Perform 12-lead ECG (Section 10.4.3).
- Collect urine and blood samples for clinical labs (chemistry [including lipid panel and thyroid function], hematology, urinalysis, and cardiac biomarkers; Section 12.1). Note: It is preferred that subjects be fasting (approximately 8 hours); 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.
- Perform standardized global photography (Section 11.1) prior to scalp micro-dot tattoo and standardized macro photography.
- Perform the scalp micro-dot tattoo procedure (Section 11.2) if it has significantly faded.
- Perform standardized macro photography (Section 11.2).
- Have subject complete the SSA questionnaires for scalp hair growth using the standardized global photos of the subject's scalp taken at Visit 1/Screening and comparing it to the current visit's photos (Section 10.3).
- Complete the IGA for scalp hair growth using the standardized global photos of the subject's scalp taken at Visit 1/Screening and comparing it to the current visit's photos (Section 10.2).
- Record LSRs (Section 10.4.4).
- Collect PK blood sample 1 to 4 hours after IP application (Section 12.5).
- Allocate new IP kit numbers using the IWRS and dispense the corresponding kits. Record IP Accountability.
- Collect, review, and dispense a new Subject Diary, as needed.
- Document any AEs.
- Schedule the next visit.

9.5 Visit 5 (Day 42 ± 3) and Visit 7 (Day 70 ± 3): Weeks 6 and 10 Phone Call

At this visit, the investigator or designee will:

- Contact the subject by telephone and query the subject for any changes in health status and document the findings.
- Remind the subject to continue to apply the IP every morning until the next clinic visit and to record all applications in the Subject Diary.
- Discuss any AEs with the investigator to determine if the subject should return to the study site for an unscheduled visit.
- Confirm the next visit.

9.6 Visit 8 (Day 84 ± 3) and Visit 9 (Day 112 ± 3): Weeks 12 and 16/End of Treatment

Note: 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.

At this visit, the investigator or designee will:

- Query the subject for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies, and document the findings.
- Perform a physical examination (Section 10.4.1).
- Measure vital signs (Section 10.4.2) with height and weight at Visit 9 only.
- Perform 12-lead ECG (Section 10.4.3).
- Collect urine and blood samples for clinical labs (chemistry [including lipid panel and thyroid function], hematology, urinalysis, and cardiac biomarkers; Section 12.1). Note: It is preferred that subjects be fasting (approximately 8 hours); 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.
- Perform standardized global photography (Section 11.1) prior to scalp micro-dot tattoo and standardized macro photography.
- Perform the scalp micro-dot tattoo procedure (Section 11.2) if the subject's micro-dot tattoo has significantly faded.
- Perform standardized macro photography (Section 11.2).
- Have subject complete the SSA questionnaires for scalp hair growth using the standardized global photos of the subject's scalp taken at Visit 1/Screening and comparing it to the current visit's photos (Section 10.3).
- Complete the IGA for scalp hair growth using the standardized global photos of the subject's scalp taken at Visit 1/Screening and comparing it to the current visit's photos (Section 10.2).
- Record LSRs (Section 10.4.4).
- Collect PK blood sample 1 to 4 hours after IP application (Section 12.5).
- Record IP Accountability. At Visit 8 only, additional IP will be dispensed.
- Collect, review, and dispense a new Subject Diary, as needed.

- Document any AEs.
- Schedule the next visit.

9.7 Visit 10 (Day 140 ± 5): Week 20/End of Study

At this visit, the investigator or designee will:

- Query the subject for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies, and document the findings.
- Perform a physical examination (Section 10.4.1).
- Measure vital signs (Section 10.4.2) if any new or worsening clinically significant abnormalities were present at EOT, or as warranted based on the subject's current medical condition.
- Perform 12-lead ECG (Section 10.4.3) if any new or worsening clinically significant abnormalities were present at EOT, or as warranted based on the subject's current medical condition.
- Collect urine and blood samples for clinical labs (chemistry [including lipid panel and thyroid function], hematology, urinalysis, and cardiac biomarkers; Section 12.1) if any new or worsening clinically significant abnormalities were present at EOT, or as warranted based on the subject's current medical condition. Note: It is preferred that subjects be fasting (approximately 8 hours); 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.
- Record LSRs (Section 10.4.4).
- Document any AEs.
- Exit subject from the study.

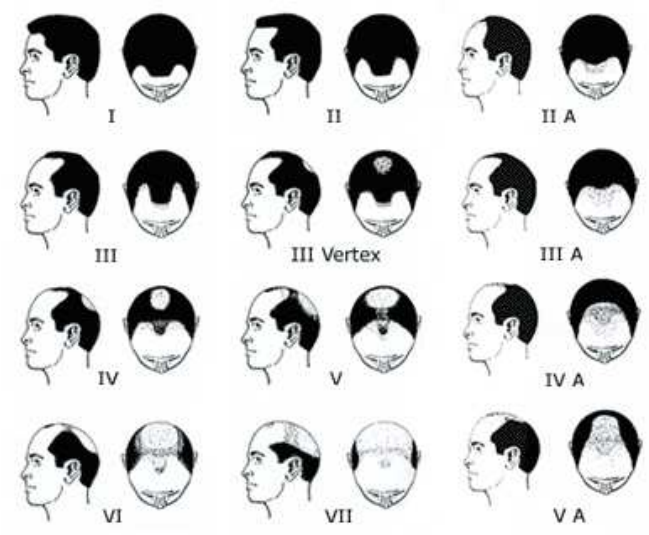
10. CLINICAL EVALUATIONS

The following clinical evaluations will be performed according to the Schedule of Events (SOE). The same expert grader who has received training on how to properly perform the clinical evaluations should ideally complete the evaluations for a given subject throughout the study. If this is not possible (e.g., scheduling conflict), a different expert grader with overlapping experience with the subject and the study should complete the evaluations.

10.1 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 [15].

Figure 10.1-1 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.

10.2 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).

10.3 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.

10.3.1 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).

10.3.2 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 …"

10.4 Safety Evaluations

10.4.1 Physical Examination

Physical examinations will be performed per the 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.

10.4.2 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 BMI will also be measured at Visit 1/Screening and Visit 9/EOT.

10.4.3 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.

The Investigator must review all the ECG reports in a timely manner. Note: The Investigator will initial and date each ECG report to indicate his/her review. The Investigator will note, directly on the report, whether or not any abnormal findings are clinically significant. The Investigator must complete an appropriate AE form for any new or worsening abnormal test results that are identified as clinically significant after Baseline.

10.4.4 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.

11. PHOTOGRAPHY

Photography documentation is required in this study. These standardized global and macro photos, using the Canfield system, are required to document the status of hair growth prior to, during, and after treatment with the IP. In addition, at any time during the study, at the discretion of the investigator, photographs may be taken to document the effects of treatment, AEs, or other findings during the study. The site will be provided with suggested guidelines to assist them in taking standardized photographs.

For any photographs taken of readily identifiable features (e.g., the face), an effort will be made to de-identify the photos (i.e., a masking bar over the eyes). In addition, subject identifiers (i.e., codes) will be used to identify photographs to the appropriate subject.

Note: Subjects who decline to have photographs taken during the conduct of study may not participate in the study given that photography is required. If a subject initially consents to photographs, then declines further photography, the Sponsor may use the photographs taken under consent for the purposes noted above.

Additional details and instructions regarding the standardized global and macro photography methods are provided by Canfield Scientific.

11.1 Standardized Global Photography

Standardized global photography (i.e., a vertex view and a superior view) for SSA and IGA will be performed per the SOE.

The standardized global photos taken at Visit 1/Screening will be used as the baseline photos for the IGA and SSA. If Screening photos are not adequate and re-shoot prior to Baseline was not performed, additional global photos will be taken at Baseline prior to scalp micro-dot tattoo and standardized macro photography. At subsequent visits where standardized global photography is performed, photos may not be repeated.

11.2 Standardized Macro Photography

A scalp micro-dot tattoo will be performed at Visit 2/Baseline to assist with standardized macro photography. At subsequent visits, the tattoo will be checked for fading and re-applied, if required.

Standardized macro photography will be performed per the SOE. If repeat macro photos are required, they must be taken within 7 days after the scheduled visit.

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 will be calculated for non-vellus and vellus/vellus-like (miniaturized) hair, separately.

12. LABORATORY TESTS

12.1 Blood Chemistries, Hematology, Urinalysis, and Cardiac Biomarkers

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.

The following 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		

§ Bicarbonate may be substituted if the participating lab does not perform assay for carbon dioxide.

Sample collection, handling, labeling, and shipping should be done following the instructions provided by the relevant certified laboratory and the applicable local regulations.

The investigator must review all the subject's laboratory reports in a timely manner. **NOTE**: The investigator will initial and date each laboratory report to indicate his/her review. The investigator

will note, directly on the laboratory report, whether or not any abnormal test results are clinically significant or not clinically significant. Clinically significant laboratory abnormalities that are present at Screening and/or Baseline must be documented in the subject's medical history. In addition, the investigator must complete an appropriate AE form for any new or worsening abnormal test results that are identified as clinically significant after Baseline.

AEs that may be associated with venipuncture and that must be included in the informed consent include:

- Pain
- Bruising
- Bleeding at the puncture site
- Fainting
- Inflammation of the vein

12.2 Serology

Blood samples will be collected for serology per the SOE. Samples will be analyzed for detection of antivirus antibodies for HIV, HBsAg, or hepatitis C. The results must be negative for the subject to be enrolled.

12.3 Drug Screen

A urine drug screen will be performed per the SOE in the clinic. Urine will be screened for the following drugs (cut off in ng/mL): amphetamines (500), barbiturates (300), buprenorphine (10), benzodiazepines (300), cocaine (150), methadone metabolite (300), ecstasy (MDMA500), methamphetamine (500), methadone (300), opiates (300), oxycodone (100), phencyclidine (25), tricyclic antidepressants (1000), and tetrahydrocannabinol (50). The results must be negative for the subject to be enrolled.

12.4 Alcohol Screen

A saliva alcohol screen will be performed per the SOE in the clinic. The results must be negative for the subject to be enrolled.

12.5 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.

The method of sample collection for PK analysis, along with specific instructions on labeling and management of these specimens, is detailed in the laboratory manual to be provided by the

laboratory vendor. The laboratory manual will also include instructions on how blood samples will be processed, stored, and transported to the analytical laboratory.

13. END OF STUDY CRITERIA

At the end of each subject's participation in the study, the investigator will complete an End of Study Disposition form for all completed and discontinued subjects.

13.1 Completion of the Study

Subjects who complete the 16-week course of treatment and complete Visit 10/EOS clinic visit as specified in this protocol will be considered to have completed the study.

13.2 Subject Discontinuation

A subject may be withdrawn from the study prior to completion for any of the following reasons:

- AEs
- Death
- Lack of efficacy[6]
- Lost to follow-up
- Non-compliance with study drug
- Physician decision
- Progressive disease[7]
- Protocol violation[8]
- Study terminated by Sponsor
- Withdrawal by subject; NOTE: if the subject decides to withdraw from the study due to an AE then it should be classified as withdrawal due to an AE
- Other (e.g., any reason that may affect the outcome of the study or safety of subjects)

If a subject withdraws from the study prematurely for any reason, the site should make every effort to have the subject return to the clinic to perform all of the required visit activities and to collect and reconcile all IPs (if applicable). If the subject will not return to the clinic, the site should make every attempt to contact the subject; otherwise the subject will be considered lost to follow-up.

When a subject is withdrawn from the study for an IP related AE (as defined in Section 14.2), when possible, the subject should be followed until resolution or stabilization of the AE.

[6] Defined as the lack of expected or desired effect related to a therapy.
[7] Defined as a disease process that is increasing in extent or severity.
[8] Defined as a significant departure from processes or procedures that were required by the protocol. Violations often result in data that are not deemed evaluable for a per-protocol analysis, and may require that the subject(s) who violate the protocol be discontinued from the study.

13.3 Study Termination

The study may be terminated by the investigator or the Sponsor. If, in the opinion of the investigator, clinical observations made during the study suggest that it may be unwise to continue, he or she may stop the study. A study termination by the investigator will be reported to the Sponsor.

In addition, a written statement fully documenting the reasons for this action will be submitted to the Sponsor by the investigator within 5 working days.

In the event that the Sponsor chooses to discontinue or terminate the study, appropriate notification will be given to the investigator.

14. ADVERSE EVENT REPORTING

Refer to the Investigator's Brochure (IB) for a list of AEs that are known to be associated with the IP(s) and/or study procedures.

14.1 Adverse Event Definitions

An **adverse event** is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered related.

An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with any drug) and from any route of administration, formulation, or dose, including an overdose.

A **suspected adverse reaction** is any AE for which there is a reasonable possibility that the drug caused the event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE.

An **adverse reaction** is any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug. For the purposes of prescription drug labeling, the term adverse reaction means an undesirable effect, reasonably associated with the use of a drug that may occur as part of its pharmacological action or may be unpredictable in its occurrence.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral

vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Timely and complete reporting of all AEs assists the Sponsor and/or their designee (e.g., Therapeutics, Inc. [TI]) in identifying any untoward medical occurrence, thereby allowing:

1) protection of the safety of study subjects;
2) a greater understanding of the overall safety profile of the IP;
3) recognition of dose-related IP toxicity;
4) appropriate modification of study protocols;
5) improvements in study design or procedures; and
6) adherence to worldwide regulatory requirements.

14.2 Adverse Event Details

AEs may be either spontaneously reported or elicited during questioning and examination of a subject. All AEs must be recorded on the AE eCRF. If known, the investigator should report the diagnosis of the underlying illness or disorder, rather than its individual symptoms. Subjects experiencing AEs that cause interruption or discontinuation of IP or those experiencing AEs that are present at the end of their participation in the study should receive follow-up as appropriate. AEs should be followed to resolution or stabilization (if possible) and, if they become serious, reported as serious adverse events (SAEs, see Section 14.3). If possible, the outcome of any AEs that caused permanent discontinuation or that were present at the end of the study, especially those considered by the investigator to be related to the IP, should be reported.

Information on the medical condition of subjects should begin following the subject's written informed consent to participate in the study and a medical history should be taken at screening. 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. Other changes in subject health information becomes AE data when the subject begins dosing with the IP; therefore AE data should be collected from the date of the first dose of IP until the date of the final study visit. These data are considered treatment-emergent AEs.

The investigator will instruct the subject to report any AEs that may occur during the study. At each visit, the investigator should ask the subject, in non-directive fashion, about any change in the subject's overall health status since the previous visit.

The severity of each AE, as judged by the investigator, will be recorded on the appropriate AE eCRF and will be graded according to the following scale:

Mild: The AE is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: The AE is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

Severe: The AE interrupts usual activities of daily living or significantly affects clinical status, or may require intensive therapeutic intervention.

The investigator must determine the relationship of the AE to the IP according to the following categories:

Definitely Related: An event that follows a reasonable temporal sequence from administration of the IP; that follows a known or expected response pattern to the IP; and that is confirmed by improvement on stopping or reducing the dosage, and reappearance of the event on repeated exposure (re-challenge).

Probably Related: An event that follows a reasonable temporal sequence from administration of the IP; that follows a known or expected response pattern to the IP; and that is confirmed by improvement on stopping or reducing the dosage of the IP; and that is unlikely to have been caused by concurrent/underlying illness or other drugs, procedures, or other causes.

Possibly Related: An event that follows a reasonable temporal sequence from administration of the IP; that follows a known or expected response pattern to the IP; but may have been caused by concurrent/underlying illness, other drug, procedure, or other causes.

Unlikely Related: An event that does not follow a reasonable temporal sequence from administration of the IP; that does not follow a known or expected response pattern to the IP, or most likely was caused by concurrent/underlying illness, other drug, procedure, or other causes, because of their known effects.

Not Related: An event almost certainly caused by concurrent/underlying illness, other drug, procedure, or other causes.

The investigator should categorize the outcome of the AE according to the following categories:

Fatal: Termination of life as a result of an AE.

Not Recovered/Not Resolved: AE has not improved or the subject has not recuperated.

Recovered/Resolved: AE has improved or the subject has recuperated.

Recovered/Resolved with Sequelae: Subject recuperated but retained the pathological conditions resulting from the prior disease or injury.

Recovering/Resolving: AE is improving or the subject is recuperating.

Unknown: Not known, not observed, not recorded or subject refused.

14.3 Serious Adverse Event

An event that is serious must be recorded on the AE eCRF and on the TI SAE Report Form, and requires expeditious handling to comply with regulatory requirements.

An AE or suspected adverse reaction is considered "serious" if, in the opinion of either the investigator or Sponsor, it results in any of the following outcomes:

- Death; the event must be the cause of death for the SAE to meet this serious criterion.
- Life-threatening event; an event in which the subject was at risk of death at the time of the event and not an event that hypothetically might have caused death if it had been more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization (for ≥24 hours).
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.
- Important medical events; a medical event(s) that may not result in death, be life-threatening, or require hospitalization but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events NOT considered to be SAEs are:

- Hospitalizations for the treatment, which was elective or pre-planned, of a pre-existing condition that did not worsen; and
- Treatment on an emergency, outpatient basis, for an event not fulfilling any of the definitions of "serious" given above and not resulting in hospital admission.

AEs classified as "serious" by either the investigator or the Sponsor require expeditious handling and reporting to TI to comply with regulatory requirements. **All SAEs, whether related or unrelated to IP, must be immediately reported by telephone to the Medical Monitor and, in the event that he/she is unavailable, to the Project Manager listed on the first page of the protocol.** Written notification of all SAEs should be sent to the Project Manager by email or

confirmed facsimile transmission. These include those SAEs listed in the protocol or IB and must include an assessment of whether there is a reasonable possibility that the IP caused the event.

Any suspected adverse reactions that are serious and unexpected represent especially important safety information that must be reported more rapidly to Health Authorities; therefore, it is important that the Investigator submit any information requested by the Sponsor or designee (e.g., TI) as soon as it becomes available.

If only limited information is initially available, follow-up reports are required. Should the investigator become aware of an SAE (regardless of its relationship to IP) that occurs within 30 days after stopping the IP, the SAE must be reported in accordance with procedures specified in this protocol. In the event of death, if an autopsy is performed, a copy of the report should be sent to TI, if available.

As required, the Sponsor or designee (e.g., TI) will notify participating investigators of all suspected adverse reactions that are serious and unexpected. This notification will be in the form of an IND safety report of potential serious risks as soon as possible but no later than 15 calendar days after the Sponsor determines that the information is "reportable" according to the criteria listed in 21 CFR Section 312.32. These are:

i) Serious and unexpected suspected adverse reactions;
ii) Findings from other studies including epidemiological studies, pooled analyses, or other clinical studies that suggest a significant risk in humans exposed to the IP;
iii) Findings from animal or in vitro tests that suggest a significant risk to humans exposed to the IP, or reports of significant organ toxicity at or near the expected human exposure; and
iv) Clinically important increases in the rate of occurrence of serious suspected adverse reactions.

Upon receiving such notices, the investigator must review and retain the notice with the IB and promptly submit a copy of this information to the responsible IRB according to local regulations. The investigator and IRB will determine if the informed consent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information. Where required, submission of safety updates by the investigator to Health Authorities should be handled according to local regulations.

The Sponsor or designee may be required to report certain SAEs to regulatory authorities (e.g., United States FDA, National Health Authorities) within 7 calendar days of being notified about the event; therefore, it is important that investigators submit any information requested by the Sponsor or designee as soon as it becomes available.

14.4 Laboratory Test Abnormalities

Any laboratory test results that are outside of normal ranges will be reviewed using the CTCAE version 5.0 classification and by the investigator for clinical significance. Post-baseline, any CTCAE Grade 2 findings or new or worsening clinically significant laboratory test results that meet the criteria for an AE (see Section 14.1) or SAE (see Section 14.3) must be recorded on the AE eCRF, in addition to being recorded on the appropriate laboratory test results eCRF and the original laboratory report, as applicable. In these cases, TI will typically require additional information about the clinically significant abnormality, including information regarding relationship to IP, any action taken, and outcome. Clinically significant laboratory abnormalities that qualify as SAEs must be reported to the Sponsor and IRB as per Section 14.3.

Any clinically significant laboratory test result that meets the criteria for an AE (see Section 14.1) or SAE (see Section 14.3) must be recorded on the AE eCRF, in addition to being recorded on the appropriate laboratory test results eCRF and the original laboratory report, as applicable. In these cases, TI will typically require additional information about the clinically significant abnormality, including information regarding relationship to IP, any action taken, and outcome. Clinically significant laboratory abnormalities that qualify as SAEs must be reported to the Sponsor and IRB as per Section 14.3.

14.5 Pregnancy

Subjects who are sexually active with a female partner and are not surgically sterile (vasectomy performed at least 6 months prior to treatment) must agree to refrain from sperm donation for at least 90 days following completion of study treatment and inform their female sexual partner to use a highly effective form of birth control as described in the informed consent form. Female partner must be confirmed according to subject to be non-pregnant at Visit 1/Screening and Visit 2/Baseline or at the visit when a subject identifies a new sexual partner. Prior to study enrollment, subjects must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

For female partners of males in the study, highly effective forms of birth control include 1) IUD (copper or hormonal); 2) implantable hormonal contraception; 3) surgical sterilization (i.e., hysterectomy, tubal ligation, or bilateral oophorectomy) performed at least 6 months prior to the subject's study entry; 4) total abstinence; or 5) using one of each of the following a) hormonal contraceptives [other than IUD or implantable, e.g., oral, transdermal, injectable, or vaginal ring] and b) double barrier methods [i.e., male or female condom, diaphragm with spermicidal foam/gel/film/cream/vaginal suppository, cervical cap with spermicides, or contraceptive sponge]. For males, adequate forms of contraception include condom and spermicide in combination with other forms of female contraception.

During the study, all subjects should be instructed to contact the investigator immediately if they suspect that their sexual partner might be pregnant (e.g., female sexual partner has missed or late menstrual period).

If the subject suspects that their sexual partner may be pregnant at any time during the study, or if following initiation of study treatment, it is subsequently discovered that a trial subject's sexual partner was pregnant or may have been pregnant at the time of IP exposure, the investigator must immediately notify the IRB of any pregnancy associated with the study treatment and keep careful source documentation of the event, including abortion (accidental, therapeutic, or spontaneous) and birth of offspring. Offspring should be followed for a minimum of 8 weeks and any congenital anomaly/birth defect in a child born to a subject's sexual partner that was exposed to the IP(s) should be documented.

15. BLINDING/UNBLINDING

This is a double-blind, randomized, placebo-controlled study. Blinding is important for the integrity of this clinical study. IPs will be packaged in identical bottles so that neither the subject, investigator nor site staff will know the identity of the contents. However, the blind may be broken in the event of a medical emergency in a subject, in which knowledge of the IP identity is critical to the subject's management. Before breaking the blind for a subject, the investigator should determine that the information is necessary (i.e., that it will alter the subject's immediate management). In many cases, particularly when the emergency is clearly not IP related, the problem may be effectively managed by assuming that the subject is receiving active product without the need for unblinding. The need to break the blind should first be discussed with the responsible Medical Monitor and the best method to do this will be determined.

The Investigator will be able to determine the treatment allocation for an individual subject using the emergency unblinding function of the IWRS.

16. CLINICAL SUPPLIES

16.1 Investigational Product Information

IPs will be packaged and labeled by the Sponsor or designee. Detailed information on the packaging/labeling, blinding/unblinding, storage and preparation, dispensing, accountability, etc. is included in Appendix 3.

16.2 Supplies Provided by Therapeutics, Inc.

- eCRFs
- Source document draft templates
- Site regulatory binder
- Urine drug screen tests
- Saliva alcohol screen tests

16.3 Supplies Provided by Investigator

- Urine collection containers for drug screen tests
- Centrifuge, per laboratory requirements, to process blood samples
- Ultra-low freezer for storage of plasma samples

16.4 Supplies Provided by the Clinical Laboratory

- Supplies to collect and transport urine and blood samples to the clinical laboratory
- Tubes and labels for plasma aliquots for PK analysis

16.5 Supplies Provided by Canfield Scientific

- Imaging equipment to perform the global and macro photography and related supplies
- Photo archive
- Micro-dot tattoo supplies

17. STATISTICAL CONSIDERATIONS

17.1 Estimands for Efficacy Endpoints

Treatment conditions of interest	Condition under study: AGA in males. IPs: • 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	The **primary endpoints** will be changes from Baseline in non-vellus TAHC using digital image analysis at Week 16, and the subject's evaluation of treatment benefit via the HGA questionnaire at Week 16. The **secondary endpoints** will be: 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.

17.2 Sample Size

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

17.3 Endpoints

17.3.1 Efficacy 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 Endpoints:

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.

17.3.2 Safety Endpoints

1. Incidence (severity and causality) of any local and systemic AEs.
2. Number of subjects with presence (and severity) of the following 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 ECG parameters and overall ECG interpretation at Week 4, Week 8, Week 12, and Week 16.

17.3.3 Pharmacokinetic Endpoints

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

17.4 Statistical Methods

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.

The Safety population will include all randomized subjects who received and applied the IP. The intent-to-treat (ITT) population will include all randomized subjects who were dispensed the IP. 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. The PK population will include those subjects in the ITT population with at least 1 measurable concentration value.

17.4.1 Efficacy Analyses

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

17.4.1.1 Primary Efficacy Analyses

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 will be presented for pairwise comparisons of treatment groups.

The HGA will be evaluated at Week 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 both non-vellus and vellus quantitative hair measurements.

17.4.1.2 Secondary Efficacy Analyses

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.

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

17.4.1.3 Dosing Compliance

Descriptive statistics will be used to summarize the total number of applications for the ITT and PP 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.

17.4.1.4 Subgroup Analyses

No subgroup analyses are planned.

17.4.2 Safety Analyses

The safety analyses will be conducted on the Safety population.

17.4.2.1 Extent of Exposure

Descriptive statistics will be used to summarize the extent of exposure in the Safety population. The duration of treatment (date of final application minus date of first application plus 1), the total amount of IP used (difference between the weight of the IP dispensed and weight of IP returned), and the mean daily amount of IP applied (total amount of IP applied divided by the duration of treatment) will be calculated.

17.4.2.2 Physical Examination

Findings from physical examinations will be recorded in medical history (from assessment at Screening and Baseline) or as AEs (from assessments after first dose).

17.4.2.3 Vital Signs

Descriptive statistics of vital signs (temperature, systolic and diastolic blood pressure, heart rate, and respiration rate), including height, weight, and BMI will be provided by treatment group.

17.4.2.4 Electrocardiograms

ECGs will be evaluated for any material changes during the study period. Descriptive statistics of ECG parameters will be provided by treatment group. Changes in overall interpretation of the ECG from Baseline to Weeks 4, 8, 12, and 16 will be examined using shift tables.

17.4.2.5 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.

17.4.2.6 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.

17.4.2.7 Adverse Events

All AEs reported during the study will be listed, documenting course, severity, investigator assessment of the relationship to the IPs, and outcome. Verbatim terms on the eCRFs will be linked to preferred terms (PTs) and system organ class (SOC) using the MedDRA mapping system. 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.

17.4.3 Pharmacokinetic Analyses

A PK analysis will be conducted on the PK population.

PK results will be summarized using descriptive statistics for each active treatment group.

17.5 Interim Analyses

No interim analyses are planned.

18. ETHICAL AND REGULATORY CONSIDERATIONS

18.1 Compliance with Good Clinical Practice

This study will be conducted in compliance with the principles of the Declaration of Helsinki, with the current Good Clinical Practice guidelines and with other applicable regulations. The investigator and all study staff will conduct the study in compliance with this protocol. The protocol, informed consent documents, recruitment advertisements, and any amendments to these items will have IRB approval, where required, prior to study initiation. Voluntary informed consent will be given by every subject prior to the initiation of any study-related procedures. The rights, safety and well-being of the study subjects are the most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training, and experience to perform their assigned responsibilities. Contact information for each site and any clinical laboratories used in the study will be maintained up to date in a separate reference document.

18.2 Institutional Review Board and Informed Consent

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to the subject. The investigator should also provide the IRB with a copy of the product labeling, information to be provided to the subject and any updates. The investigator will submit documentation of the IRB approval to TI.

The IRB approved consent form must include all elements required by FDA or other national health authorities, state, and local regulations, and may include appropriate additional elements.

The investigator/designee will explain the study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The investigator must provide the subject with a copy of the consent form, in a language the subject understands.

The investigator will maintain documentation that informed consent was obtained prior to the initiation of any study-specific procedures.

18.3 Protocol Compliance

The IRB approved protocol must be followed except in the case of a change that is intended to eliminate an immediate risk to subjects. All protocol deviations must be documented.

18.4 Protocol Revisions

TI must prepare all protocol revisions. All protocol amendments must receive IRB approval prior to implementation. All administrative letters must be submitted to the IRB for their information. Copies of all correspondence with the IRB regarding this study must be sent to TI.

New or altered consent forms required by the IRB due to a protocol change must be signed by all subjects currently enrolled in the study and must be used for any subsequent subject enrollment.

18.5 Study Monitoring

Representatives of TI and/or the Sponsor must be allowed to visit all study sites, to review study records, and to directly compare them with source documents (including, but not limited to patient and hospital records), to discuss the study conduct with the investigator and study staff, and to verify that the investigator, study staff, and facilities remain acceptable for the conduct of the study. This study may incorporate the use of remote monitoring activities. To facilitate remote monitoring visits, the Investigator or designee may be requested to upload copies of study-related source documents to a secure file share portal. Where necessary, the investigator or designee shall de-identify patient Protected Health Information in accordance with the safe harbor method defined in 45 CFR 164.514.

Representatives of government regulatory authorities may also evaluate the study records, source documents, investigator, study staff, and facilities.

The investigator should immediately notify TI of any audits of this study by any regulatory agency and must promptly provide copies of any audit reports.

18.6 Case Report Form Requirements

For eCRFs, validated 21 CFR Part 11 compliant electronic data capture (EDC) software will be used to collect data. All requested information must be entered on the eCRFs in the areas provided in a timely manner. When changes or corrections are made in the eCRF, the EDC system will maintain a complete audit trail of the person making the changes, the date and time of the change, and the reason for the change. Only individuals who have completed EDC training and are listed on the Delegation of Responsibilities Log with responsibility for eCRF completion will be provided usernames and passwords in order to access the system and make entries on the eCRF.

The investigator or physician sub-investigator must electronically sign and date each subject's eCRF. Individuals who will be providing electronic signatures must first submit documentation

with a handwritten signature acknowledging that their electronic signature is a legally binding equivalent to their handwritten signature.

18.7 Reports to Institutional Review Board

The investigator should provide the IRB with reports, updates, and other information (e.g., safety updates, protocol amendments, and administrative letters) according to regulatory requirements or Institution procedures.

18.8 Quality Assurance Audits

Representatives from TI and/or the Sponsor or a third party selected by the Sponsor may conduct a quality assurance audit of this study. During the audit, the investigator must provide the auditor with direct access to all relevant documents and discuss any findings with the auditor.

In the event of an inspection by the FDA, National Health Authorities, or other regulatory authorities, the investigator must give the inspector direct access to relevant documents and to discuss any findings with the inspector. The investigator must notify TI in the event of a site audit by the FDA and/or other regulatory authority.

18.9 Records Retention

The investigator must maintain all study records (including IP disposition, informed consents, eCRFs, source documents, correspondence, regulatory documents, contracts, etc.) for the maximum period required by TI or the institution where the study is conducted, whichever is longer. Original IP Accountability Logs must be kept with study records at the site.

The investigator must contact TI or the Sponsor prior to destroying any records associated with this study.

If the investigator withdraws from the study, the records shall be transferred to a mutually agreed upon designee. Written notification of such a transfer must be given to TI.

18.10 Record Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject, except as necessary for monitoring by TI or the Sponsor, the FDA, National Health Authorities, or other regulatory authority, or the IRB.

The investigator and all employees and coworkers involved with this study shall not disclose or use for any purpose other than performance of the study, any data, records, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written

agreement from TI or the Sponsor must be obtained for the disclosure of any said confidential information to other parties.

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APPENDIX 1 SAMPLE SUBJECT INSTRUCTION SHEET

Copies of the following sample subject instructions will be provided to the study site. The investigator must give each subject a copy of this instruction sheet at Visit 2/Baseline prior to dispensing the IP.

SAMPLE SUBJECT INSTRUCTION SHEET
PROTOCOL 239-11651-203

Please follow these instructions carefully. Contact the study staff at the telephone number noted below if you have any questions about the study:

Contact:_____ At:_____

Please apply the study medication to the balding areas of your scalp
ONCE DAILY at approximately the same time as Day 1 application every morning.

STUDY MEDICATION APPLICATION INSTRUCTIONS:

1. Wash the scalp with your typical shampoo and dry the hair each morning before your daily study medication application.
2. For those days when you have a clinic visit, remember to bring your study medication supplies with you to the clinic.
3. Wash and dry your hands thoroughly.
4. Apply 1 mL of the study medication to the balding and thinning areas of your scalp using the provided dropper (see directions below on using the dropper).
5. Spread the solution evenly over the hair loss area and **gently massage** the solution into the scalp with an emphasis over the entire balding area and adjacent regions with thinning hair. It may be helpful to apply the study medication in front of a mirror.
6. Wash and dry your hands thoroughly after application.
7. Record the date and time of study medication application in your Subject Diary. If the full 1 mL was applied, check YES box indicating that the full dose was applied. If the full 1 mL dose was not applied, check NO and include an explanation as to why the full dose was not applied.
8. If you miss a dose, record MISSED in your Subject Diary and then, apply the next dose at the regular time. Apply the dose at approximately the same time every morning.
9. Continue use of the study medication unless directed otherwise by the study doctor. Contact the study staff or study doctor at the number above if you have questions or before stopping use of the study medication for any reason.

USING THE DROPPER APPLICATOR:

1. Each unit dose dropper contains enough study medication to dispense approximately 1 ml of solution.
2. Remove the cap.
3. Invert the dropper with the tip side down over the area of the scalp to be treated.
4. Study medication may be applied as a:
   i) Grouping of Single Drops - which may be dispensed by holding the dropper over the affected area of the scalp and as necessary gently squeezing the unit dose dropper, and/or

ii) Single Line of Solution – which may be applied by (i) parting the thinning hair (or use an imaginary line on the bald scalp), (ii) place the dropper tip on to the scalp surface at the top of the part, (iii) keeping the tip in contact with the scalp along the part as you gently squeeze the unit dose dropper while you advance the dropper along the entire part line.

NOTE: apply only a few drops or a fine line of solution, one at a time, to avoid having the study medication drip off your scalp then proceed to Step #5

5. After applying the study medication, spread the solution evenly over the hair loss area and gently massage the solution into the scalp.
6. Repeat steps 4 and 5 focusing on all bald and thinning scalp areas not treated with the solution until all areas of balding are treated AND the entire content of the unit dropper is used.

REMINDERS:

- Only apply the study medication as directed by the study doctor.
- **Do not wash the treated area, bathe, shower, swim, or have exposure to water for at least approximately 4 hours following application of the study medication.**
- **Avoid rigorous exercise for at least approximately 4 hours following application of the study medication.**
- **Avoid wearing a cap or hat within at least approximately 30 minutes following application of the study medication.**
- **General hair care products and regimen must be continued for the entire study.**
- Store the study medication according to the instructions on the label.
- Bring all containers of the study medication (used and unused) and the completed Subject Diary to each visit.
- Do not allow anyone else to use the study medications: keep containers of study medication away from children/pets. Avoid inadvertent transfer of the study medication to close contacts.
- If skin irritation develops, contact the study site immediately.
- Avoid contact with eyes and all mucous membranes. If contact with eyes occurs, rinse thoroughly with water. If inadvertent transfer of the study medication occurs with a close contact, such areas of contact should be washed with soap and water as soon as possible.

STUDY VISIT SCHEDULE:

Visit 3	Visit 4	Visit 5 Phone	Visit 6	Visit 7 Phone	Visit 8	Visit 9	Visit 10
Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:	Date: Time:

APPENDIX 2 SAMPLE SUBJECT DIARY

A copy of the following sample Subject Diary will be provided to the study site. The investigator must give each subject a copy of this Subject Diary at Visit 2/Baseline and all follow-up visits, as necessary.

PROTOCOL:	SITE:	SUBJECT NO.:	INITIALS:
239-11651-203	_____ _____	_____ _____ _____	_____ _____ _____

SAMPLE SUBJECT DIARY

Contact the study staff at the telephone number below if you have any questions.

Contact: _____ At: _____

Please apply the study medication to the balding areas of your scalp
ONCE DAILY at approximately the same time as Day 1 application every morning.

Day 1 Application Time: _____ **:** _____ AM

After dosing, record the date and time of the study medication application.
If you miss a dose, write *MISSED* in the space for time.

DATE (dd/MMM/yyyy)	TIME		Full Dose Applied		If No, Explain
	12-hour clock	Circle One			
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	

BACK OF SAMPLE SUBJECT DIARY

/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	
/ /	:	AM / PM	☐ Yes	☐ No	

Next Appointment: _____ _____/_____/_____at _____AM/PM
Weekday dd MMM yyyy

Site Use Only:	**Diary Dispensed at:**	**Date Dispensed:**	**Date Returned:**
	☐ Visit 2 ☐ Visit 3 ☐ Visit 4 **☐ Visit 6 ☐ Visit 8**		

APPENDIX 3 INVESTIGATIONAL PRODUCT INFORMATION

A 3.1 Investigational Product Packaging and Labeling

The IP will be packaged and labeled by the Sponsor or designee. The different concentrations of TDM-105795 solution and Placebo will be packaged in identical unit dose droppers contained within labeled Subject Kits.

Each dropper of the IP within the kit will contain, at a minimum, the following information: the protocol number, kit number, the contents, storage conditions, and an investigational IP disclaimer (e.g., Caution: New Drug Limited by Federal (or United States) Law to investigational use).

Subject Kit labels must be completed entirely with the necessary information and recorded in the IP Accountability Log at the investigational site. In the event of an emergency, the contents of the kit can be unblinded using the proper procedures as outlined in the protocol (see Section 15) and by instructions provided to the site.

A 3.2 Investigational Product Storage and Preparation

IPs will be stored under secure conditions until they are dispensed to the subjects. IPs should be stored in accordance with the temperature specified on the label.

A 3.3 Dispensing Investigational Product

Sites will receive shipments of IP kits from the Sponsor or designee. Subjects who are eligible for enrollment into the study will be randomized using the IWRS and dispensed the kit numbers assigned by the IWRS. Subjects will be dispensed two kits each containing 20 unit dose droppers of the IP on a monthly basis for the duration of the treatment phase. In the event that the "use by" date of the IP will be reached prior to the next scheduled visit, subjects should contact the study site to arrange for a fresh supply.

The IP must be dispensed only to study subjects and only at study sites specified on the signed 'Statement of Investigator' (e.g., Form FDA 1572 or equivalent) required by applicable regulations and guidelines.

Each unit dose dropper will deliver ~1 mL per application and will be provided to the subject in a storage container.

Information will be recorded on the IP Accountability Log. Prior to dispensing to the subject, the total group of unit dose droppers will be weighed. The subjects will be instructed to bring all droppers of the IP (used and unused) to each clinic visit.

At each post-Baseline visit, site staff will collect all droppers (used and unused) of the IP and record the necessary information in the IP Accountability Log. Site staff will review the IP application procedure and subjects will be counseled on IP compliance, as necessary. Any

discrepancies or concerns with the subject regarding the use of the Subject Diary to record IP applications should be addressed. At the end of subject's participation in the treatment phase, the total group of returned unit dose droppers will be weighed.

A 3.4 Investigational Product Supply Records at Study Sites

It is the responsibility of the investigator to ensure that a current record of IP disposition is maintained. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of the person responsible for each product inventory entry/movement.
- Amount (number and units and weights) dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount returned to Sponsor.
- Amount destroyed at study site, if applicable.

TI will provide forms to facilitate inventory control if the staff at the study site does not have an established system that meets these requirements.

A 3.5 Dose Modifications

The subject should not modify the treatment regimen without consultation with the Investigator. Subjects should be instructed to discontinue use if skin irritation or rash develops and to contact the study site immediately. In the event that the Investigator believes that dose modification is necessary (e.g., problems with tolerance), the subject's care should be discussed with the Medical Monitor prior to making any dose modifications. All dose modifications must be reported on the appropriate eCRF.

A 3.6 Documentation of Application and Compliance

The date of the first and last application of the IP will be recorded on the appropriate eCRF. Dosing times relative to PK blood draws will also be collected in the appropriate eCRF. An eCRF will also be used to record any changes from the application specified in the protocol (e.g., investigator directed reduction in application frequency or drug holiday).

A Subject Diary will be dispensed to subjects to record the dates and times of all applications and to record any missed doses of the IP (Appendix 2). Subjects will be instructed to bring the Subject Diary with them to each study visit.

A 3.7 Return and Destruction of Investigational Product Supplies

Upon completion or termination of the study, all remaining IP containers must be a) returned to the Sponsor or designee by a traceable method for final accountability and destruction or b) appropriately destroyed in accordance with applicable regulations with the provision of a certificate of destruction. All missing containers of IP must be explained on the completed IP Accountability Log. A copy of the IP Accountability Log and Label Pages (if applicable) will be returned to the Sponsor or designee. Upon receipt of the IP, a Sponsor representative will perform a final reconciliation. TI will be notified of any missing IP.