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**Study ID:** 1922-201-002

**Title:** MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED,  
PHASE 2A STUDY OF SETIPIPRANT TABLETS IN ANDROGENETIC ALOPECIA IN  
MALES

**Protocol Amendment 1 Date:** 17-Feb-2017

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MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE  
2A STUDY OF SETIPIPRANT TABLETS IN ANDROGENETIC ALOPECIA IN MALES

Protocol Number: 1922-201-002

Phase: 2A

Name of Investigational  
Product: Setipiprant Tablets

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Serious Adverse Event  
Reporting Fax Numbers:



Approval Date: 17-Feb-2017

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Contact Information:

[REDACTED]

Allergan Signatory:

[REDACTED]

Refer to the final page of this protocol for electronic signature and date of approval.

The following information can be found on FDA Form 1572 and/or study contacts page: Name and contact information of Allergan study personnel and Emergency Telephone Numbers; name, address, and statement of qualifications of each investigator; name of each subinvestigator working under the supervision of the investigator; name and address of the research facilities to be used; name and address of each reviewing IRB; US 21 CFR 312.23 section 6(iii)b.

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**INVESTIGATOR SIGNATURE PAGE**

INVESTIGATOR:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices, and all applicable laws and regulations.
- Maintain all information supplied by the sponsor in confidence and, when this information is submitted to an institutional review board (IRB), independent ethics committee (IEC) or another group, it will be submitted with a designation that the material is confidential.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

I have read this protocol in its entirety and I agree to all aspects.

---

Investigator Printed Name

---

Signature

---

Date

Approval Date: 17-Feb-2017

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[illegible]



## Protocol Summary

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**Study Compound:** Setipiprant, a tetrahydropyridoindole derivative

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**Phase:** 2a

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### Study Objectives

1) To evaluate the safety, tolerability, and efficacy of oral administration of setipiprant tablets 1000 mg twice daily (BID) relative to placebo in males with androgenetic alopecia (AGA) who are 18 to 49 years old and in generally good health.

[REDACTED]

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### Clinical Hypotheses

- Setipiprant tablets 1000 mg BID have an acceptable safety profile following oral administration for 24 weeks.
  - Setipiprant tablets 1000 mg BID are more effective than placebo in increasing hair growth, as measured by the change from baseline in target area hair count (TAHC) in terminal hairs/cm<sup>2</sup> using digital image analysis at 24 weeks after oral administration.
  - Setipiprant tablets 1000 mg BID are more effective than placebo in increasing scalp hair growth, as measured by the distribution of the Subject Self-Assessment (SSA) scores using a 7-point scale at 24 weeks after oral administration.
- 

### Study Design

*Structure:* Multicenter, randomized, double-blind, placebo-controlled study designed to determine the effect of treatment with setipiprant tablets 1000 mg BID on scalp hair growth as assessed by objective (ie, imaging-based) and subjective (ie, [REDACTED] subject-reported) measures.

*Duration:* Approximately 32 weeks (enrollment through exit)

*Study Treatment Group:* Setipiprant tablets 1000 mg BID

*Control:* Placebo BID

*Dosage/Dose Regimen:* Setipiprant tablets 1000 mg BID or placebo tablets BID

*Enrollment/Stratification:*

- [REDACTED]
  - [REDACTED] subjects will be randomized in a 1:1 ratio to receive setipiprant tablets 1000 mg BID or placebo BID, and stratified by baseline age 18 to 34 and 35 to 49 years.
- [REDACTED]
- 

### Study Population Characteristics

*Number of Subjects:* Approximately 187 will be enrolled in up to 20 US sites

*Condition/Disease:* Androgenetic alopecia with vertex patterns IIIv, IV, or V as assessed with the Norwood-Hamilton Hair Loss Scale (NHS)

*Key Inclusion Criteria:*

- Male subjects in generally good health, aged 18 to 49 years (inclusive)
  - Androgenetic alopecia with vertex patterns IIIv, IV, or V on the NHS
  - [REDACTED]
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*Key Exclusion Criteria:*

- History or evidence of hair loss for reasons other than AGA
- Scarring of the scalp or any condition or disease of the scalp, hair, or hair shaft ( [REDACTED] )

**Response Measures**

*Coprimary Efficacy Measures:* change from baseline in TAHC of terminal hairs/cm<sup>2</sup> as measured using digital image analysis and subject self-assessment of change from baseline in hair growth as measured by the distribution of SSA scores

**General Statistical Methods and Types of Analyses**

Two analysis populations are defined: modified intent-to-treat (mITT) and safety. The mITT population, consisting of all randomized subjects who have a baseline and at least 1 postbaseline primary efficacy measurement, will be used for analyses of efficacy data based on the randomized treatment group. The safety population, consisting of all treated subjects, will be used for analyses of all safety data based on the actual treatment received. Hypothesis testing will be 2-tailed with a significance level of 0.05. Pairwise comparisons of setipiprant tablets 1000 mg BID versus placebo will be made. The finasteride subjects enrolled prior to protocol Amendment 1 will be summarized alone and will not be included in the analysis models to compare with the other treatment groups. For all efficacy analyses, no adjustment of significance levels will be made for multiplicity of treatment comparisons.

*Efficacy Analyses:* The 2 coprimary efficacy variables are: 1) change from baseline in TAHC of terminal hairs/cm<sup>2</sup> within a 1 cm<sup>2</sup> circular area on the left side at Week 24; and 2) SSA of change from baseline in hair growth at Week 24. The 2 coprimary efficacy variables will be analyzed using an analysis of covariance (ANCOVA) model with treatment (excluding the finasteride group as described above) as a fixed effect and age and baseline value as covariates (if applicable). The treatment difference for setipiprant tablets 1000 mg BID versus placebo BID will be constructed based on this ANCOVA model, along with the 2-sided p-value.

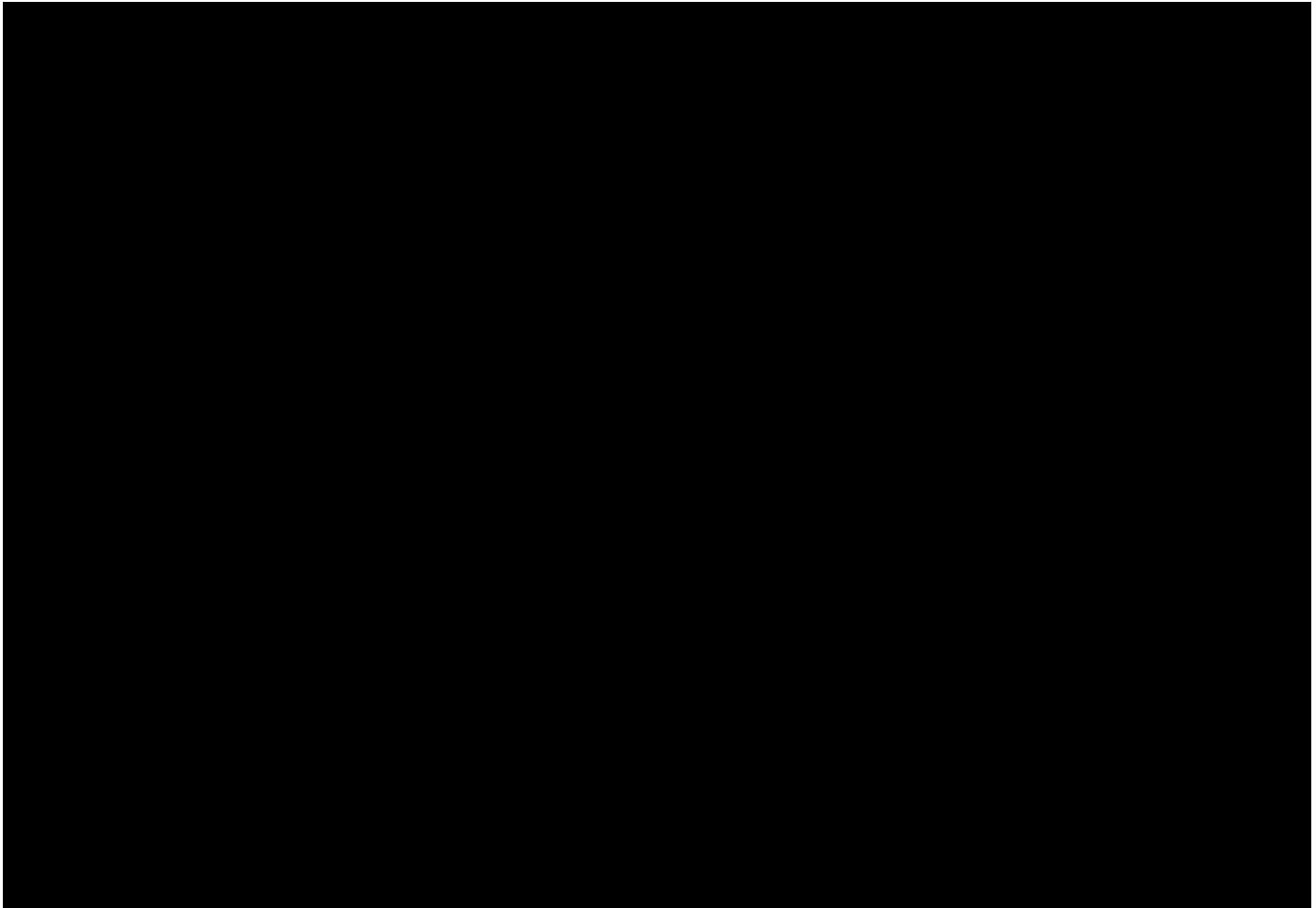
[REDACTED]. Missing data of TAHC and SSA will be imputed up to Week 24 using last observation carried forward (LOCF).

*Safety Analyses:* All safety analyses will be performed on the safety population. Adverse events will be coded from the verbatim text into preferred term (PT) and primary system organ class (SOC) by using the Medical Dictionary for Regulatory Activities. The number and percent of subjects reporting treatment-emergent AEs at least once regardless of causality will be tabulated. Similarly, treatment-related AEs will be tabulated. The tables will be generated by primary PT and SOC as well as by severity. Safety data will be summarized by frequency distributions or descriptive statistics and described in the detailed analysis plan.

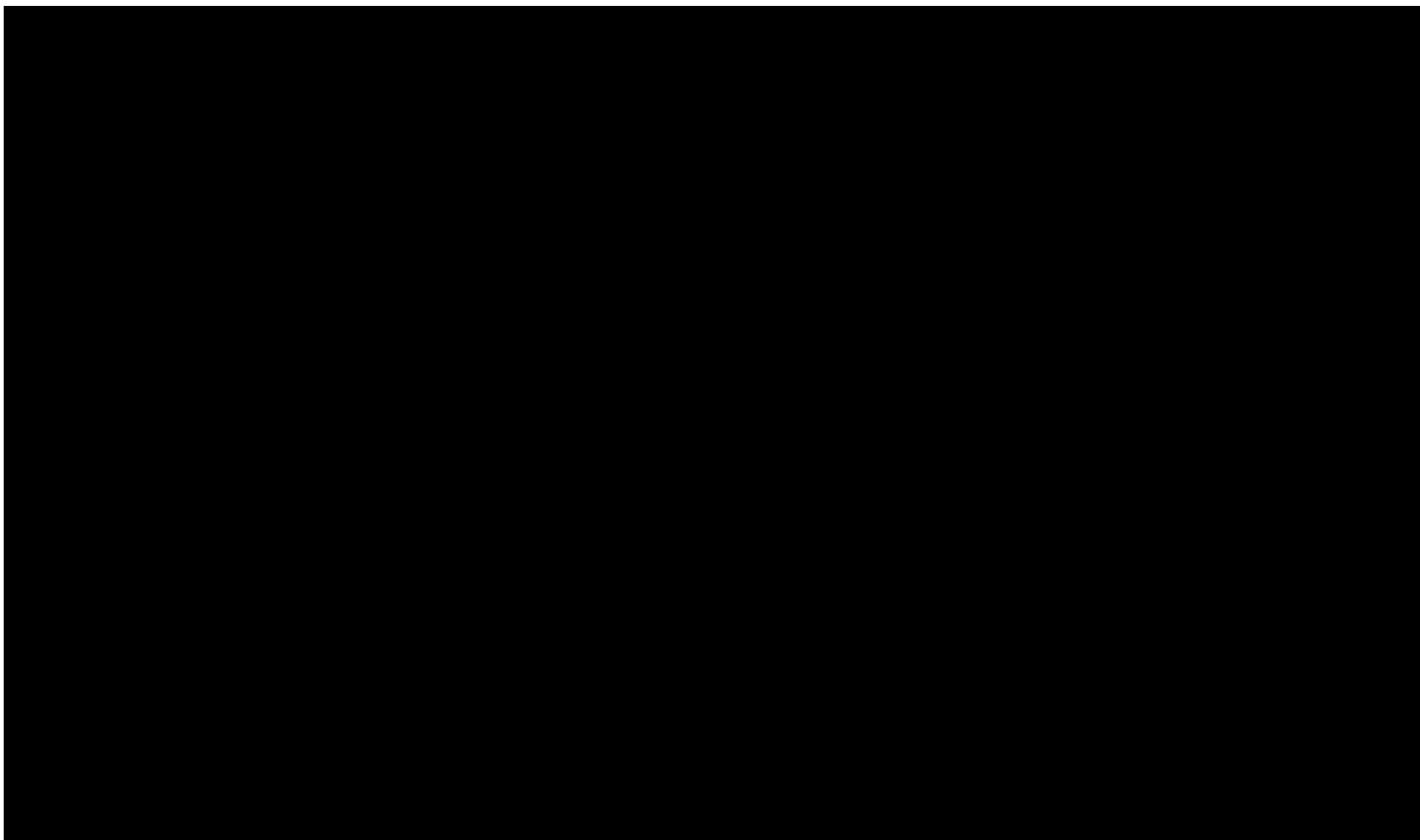
[REDACTED]

*Sample Size Calculation:* The study plans to enroll approximately 152 subjects in the setipiprant 1000 mg BID (n = 80) and placebo BID (n = 72) groups. Of the 152 subjects to be enrolled, 12 subjects will be randomized to the [REDACTED] The remaining 140 subjects will be randomized at 1:1 ratio and stratified by baseline age group (18 to 34 and 35 to 49 years). [REDACTED]

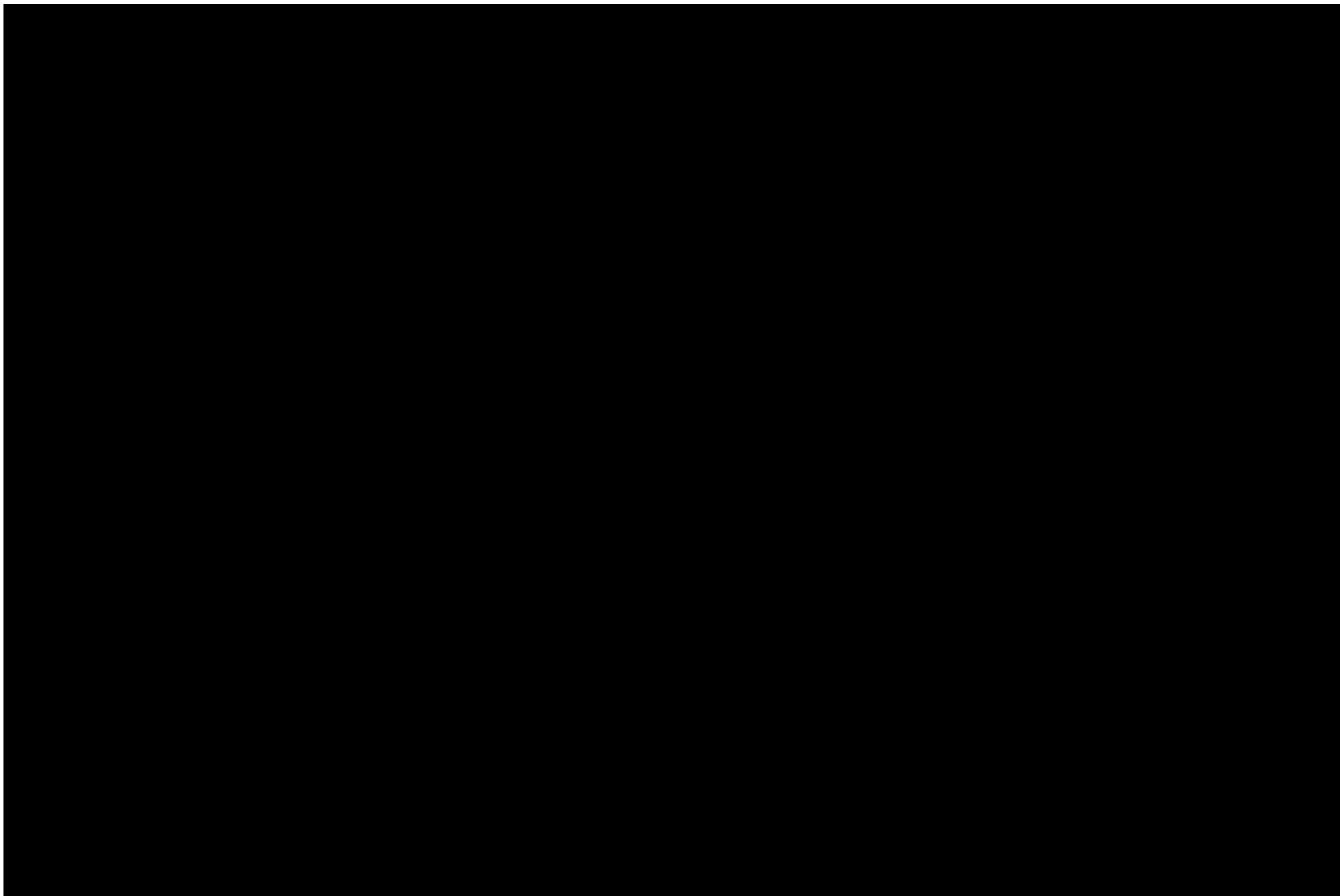
[REDACTED]

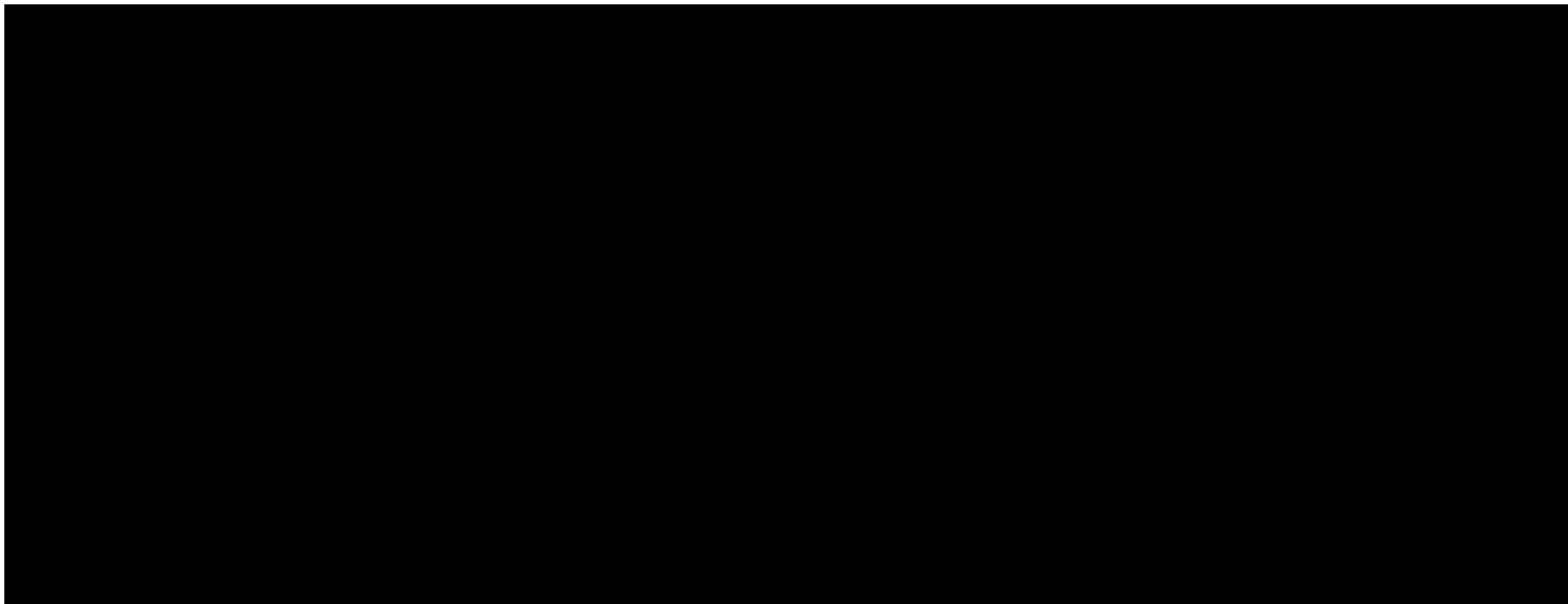


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## 1. Background and Clinical Rationale

Androgenetic alopecia (AGA) is the most prevalent cause of hair loss in both men and women (Sinclair, 1998; Severi et al, 2003; Stough et al, 2005). It has been estimated that across the lifespan of a person, AGA may affect approximately 70% of men and 40% of women (McElwee and Shapiro, 2012). For many among those affected by AGA, research suggests that negative psychological effects can occur as a result of the condition (Tabolli et al, 2013). As such, the field of dermatology has had a high interest in developing effective treatments for AGA. Currently available treatment options provide some clinical benefit in treating AGA. However, monotherapy with these agents provide either limited efficacy or have been associated with unfavorable side effect profiles (Falto-Aizpurua et al, 2014; DiLoreto et al, 2014; Altomare et al, 2002; Caruso et al, 2015). Finasteride is approved only for male patients. Thus, innovative treatment approaches are needed in the search for agents that provide improved efficacy and tolerability for treatment of subjects with AGA.

Research suggests a role of the prostaglandin pathway in the inhibition of hair growth and is based on the following findings: a) the level of prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) in the balding scalp of men with AGA is significantly elevated when compared with the level in nonbalding scalp in the same individual; b) PGD<sub>2</sub> blocks the growth of human hair follicle mini organ in ex vivo cultures; and c) topical application of PGD<sub>2</sub> to the back of wild type mice prevents hair growth (Garza et al, 2012). The enzyme responsible for synthesizing the agonist to PGD<sub>2</sub>, prostaglandin-D<sub>2</sub> synthase (PTGDS), is expressed in nonpermanent keratinocytes of the human hair follicle (Garza et al, 2012). Mice genetically engineered to overexpress the mouse PTGDS homolog (ptgs2) are unable to grow hair suggesting that increased PGD<sub>2</sub> prevents hair growth (Garza et al, 2012). The G-protein-coupled receptor for PGD<sub>2</sub> is a chemoattractant receptor-homologous molecule expressed on T helper 2 cells (CRTH2). CRTH2 is expressed in the dermal papilla and outer root sheath cells of human hair follicles (Colombe et al, 2008). In CRTH2 knockout mice, hair growth is insensitive to topical PGD<sub>2</sub> application, thereby suggesting that the growth inhibitory effect is mediated by the CRTH2 receptor (Garza et al, 2012). The growth inhibitory effect of PGD<sub>2</sub> can be abolished in human hair follicle mini organ culture with CRTH2 antagonists (Cotsarelis et al, 2015a).

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Setipiprant effectively prevents PGD<sub>2</sub>-induced hair growth inhibition in human hair follicle mini organ cultures ([Cotsarelis et al, 2015b](#)). Thus, the purposes of this study include the use of the

study data to develop a better understanding of whether setipiprant tablets are capable of treating AGA in males and to assist in the design of future clinical trials.

## **2. Study Objectives and Clinical Hypotheses**

### **2.1 Study Objectives**

The study objectives are:

1) To evaluate the safety, tolerability, and efficacy of oral administration of setipiprant tablets 1000 mg BID relative to placebo in males with AGA who are 18 to 49 years old and in generally good health.

[REDACTED]

### **2.2 Clinical Hypotheses**

- Setipiprant tablets 1000 mg BID have an acceptable safety profile following oral administration for 24 weeks.
- Setipiprant tablets 1000 mg BID are more effective than placebo in increasing hair growth, as measured by the change from baseline in target area hair count (TAHC) of terminal hairs (1 cm<sup>2</sup> circular area) using digital image analysis at 24 weeks after oral administration.
- Setipiprant tablets 1000 mg BID are more effective than placebo in increasing scalp hair growth, as measured by the distribution of Subject Self-Assessment (SSA) scores using a 7-point scale at 24 weeks after oral administration.

## **3. Study Design**

This is a multicenter, randomized, double-blind, placebo-controlled study with an active comparator group designed to determine the effect of treatment with setipiprant tablets 1000 mg BID on scalp hair growth as assessed by objective (ie, imaging-based) and subjective (ie, investigator- and subject-reported) measures.

All investigators, site staff, and subjects will be blinded to whether subjects receive setipiprant or matching placebo during the study.

Subjects must complete all screening and baseline procedures and meet all eligibility requirements to qualify for enrollment and randomization on Day 1 when they will be randomly

assigned to 1 of 2 treatment groups (setipiprant or placebo). All subjects will self-administer the assigned study drug over a 24 week period to evaluate the safety and effects on hair growth. After randomization, subjects will return to the research facility at Weeks [REDACTED], [REDACTED] 24 for protocol-defined efficacy and/or safety assessments and procedures, confirmation of compliance with study drug usage, and new study drug dispensation (except for Week 24). A follow-up visit will occur at Week 32 (ie, 8 weeks posttreatment) or the early exit visit for protocol-defined efficacy and safety evaluations and procedures.

Safety and efficacy assessments and study procedures are outlined in the Study Design and Schedule of Assessments (Table 1). The SSA will be evaluated at Weeks [REDACTED] 24, and 32 (or early exit visit) using the subject's paired and randomly blinded screening (the screening photograph is defined as the subject's baseline) and postbaseline photographs, and at Weeks 24 and 32 (or early exit visit) using the subject's paired, unblinded screening and postbaseline photographs.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### **3.2 Data Monitoring Committee**

Although a data monitoring committee will not be established for this study, the medical safety physician (MSP) will perform an ongoing review of safety data in a blinded manner throughout the 24-week treatment period.

## **4. Study Population and Entry Criteria**

### **4.1 Number of Subjects**

Approximately 152 subjects will be randomized to 1 of 2 treatment groups (setipiprant 1000 mg BID, n = 80; placebo BID, n = 72) at up to 20 study centers in the US.

[REDACTED]

[REDACTED]

[REDACTED] Approximately 140 subjects will be randomized in a 1:1 ratio to [REDACTED] group (setipiprant 1000 mg BID, placebo BID), and stratified by baseline age, 18 to 34 and 35 to 49 years.).

[REDACTED]

## 4.2 Study Population Characteristics

Males, aged 18 to 49 years (inclusive) and in generally good health, with AGA vertex patterns IIIv, IV, or V on the Norwood-Hamilton Hair Loss Scale (NHS; [Norwood, 1975](#); A12.1.2), will be included in this study. Males aged 18 to 41 years were also assigned to finasteride prior to protocol Amendment 1.

## 4.3 Inclusion Criteria

The following are requirements for entry into the study:

1. Written informed consent
2. Written documentation in accordance with the relevant country and local privacy requirements, where applicable (eg, Written Authorization for Use and Release of Health and Research Study Information)
3. Males, aged 18 to 49 years (inclusive) and in generally good health
4. Androgenetic alopecia with vertex patterns IIIv, IV, or V on the NHS

- [REDACTED]
- [REDACTED]
6. Agreement from the subject to maintain current hair care regimen [REDACTED] [REDACTED] and refrain from hair weaving, hair colorants or dyes, and nonstudy hair growth products for the duration of the study



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## **4.5 Permissible and Prohibited Medications/Treatments**

### **4.5.1 Permissible Medications/Treatments**

Therapy considered necessary for the subject's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/treatment is in question, please contact the sponsor.

### **4.5.2 Prohibited Medications/Treatments**

The decision to administer a prohibited medication/treatment is done with the safety of the subject as the primary consideration. When possible, the sponsor should be notified before the prohibited medication/treatment is administered.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

█ [REDACTED]

█ [REDACTED]

█ [REDACTED]

█ [REDACTED]

█ [REDACTED]

█ [REDACTED]

█ [REDACTED]

█ [REDACTED]

The investigator will record details of all concomitant medication use and concurrent procedures.

#### **4.5.3 Special Activities**

Subjects must refrain from changing their hair style and hair color for the duration of the study. Excessive use of hair sprays or hair dryers should be avoided.

### **5. Study Treatments**

#### **5.1 Study Treatments and Formulations**

From randomization [REDACTED], the study drug will be dispensed for oral dosing to subjects in tablet form as follows:

Setipiprant: Two setipiprant tablets at 500 mg BID

[REDACTED]  
[REDACTED]  
[REDACTED]

## 5.2 Control Treatments

Placebo: Two placebo tablets BID

[REDACTED]

[REDACTED]

[REDACTED]

## 5.3 Methods for Masking/Blinding

Evaluation of the setipiprant and placebo treatment groups will be conducted in a double-blind manner so that neither the site personnel nor the subject is aware of which treatment is administered. Both treatments will be identical in appearance

Except when it is essential for the medical management of the subject or bioanalytical reasons (ie, to enable bioanalysis of samples only from subjects who receive active treatment), unblinding the treatment assignment will be considered a protocol deviation. Instructions for access to emergency treatment allocation information will be available by secured access to the interactive web response system (IWRS). If possible, the investigator should contact the sponsor before unblinding any subject's treatment assignment. In the event that this is not possible, the sponsor must be notified within 24 hours after the unblinding event. After unblinding, the subject will be discontinued from study drug treatment and will return for a final follow-up (ie, Week 32 or early exit visit).

## 5.4 Treatment Allocation Ratio and Stratification

[REDACTED]

[REDACTED]. The 140 subjects [REDACTED] will be randomized to setipiprant and placebo at a 1:1 ratio to be stratified by baseline age group (18 to 34 and 35 to 49 years).

## 5.5 Method for Assignment to Treatment Groups/Randomization

At screening, each subject who provides informed consent will be assigned a subject number that will serve as the subject identification number on all study documents.

At the time of randomization (ie, Day 1 [baseline] visit), eligible subjects will be randomly assigned. [REDACTED]

[REDACTED] subjects will be

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randomized in a 1:1 ratio to receive setipirant tablets 1000 mg BID or placebo BID stratified by baseline age group (18 to 34 and 35 to 49 years).

An automated IWRS will be used to manage the randomization and treatment assignment based on a randomization scheme prepared by Allergan Biostatistics.

Study medication will be labeled with medication kit numbers. The IWRS system will provide the site with the specific medication kit number(s) for each randomized subject at the time of randomization. Sites will dispense study drugs according to the IWRS instructions. Sites will also log into the IWRS at subsequent visits to obtain a study drug kit number(s) for study drugs as required. Sites will receive the IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

## **5.6 Treatment Regimen and Dosing**

Each subject will self-administer their respective treatment for 24 weeks as follows:

Setipirant and placebo regimen: Subjects will self-administer the assigned study drug (2 tablets of setipirant 500 mg or placebo) orally with water at approximately 12-hour intervals and at least 1 hour before or 2 hours after eating, eg, 1 hour before breakfast in the morning and at least 2 hours after dinner. Subjects assigned to the finasteride group prior to protocol Amendment 1 will continue treatment until they complete the study.

## **5.7 Storage of Study Drugs**

Study drugs must be stored in a secure area and dispensed only to subjects entered into the clinical study, at no cost to the subject, in accordance with the conditions specified in the protocol.

Sites should store study drugs at controlled room temperature between [REDACTED]. Sites will monitor the temperature of the storage area and report any temperature excursions as described in the study reference manual or contact the sponsor or its designee for further instructions.

Subjects will be instructed on the proper storage of study drugs and to keep it out of the reach of children. All study drug packages will have child-resistant features.

## **5.8 Preparation of Study Drugs**

Not applicable

## 5.9 Treatment Administration

From randomization through Week 24, subjects will self-administer 2 setipiprant 500 mg tablets BID or 2 placebo tablets BID.

Setipiprant and placebo packaging and dosing: Setipiprant and placebo will be packaged in blister packs containing the coated tablets and combined into a weekly wallet. Each weekly wallet of setipiprant or placebo will contain a total of 14 doses (ie, a week's worth of BID dosing).

[REDACTED]

The investigator will dispense an appropriate number of weekly wallets for the time interval until the subject's next clinic visit. Because this is a double-blind study, labeling of the subject treatment kit will not show the treatment allocation. All other information required by regulation will appear on each treatment kit.

## 6. Response Measures and Summary of Data Collection Methods

### 6.1 Efficacy Measures

Multiple products have been studied and approved for the treatment of AGA in recent years and have employed objective hair counts, cumulative width, and darkness estimates via macrophotography; independent investigator, subject, and expert panel comparative evaluations of pre- and posttreatment global photographs; and multi-item subject questionnaires. Similar procedures, assessments, and questionnaires will be utilized in this study.

To avoid introducing response bias during the study, the subject must complete the self-assessments independently and prior to evaluation by the investigator (ie, the subject-reported assessments must be completed before the investigator-reported assessments). The investigator's current or previous evaluations must not be disclosed to the subject nor must the subject be reminded of any of his previous responses provided during any assessment. For unbiased investigator assessments, subject responses must also not be disclosed to the evaluating investigator.

All staff and subjects will be blinded to whether subjects receive setipiprant or matching placebo during the study. Staff must administer all subject assessments and not divulge the results of these assessments to the evaluating investigator. The sponsor will provide guidance regarding what study personnel may say and must not say to a subject regarding any perceived improvement to avoid influencing responses on the subject-reported assessments. When possible, the evaluator(s) performing the [REDACTED] at an individual study center should perform all evaluations for a given subject, and if possible, all subjects throughout the study. In the rare event that there is a change in the assigned evaluator for a given subject, the reason for change must be documented. If it is not possible to use the same evaluator to follow a given subject, the sponsor recommends that evaluations between the primary and subsequent evaluator overlap (ie, both evaluators should examine the subject together and discuss findings without the subject present) for at least 1 visit; this should be documented.

### **6.1.1 Primary Efficacy Measures**

#### **6.1.1.1 Target Area Hair Count (Within a 1 cm<sup>2</sup> Circular Area)**

One of the coprimary efficacy measures will be the subjects' TAHC as measured in terminal hairs (1 cm<sup>2</sup> circular area on the left side) using digital image analysis (A12.1.4). [REDACTED]

The total number of terminal hairs (hair width  $\geq 30 \mu\text{m}$ ) will be calculated from macrophotographs. The target area used to count TAHC will be a 1 cm<sup>2</sup> circular area of clipped hair (length approximately 1 mm) located at the anterior leading edge of the vertex thinning area of the scalp and centered with a semipermanent microdot tattoo to ensure the same target area is reproduced at each visit.

#### **6.1.1.2 Subject Self-Assessment**

The SSA (A12.1.7) is a coprimary measure that consists of a single item that assesses each subject's perception of change in scalp hair growth. The subject uses a standardized global photograph of his scalp taken at the screening visit (the screening photograph is defined as the subject's baseline) presented side by side with a standardized global photograph taken at the postbaseline visit to give a comparative score. The photographs are presented in a blinded and randomized manner, and response options are on a 7-point ordinal scale. Refer to the imaging vendor manual for the methodology for obtaining global photographs.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

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## 6.3 Safety Measures

Safety measures will include AEs, vital sign measurements (pulse rate, blood pressure, and respiratory rate), physical examinations, 12-lead ECG, and laboratory tests (biochemistry, hematology, and urinalysis).

### 6.3.1 Adverse Events

The investigator will question the subject to ascertain whether any AEs were experienced since the previous visit. All pertinent information regarding AEs (ie, date of onset and stop, duration, outcome, severity, relationship to study drug, action or required treatment) will be obtained and recorded in the source documents and appropriately transcribed on the electronic case report form (eCRF) page.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

\_\_\_\_\_

[illegible]

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

### 6.3.6 Nonscalp Hair Growth

Starting at Week 8, subjects will be queried at each visit whether they have noticed any hair growth in nonscalp areas (yes/no) and this response will be captured in the eCRF. If judged by the investigator as clinically significant, nonscalp hair growth may be reported as an AE.

[REDACTED]

[REDACTED]

[REDACTED]

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## 6.4 Examination Procedures, Tests, Equipment, and Techniques

All study photographs will be standardized for lighting, camera angle, and position of the subject's head [REDACTED]. Images will be uploaded to a secure website made available by the photography vendor, [REDACTED] via flash drive or internet transfer. Detailed instructions for all aspects of the photography procedures will be supplied separately [REDACTED].

### 6.4.1 Semipermanent Microdot Tattoo

For standardized photography, during the Day 1 (baseline) visit, subjects will receive two 1-mm semipermanent microdot tattoos [REDACTED]

[REDACTED]. As the dots begins to fade or are at risk of fading before the next scheduled visit, they may be refreshed in the exact same locations.

### 6.4.2 Global Photographs

Two standardized global photographs (vertex target area and frontal area) will be taken at screening (the screening photograph is defined as the subject's baseline) and at Weeks [REDACTED], 24, and 32 (or early exit visit). At Weeks [REDACTED], 24, and 32 (or early exit visit), after refreshing the semipermanent microdot tattoo (if necessary) and parting and combing the hair radially away from the part, standardized global photographs of the subject's vertex target area will be presented in pairs (ie, 1 photograph taken at screening and the other photograph taken at a given treatment week [REDACTED])

[REDACTED]

### 6.4.3 Macrophotography

Macrophotography will be performed at Day 1 (baseline) and Weeks [REDACTED], 24, and 32 (or early exit visit). [REDACTED]

[REDACTED]

### 6.5 Summary of Methods of Data Collection

This study will use eCRFs using remote electronic data capture through a qualified third party vendor. The data will be entered on the eCRFs in a timely manner on an ongoing basis. The investigator is responsible for ensuring that data are properly recorded on each subject's eCRFs and related documents. An investigator who has signed the protocol signature page should personally electronically sign for the eCRFs (as indicated in the eCRFs) to ensure that the observations and findings are recorded on the eCRFs correctly and completely. A certified electronic copy of the eCRFs including data corrections will be provided to the site for archiving at the end of the study.

[REDACTED]

[REDACTED]

Approval Date: 17-Feb-2017

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 6.6 Other Study Supplies

The following will be provided by the sponsor:

- Modified NHS

The following will be provided by the investigator:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- Sterile pads
- Gloves
- Sphygmomanometer
- Equipment to measure height and body weight
- Equipment (stethoscope, otoscope, etc) to conduct physical examinations
- Internet connection (high-speed connection for eCRF completion and digital image uploads)

The following will be provided by the central laboratory:

- All supplies needed for [REDACTED]
- Shipping materials for shipment [REDACTED]

The following will be supplied by [REDACTED]:

- Standardized photography equipment, including the instruction manual
- Equipment for tattoo and shaving

[REDACTED]

- [REDACTED]

## **7. Statistical Procedures**

### **7.1 Analysis Populations**

Two analysis populations are defined: modified intent-to-treat (mITT) and safety. The mITT population, consisting of all randomized subjects who have a baseline and at least 1 postbaseline measurement for 1 of the coprimary efficacy measures, will be used for analyses of efficacy data based on the randomized treatment group. The safety population, consisting of all subjects who receive at least 1 dose of study drug (ie, all treated subjects), will be used for analyses of all safety data based on the actual treatment received. All subjects who ingest at least 1 dose of study drug will be included in the safety analysis population included in the summaries of all safety and demographic data. All efficacy variables will be summarized and analyzed using the mITT population.

### **7.2 Collection and Derivation of Primary and Other Efficacy Assessments**

The coprimary efficacy variables will be based on the following 2 measures: TAHC within a 1 cm<sup>2</sup> circular area on the left side of the scalp and SSA.

- The TAHC is a standardized objective quantification of each subject's number of terminal hairs (hair width  $\geq 30 \mu\text{m}$ ) within a 1 cm<sup>2</sup> target circular area on the left side located at the anterior leading edge of the vertex thinning area of the scalp using digital image analysis.
- The SSA score is the subject's assessment of change of hair growth, scored on a 7-point scale ( $-3$  = greatly decreased,  $-2$  = moderately decreased,  $-1$  = slightly decreased,  $0$  = remained the same,  $+1$  = slightly increased,  $+2$  = moderately increased, and  $+3$  = greatly increased). The analyses of the SSA from the blinded photograph assessments will be based on the actual change from the screening photographs (ie, if the postbaseline photograph is used as Photo A, the assessment score will be reversed for analyses).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Approval Date: 17-Feb-2017

[REDACTED]

[REDACTED]

[REDACTED]

### 7.2.1 Primary Efficacy Variables

The 2 coprimary efficacy variables are based on the measurements of TAHC and SSA (blinded).

- Change from baseline in TAHC within a 1 cm<sup>2</sup> target circular area on the left side located at the anterior leading edge of the vertex thinning area of the scalp at Week 24
- Subject Self-Assessment of change from baseline in hair growth as viewed on the subject's paired (before and after presented in a blinded fashion) global photographs of the vertex target area at Week 24 and measured by the distribution of SSA scores

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

- [REDACTED]

[REDACTED]

### 7.3 Hypothesis and Methods of Analysis

Finasteride subjects enrolled prior to protocol Amendment 1 will be summarized alone and will not be included in the analysis models. Hypothesis testing will be 2-tailed with a significance level of 0.05. Comparisons of setipiprant tablets 1000 mg BID versus placebo BID will be made. For all efficacy analyses, no adjustment of significance levels will be made for multiplicity of treatment comparisons.

#### 7.3.1 Primary Efficacy Analyses

For analyses of TAHC, the following set of hypotheses will be used to compare setipiprant tablets 1000 mg BID versus placebo BID:

- Null hypothesis: There is no difference between setipiprant tablets 1000 mg BID and placebo BID in increasing TAHC (terminal hairs in a 1 cm<sup>2</sup> circular area) as measured by the change from baseline at Week 24 using digital image analysis.
- Alternative hypothesis: There is a difference between setipiprant tablets 1000 mg BID and placebo BID in increasing TAHC (terminal hairs in a 1 cm<sup>2</sup> circular area) as measured by the change from baseline at Week 24 using digital image analysis.

For analyses of the SSA, the following set of hypotheses will be used to compare setipiprant tablets 1000 mg BID versus placebo BID:

- Null hypothesis: There is no difference between setipiprant tablets 1000 mg BID and placebo BID in SSA (blinded) of hair growth from baseline at Week 24.
- Alternative hypothesis: There is a difference between setipiprant tablets 1000 mg BID and placebo BID in SSA (blinded) of hair growth from baseline at Week 24.

Change from baseline in TAHC at Week 24 and SSA of the change of hair growth from baseline at Week 24 will be analyzed using an analysis of covariance (ANCOVA) model with treatment as a fixed effect and age and baseline value as covariates (if applicable). The treatment difference (setipiprant tablets 1000 mg BID versus placebo BID) will be constructed based on this ANCOVA model, along with the 2-sided p-value. Finasteride subjects enrolled prior to protocol Amendment 1 will be summarized alone and will not be included in the analysis models.

[illegible]

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\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

[REDACTED]  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]

(b) (7)(C), (b) (7)(D)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### 7.3.3 Safety Analyses

Adverse events will be coded from the verbatim text into preferred term (PT) and primary system organ class (SOC) by using the Medical Dictionary for Regulatory Activities. The number and percent of subjects reporting treatment-emergent AEs at least once regardless of causality will be tabulated. Similarly, treatment-related AEs will be tabulated. The tables will be generated by primary SOC and PT as well as by severity.

Safety data will be summarized by frequency distributions or descriptive statistics and described in the detailed analysis plan.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 7.4 Other Analyses

Subject disposition, demographic data, and variables relating to the conduct of the study (eg, number of subjects attending each visit) will be summarized overall and by treatment. All data will be listed. The number of subjects enrolled will be summarized, overall and by treatment

[REDACTED]

## 7.5 Sample Size Calculation

[REDACTED]

[REDACTED]

## 7.6 Interim Analyses

No interim analyses are planned.

## 8. Study Visit Schedule and Procedures

Please see Figure 1 for a flow diagram of study design. Table 1 provides the schedule of visits and procedures.

## 8.1 Subject Entry Procedures

### 8.1.1 Overview of Entry Procedures

Prospective subjects as defined by the criteria in Section 4.3 and Section 4.4 (inclusion/exclusion criteria) will be considered for entry into this study.

### 8.1.2 Informed Consent and Subject Privacy

The study will be discussed with the subject, and a subject wishing to participate must give informed consent prior to any study-related procedures or change in treatment. The subject must also give authorization and other written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

Each subject who provides informed consent will be assigned a subject number via the IWRS that will be used on subject documentation throughout the study.

[REDACTED]

## 8.3 Procedures for Final Study Entry

A subject is considered to have entered the study once the informed consent form is signed at the time of screening.

## 8.4 Instructions for the Subjects

Subjects will be instructed to self-administer the setipirant tablets 1000 mg BID or placebo BID orally with water at least 1 hour before or 2 hours after eating, eg, 1 hour before breakfast in the morning and at least 2 hours after dinner.

[REDACTED]

[REDACTED]

In addition, subjects will be required to follow further instructions outlined in Section 4.5.3 and in the procedure manual.

## 8.5 Unscheduled Visits

If a subject is seen for an unscheduled visit, an assessment and record of AEs should be completed. Additional examinations may be performed as necessary to ensure the safety and well-being of patients during the study. The eCRFs should be completed for each unscheduled visit.

## 8.6 Compliance With Protocol

At Weeks [REDACTED] 24 clinic visits, site personnel will reconcile subject drug usage reports with inspection of wallets (setipirant or placebo) returned by the subject (ie, numbers of open blisters, unused tablets in any blister, and unopened blisters) in the subject's weekly supplies to document the level of subject compliance with the dosing schedule. [REDACTED]

[REDACTED] Study drug inventory and accountability records must be kept current and available for review by the clinical site monitor. All used and unused [REDACTED] for setipirant or placebo should remain with their weekly wallet for reconciliation with reported usage (see above). Authorized study personnel, with the monitor's guidance, are responsible to reconcile any discrepancies.

If the subject is noncompliant with the dosing schedule (eg, frequent or lengthy periods of missed doses, overdosing), additional treatment kits will not be dispensed (ie, the subject may be discontinued from study drug treatment at the investigator's discretion after consultation with the sponsor).

## **8.7 Early Discontinuation of Subjects**

Subjects may voluntarily withdraw from the study at any time. Notification of early subject discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate case report form.

## **8.8 Withdrawal Criteria**

A subject should be withdrawn from the study if the subject wishes to discontinue, or experiences an AE or has an abnormal laboratory result where, in the judgment of the investigator, continuation in the study would be detrimental to the subject's health. Whenever possible, the decision to withdraw a subject from the study or study treatment should be discussed with the sponsor prior to discontinuation of the subject.

## **8.9 Study Termination**

The study may be stopped at his/her study site at any time by the site investigator. The sponsor may stop the study (and/or the study site) for any reason with appropriate notification.

## **9. Adverse Events**

Adverse events occurring during the study will be recorded on an AE case report form. If AEs occur, the first concern will be the safety of the study participants.

### **9.1 Definitions**

#### **9.1.1 Adverse Event**

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. In addition, during the screening period, AEs will be assessed regardless of the administration of a pharmaceutical product.

Note: Adverse events must be collected once informed consent has been obtained, regardless of whether or not the subject has been administered study drug.



Progression of treatment indication including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and/or lack of efficacy, should NOT be reported as AEs unless the disease progression is greater than anticipated in the natural course of the disease.

Adverse events will be assessed, documented, and recorded in the CRF throughout the study (ie, after informed consent has been obtained). [REDACTED]

[REDACTED]. All reported AEs will be documented on the appropriate case report form.

### 9.1.2 Serious Adverse Event

A serious AE is any AE occurring at any dose that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious AE when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. (See Section 9.3 for procedures for reporting a serious AE.)

The sponsor considers all cancer AEs as serious AEs.

Preplanned surgeries or procedures for pre-existing, known medical conditions for which a subject requires hospitalization is not reportable as a serious AE.

Any preplanned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the subject's entry into the study. If it has not been documented at the time of the subject's entry into the study, then it should be documented as a serious AE and reported to the sponsor.

### 9.1.3 Severity

A clinical determination will be made of the intensity of an AE. The severity assessment for a clinical AE must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity
Severe	Incapacitating with inability to work or do usual activity
Not applicable	In some cases, an AE may be an <i>all or nothing</i> finding which cannot be graded.

### 9.1.4 Relationship to Study Drug or Study Procedure

A determination will be made of the relationship (if any) between an AE and the study drug or study procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the AE may have been caused by the drug or study procedure.

## 9.2 Procedures for Reporting Adverse Events

Any AE must be recorded on the appropriate case report form.

All AEs that are drug-related and unexpected (not listed as treatment-related in the current investigator's brochure) must be reported to the governing institutional review board/independent ethics committee (IRB/IEC) as required by the IRB/IEC, local regulations, and the governing health authorities. An AE that is marked *ongoing* at the exit visit may need to be followed up as appropriate.

[REDACTED]

In the event of a serious AE, the investigator must:

1. Notify the sponsor immediately by fax or email using the serious AE form (contact details can be found on page 1 of the serious AE form); phone numbers and relevant sponsor's personnel contacts are also on the front page of protocol and study contacts page.
2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject.
3. Provide the sponsor with a complete, written description of the AE(s) on the serious AE form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the AE(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the investigational drug.
4. Promptly inform the governing IRB/IEC of the serious AE as required by the IRB/IEC, local regulations, and the governing health authorities.

[REDACTED]

The treatment assignment for the subject can be determined by designated site personnel logging into the IWRS system via password protected access. The reason for breaking the code must be recorded in the subject's source documents.

## 10. Administrative Items

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines, eg, the ICH Guideline on GCP.

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## **10.1 Protection of Human Subjects**

### **10.1.1 Compliance with Informed Consent Regulations (US 21 CFR Part 50) and Relevant Country Regulations**

Written informed consent is to be obtained from each subject prior to any study-related activities or procedures in the study, and/or from the subject's legally authorized representative.

### **10.1.2 Compliance With IRB or IEC Regulations**

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) or applicable IEC regulations. The investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. The sponsor is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator should be provided to the sponsor.

### **10.1.3 Compliance With Good Clinical Practice**

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

### **10.1.4 Compliance With Electronic Records; Electronic Signatures Regulations (US 21CFR Part 11)**

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

## **10.2 Changes to the Protocol**

The investigator must not implement any deviation from or changes of the protocol without approval by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study subjects, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

## **10.3 Subject Confidentiality**

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the subject's name will

not be disclosed in these documents. The subject's name may be disclosed to the sponsor of the study, Allergan, or the governing health authorities or the FDA if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

### **10.3.1 Subject Privacy**

Written authorization and other documentation in accordance with the relevant country and local privacy requirements (where applicable) is to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (eg, HIPAA).

In accordance with HIPAA requirements, additional purposes of this study may include publishing of anonymous patient data from the study.

## **10.4 Documentation**

### **10.4.1 Source Documents**

Source documents may include a subject's medical records, hospital charts, clinic charts, secure digital cards, photographs, patient-reported outcomes, the investigator's subject study files, as well as the results of diagnostic tests [REDACTED]. The investigator's copy of the case report forms serves as part of the investigator's record of a subject's study-related data.

The following information should be entered into the subject's medical record:

- Subject's name
- Subject's contact information
- Date that the subject entered the study, subject number, and subject randomization (or medication kit[s]) number
- Study title and/or protocol number of the study and the name of the sponsor
- A statement that informed consent was obtained (including the date) and a statement that written authorization or other country and local subject privacy required documentation for this study has been obtained (including the date)

- Dates of all subject visits
- Medical history, including HIV status
- Eligibility criteria
- Count of returned study medication
- Record of all hair products used by the subject
- Date the subject exited the study and a notation as to whether the subject completed the study or reason for discontinuation
- Date of global and macrophotography (and approval of global photography at screening)
- All subject and investigator assessments
- Physical examination
- Vital sign measurements
- All concomitant medications (List all prescription and nonprescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded.)
- Occurrence and status of any AEs

[REDACTED]

[REDACTED]

- Modified Norwood-Hamilton classification
- Global photographs
- Macrophotographs

#### 10.4.2 Case Report Form Completion

The investigator is responsible for ensuring that data are properly recorded on each subject's case report forms and related documents. An investigator who has signed the protocol signature page

should personally sign for the case report forms (as indicated in the case report forms) to ensure that the observations and findings are recorded on the case report forms correctly and completely. The case report forms are to be submitted to the sponsor in a timely manner at the completion of the study, or as otherwise specified by the sponsor and will be maintained in a central data repository.

### **10.4.3 Study Summary**

An investigator's summary will be provided to the sponsor within a short time after the completion of the study, or as designated by the sponsor. A summary is also to be provided to the responsible IRB/IEC.

### **10.4.4 Retention of Documentation**

All study-related correspondence, subject records, consent forms, subject privacy documentation, records of the distribution and use of all investigational products, and copies of case report forms should be maintained on file.

For countries falling within the scope of the ICH guidelines, the sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

The sponsor requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

## **10.5 Labeling, Packaging, and Return or Disposal of Study drugs/Treatments**

### **10.5.1 Labeling/Packaging**

Setipiprant and placebo will be packaged [REDACTED] and combined into a weekly wallet. Each weekly wallet of setipiprant or placebo will contain a total of 14 doses (ie, a week's worth of BID dosing). The investigator will dispense an appropriate number of weekly wallets for the time interval until the subject's next clinic visit.

As this is a double-blind study, labeling of the subject treatment kit will not show the treatment allocation. All other information required by regulation will appear on each treatment kit.

### 10.5.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units received from the sponsor, dispensed to the subjects, the number of units returned to the investigator by the subject (if applicable), and the number of units returned to the sponsor during and at the completion of the study. A detailed inventory must be completed for the study drug. The study drug must be dispensed only by appropriately qualified site personnel to subjects in the study. The medication is to be used in accordance with the protocol for subjects who are under the direct supervision of an investigator.

### 10.5.3 Return or Disposal of Study Drugs and/or Supplies

All clinical study drugs/treatments and/or supplies will be returned to the sponsor or sponsor designee for destruction.

## 10.6 Monitoring by the Sponsor

A representative of the sponsor will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Authorized representatives of the sponsor or regulatory authority representatives will conduct onsite visits to review, audit and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]. All samples will be returned to the sponsor or sponsor designee at the completion of the study. The sponsor shall have full ownership rights to any biological specimens/samples derived from the study.

Details about the handling of [REDACTED] are provided in the study laboratory manual.

## **10.8 Publications**

The sponsor as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and the sponsor personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with the sponsor.

## **10.9 Coordinating Investigator**

A signatory coordinating investigator will be designated prior to the writing of the clinical study report.

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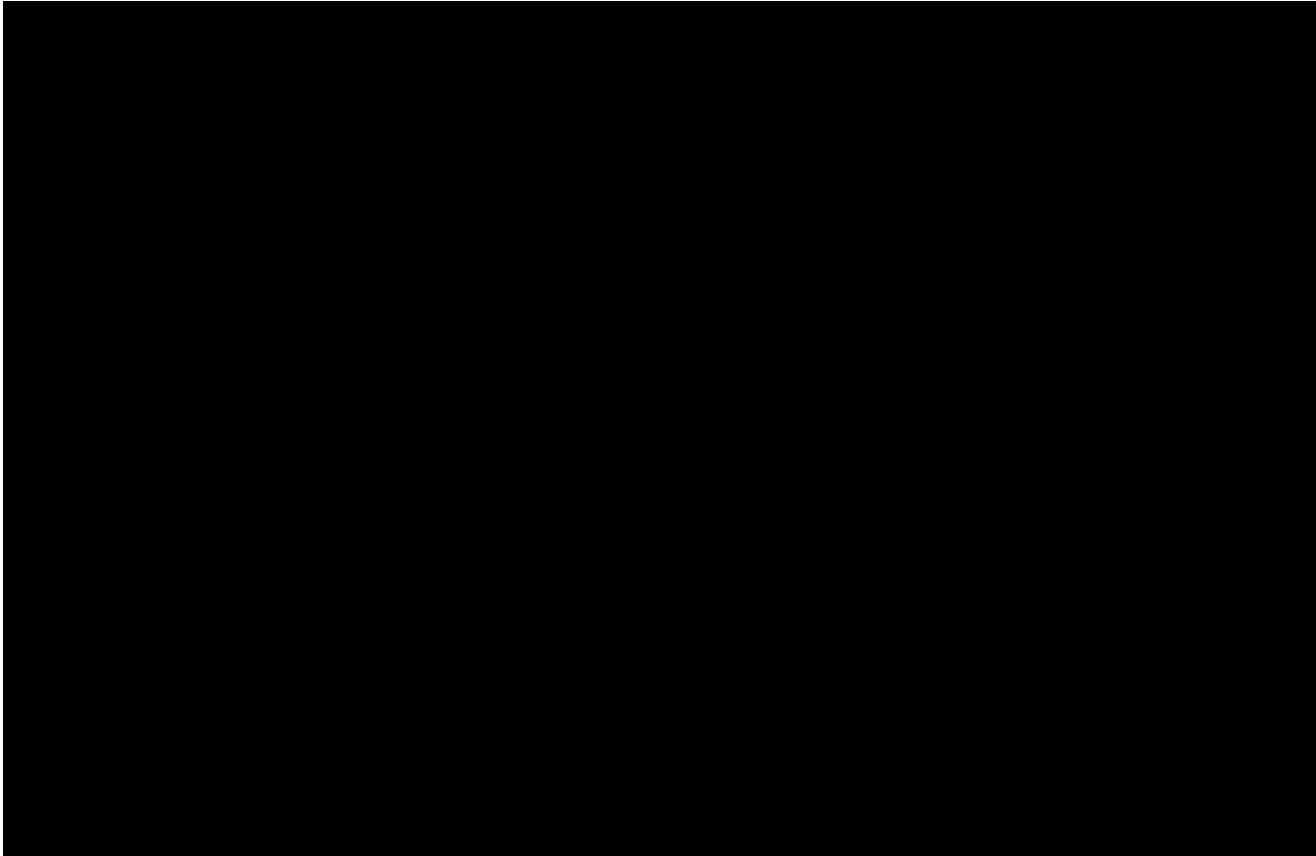
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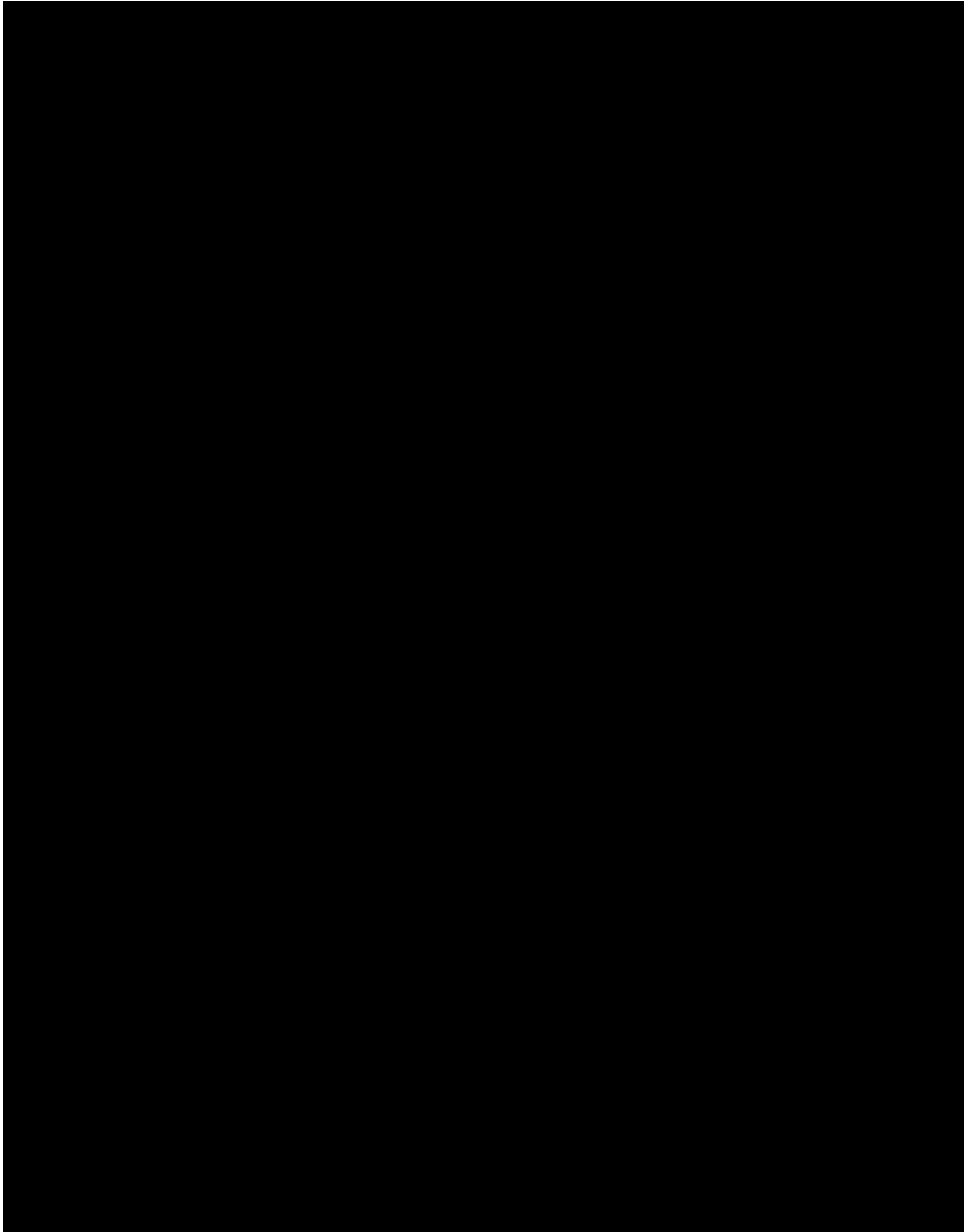
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## **12. Attachments**

### **12.1 Examination Procedures, Tests, Equipment, and Techniques**



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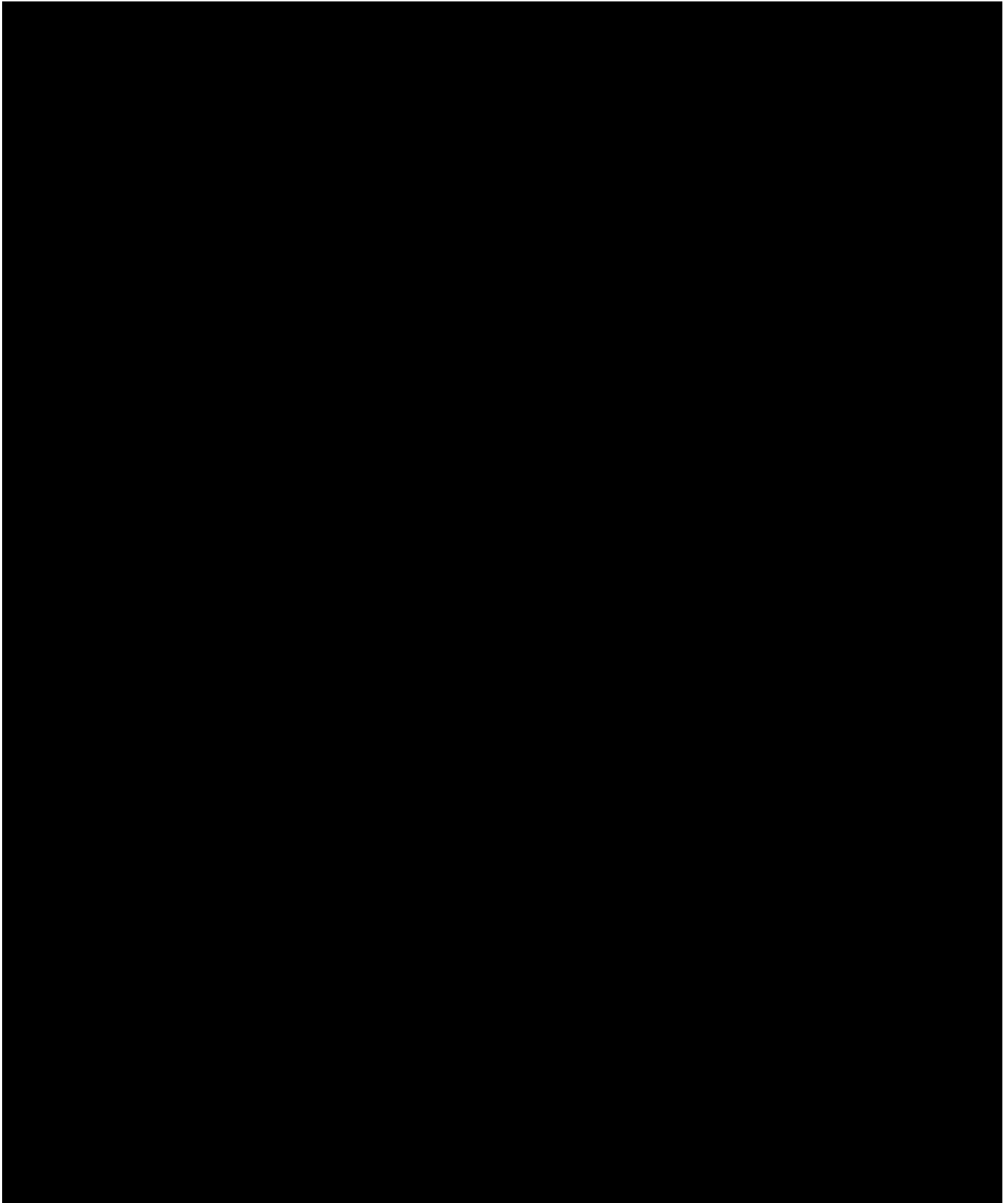
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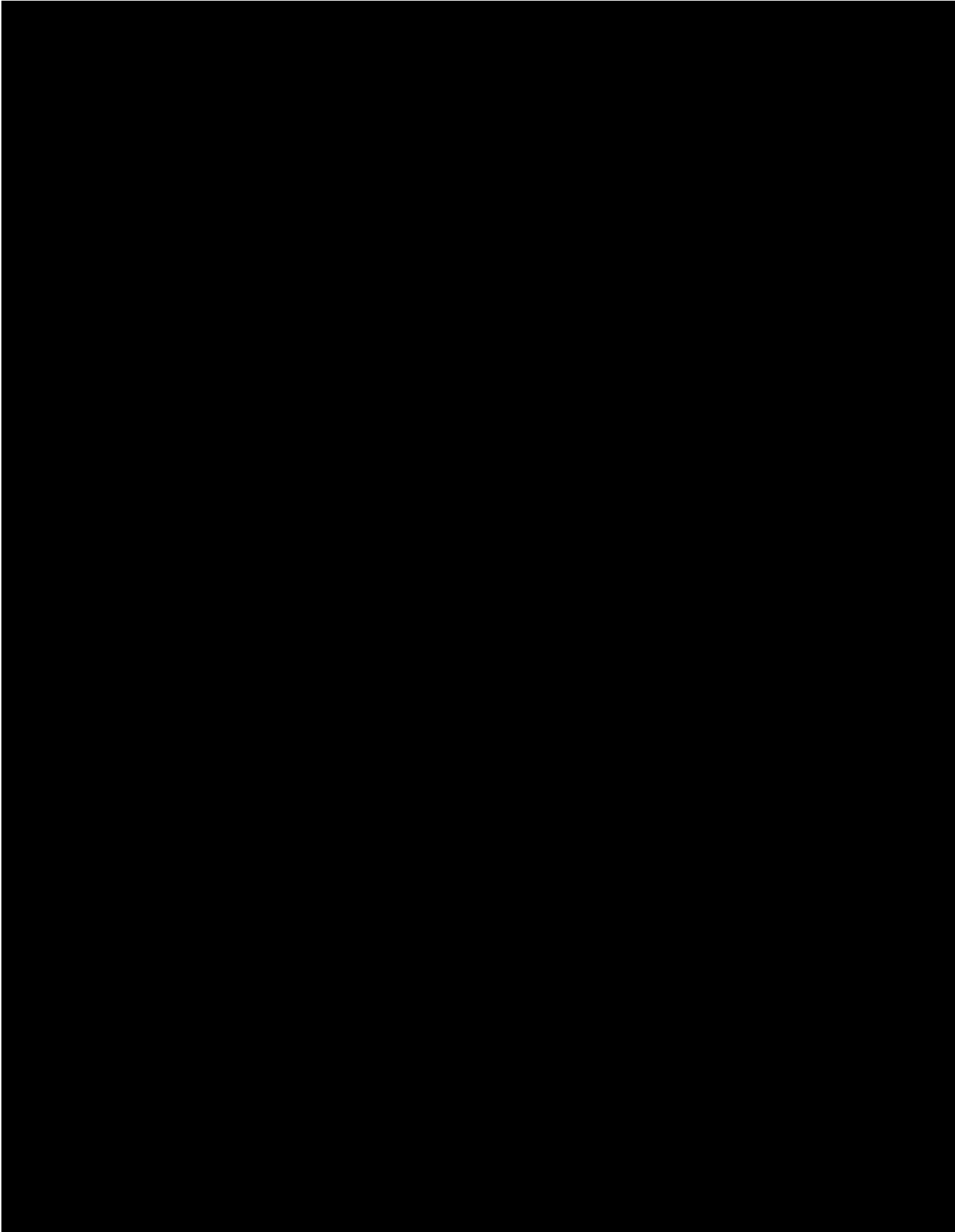
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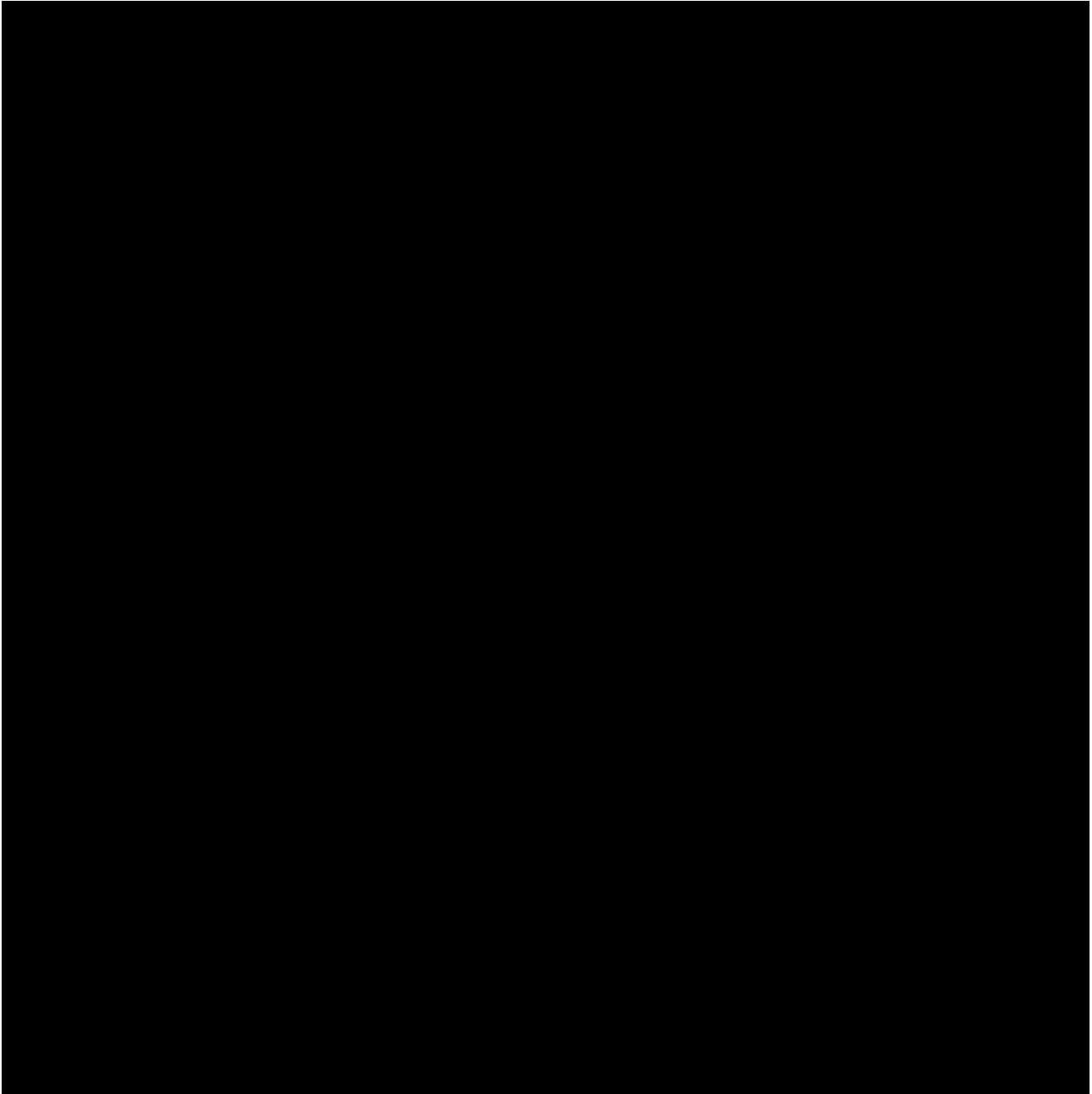
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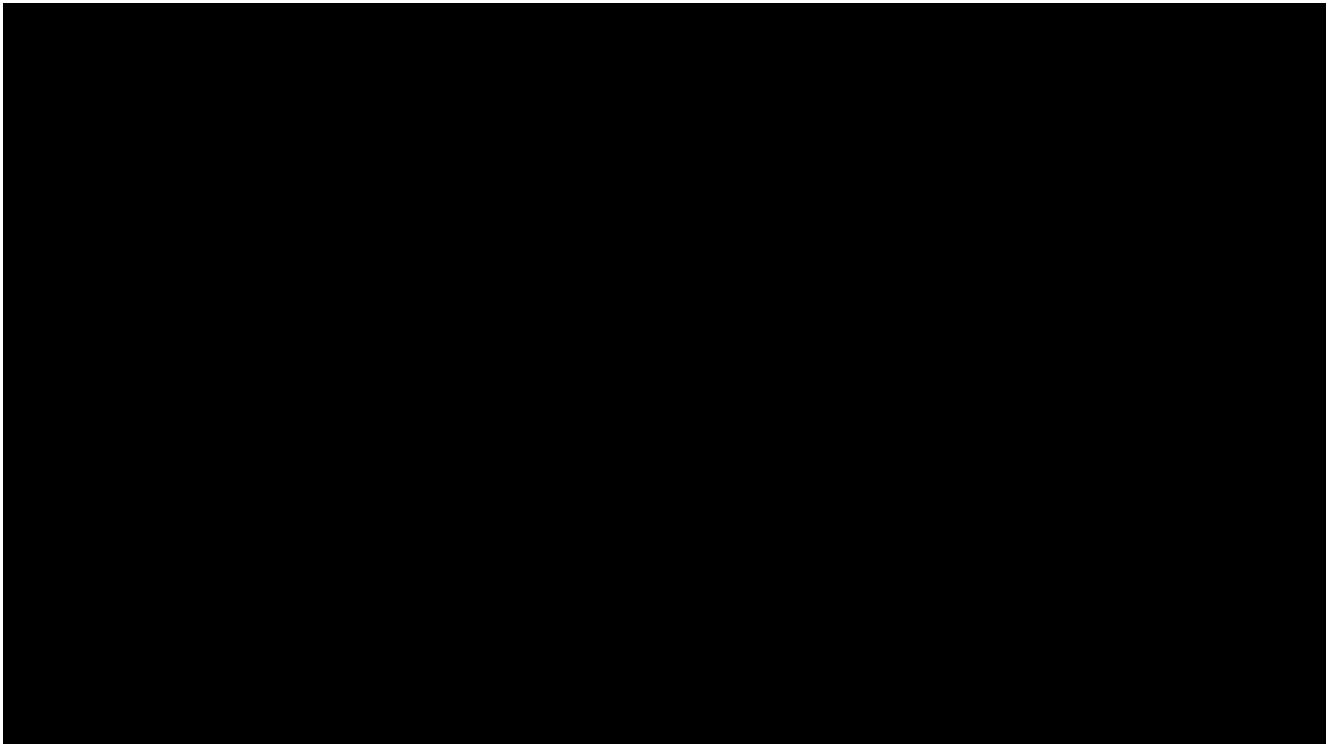


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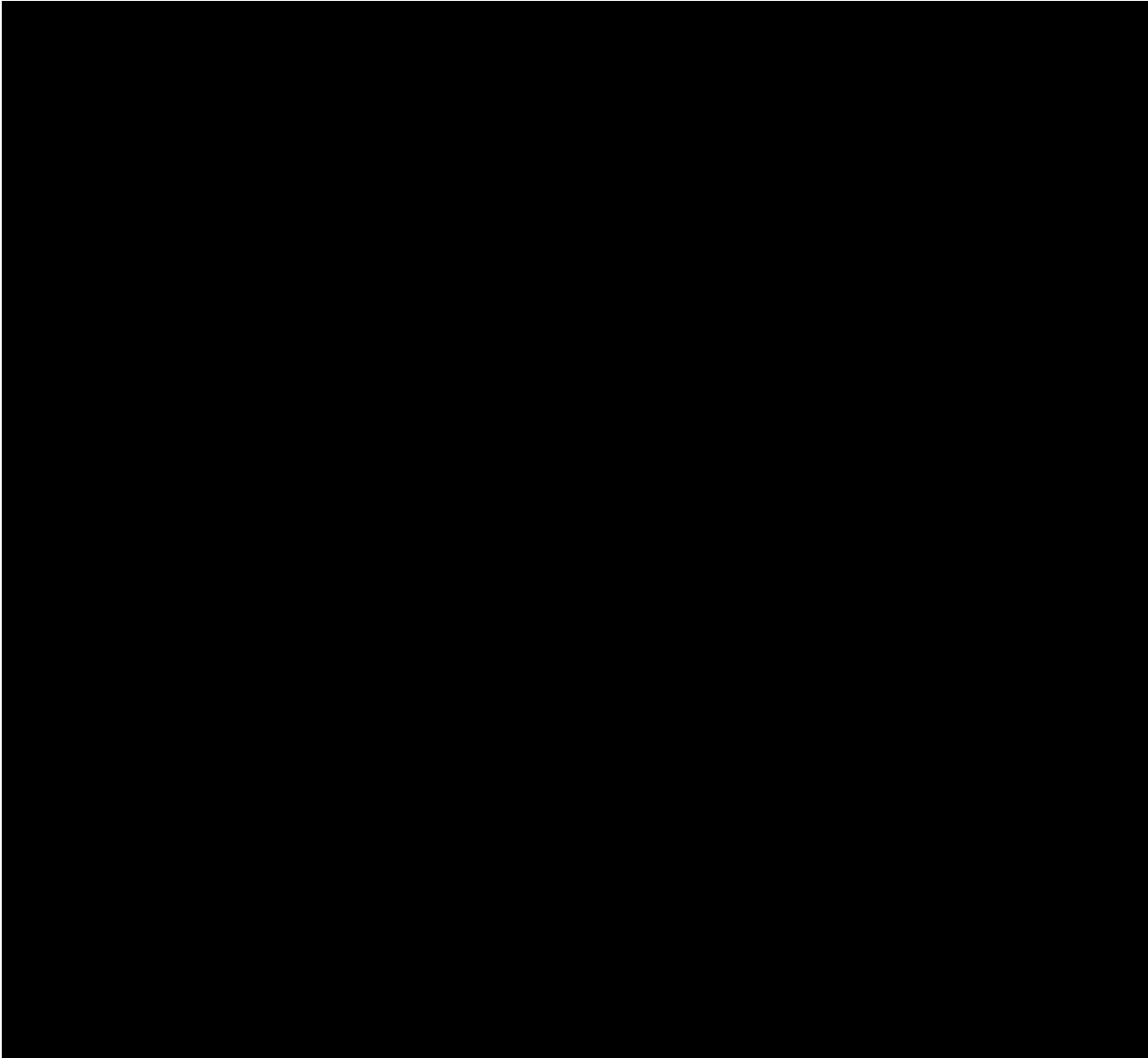


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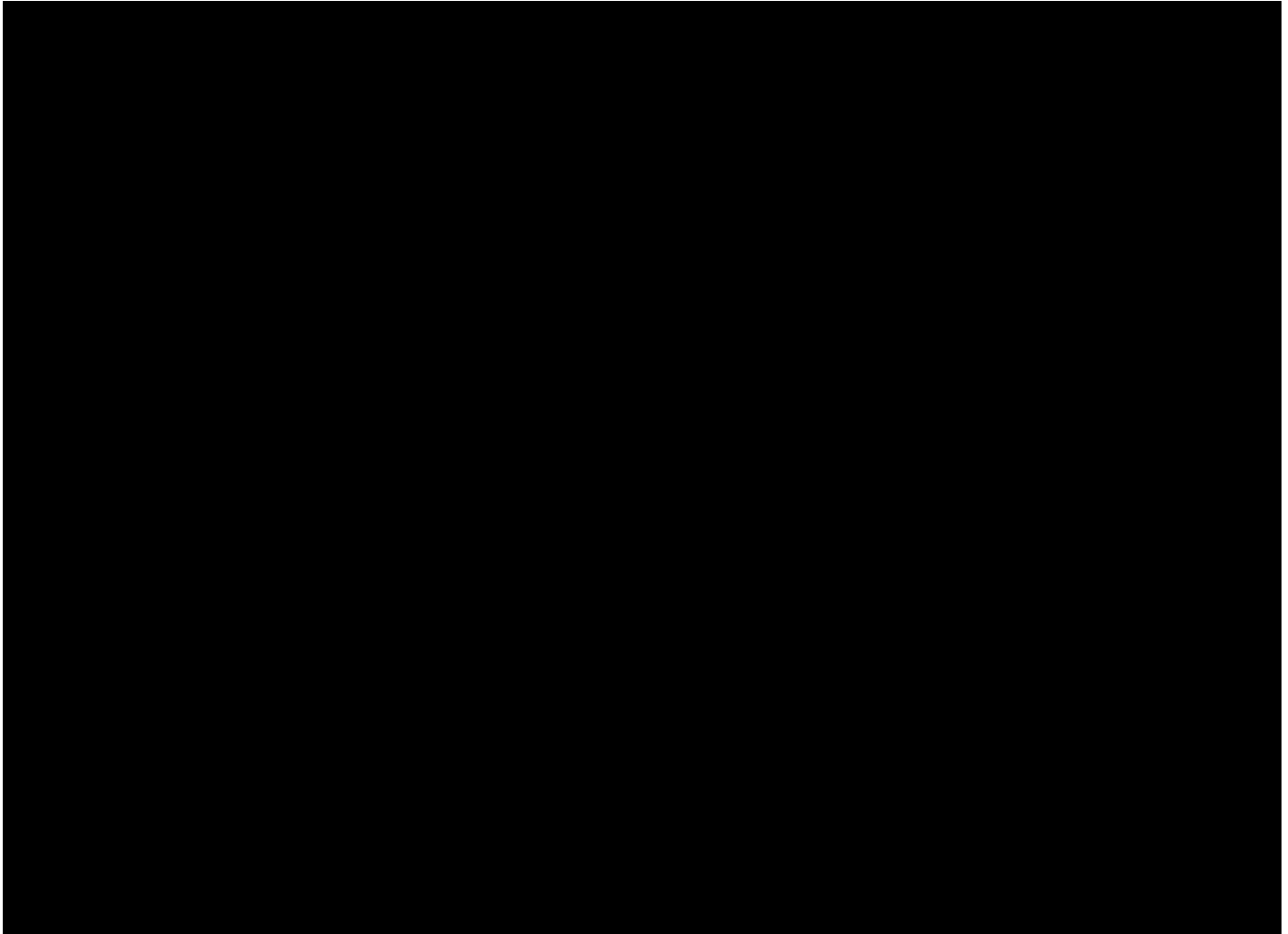




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## 12.2 Safety Measures

- Adverse events

The investigator will question the subject in order to ascertain whether any AEs were experienced since the previous visit. All pertinent information regarding AEs (ie, date of onset and stop, duration, outcome, severity, relationship to study drug, action or treatment required) will be obtained and recorded in the source documents and appropriately transcribed on the eCRF page.

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## 12.3 Glossary of Abbreviations

Term/Abbreviation	Definition
5AR	5 $\alpha$ -reductase
AE	adverse event
AGA	androgenetic alopecia
█	█
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASA	Alopecia Symptom Assessment
AST	aspartate aminotransferase
█	█
█	█
█	█
AUC <sub>0-inf</sub>	area under the concentration-time curve from time 0 to infinity
BID	twice daily
bpm	beats per minute
█	█
CMH	Cochran-Mantel-Haenszel
CRTH2	chemoattractant receptor-homologous molecule expressed on T helper 2 cells
█	█
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
█	█
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
█	█
█	█
█	█
IRB	Institutional Review Board
IWRS	interactive web response system
LOCF	last observation carried forward

MSP	medical safety physician
mITT	modified intent-to-treat
NHS	Norwood-Hamilton Hair Loss Scale
PGD <sub>2</sub>	prostaglandin D <sub>2</sub>
PT	preferred term
PTGDS	prostaglandin-D <sub>2</sub> synthase
ptgs2	mouse prostaglandin-D <sub>2</sub> synthase homolog
SOC	system organ class
SSA	Subject Self-Assessment
TAHC	target area hair count
TBL	total bilirubin
ULN	upper limits of normal
WBC	white blood cell

## 12.4 Protocol Amendment Summary

Title: Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study of Setipiprant Tablets in Androgenetic Alopecia in Males With a Comparator Arm

Protocol 1922-201-002 Amendment 1

Date of Amendment: February, 2017

### Amendment Summary

This summary includes changes made to the original Protocol 1922-201-002 (25 March 2016). This protocol was amended to remove the finasteride arm, expand the upper range of the study population to age 49 years, and to remove some of the exclusionary concomitant medications. It is anticipated that these changes that are designed to simplify the protocol will result in an increased rate of study enrollment.

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Approval Date: 17-Feb-2017



Section	Revision	Rationale
Protocol Title Page	Deleted “With a Comparator Arm” from study title.	Finasteride arm deleted. Data from the small number of finasteride subjects enrolled prior to protocol Amendment 1 will not be compared to other treatment groups.
Protocol Title Page	Revised fax number for Allergan Medical Safety Physician	Previous fax number was incorrect.
Protocol Summary, Study Objectives	Revised overall age range of subjects in the setipiprant and placebo groups from 18 - 41 to 18 - 49 years. Deleted finasteride arm.	To increase the rate of study enrollment. Removed finasteride arm to simplify study design, allowing the age range to be expanded to up to 49 years. The finasteride arm was deemed not critical in determining the efficacy or safety of setipiprant.
Protocol Summary, Study Design, <i>Structure</i>	Deleted finasteride arm.	To be consistent with the removal of the finasteride arm.
Protocol Summary, Study Design, <i>Control</i>	Deleted finasteride arm.	See rationale above.
Protocol Summary, Study Design, <i>Dosage/Dose Regimen</i>	Deleted finasteride arm	See rationale above.
Protocol Summary, Study Design, <i>Enrollment/Stratification</i>	Deleted finasteride arm. Changed the randomization ratio for [REDACTED] (setipiprant:placebo:finasteride) to 1:1 (setipiprant:placebo). Changed the age range for stratification from 35 – 41 years to 35 - 49 years.	See rationale above. To be consistent with the revised study population.
Protocol Summary, Study Population Characteristics, <i>Key Inclusion Criteria</i>	Expanded the age range from 18 – 41 years to 18 - 49 years.	To be consistent with the revised study population.
Protocol Summary, General Statistical Methods and Types of Analyses	Deleted pairwise comparison of finasteride and placebo. Added finasteride subjects will be summarized alone.	Finasteride arm was removed. To address how data from subjects treated with finasteride prior to protocol Amendment 1 will be analyzed.
Protocol Summary, General Statistical Methods and Types of Analyses, <i>Efficacy Analyses</i>	Added the finasteride group is excluded from analysis. Changed the age stratification in efficacy analysis model from 18 - 34 and 35 - 41 years to < 35 and ≥ 35 years.	For clarification. To include those in the 42 - 49 years age group (ie, ≥ 35 years)

Section	Revision	Rationale
Protocol Summary, General Statistical Methods and types of Analyses, <i>Sample Size Calculation</i>	Deleted finasteride arm (n = 35). Reduced enrollment target for setipiprant and placebo from 187 to 152 subjects and [REDACTED] enrollment target from 175 to 140 subjects.  Randomization ratio for [REDACTED] subjects changed from 2:2:1 (setipiprant:placebo:finasteride) to 1:1 (setipiprant:placebo).	Finasteride arm removed.
[REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED]
1 Background and Clinical Rationale	Deleted the finasteride arm.	To be consistent with the removal of the finasteride arm.
2.1 Study Objectives	Revised overall age range of subjects in the setipiprant and placebo groups from 18 - 41 to 18 - 49 years.	See rational above.
3 Study Design	Deleted finasteride arm. Deleted finasteride arm.  Deleted requirement for blinded investigator to give efficacy assessments to finasteride subjects while subject/staff are unblinded.	Removed finasteride arm.
4.1 Number of Subjects	Deleted finasteride arm (n = 35); changed number of setipiprant and placebo subjects from 187 to 152.	Removed the finasteride arm. Increased overall age range of subjects in the setipiprant and placebo groups from 18 - 41 to 18 - 49 years.

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Section	Revision	Rationale
4.2 Study Population Characteristics	Revised overall age range of subjects in the setipiprant and placebo groups from 18 - 41 to 18 - 49 years.  Noted that subjects were assigned to finasteride under the original protocol.	To increase the rate of study enrollment. For clarification.
4.3 Inclusion Criteria, 3	Expanded the age range from 18 – 41 years to 18 – 49 years.	To be consistent with the revised study population.
4.3 Inclusion Criteria, 6	Revised the required maintenance of hair length from $\geq 2.54$ cm (1 in) to $\geq 2$ cm (0.75 in).	To increase the rate of study enrollment
4.4 Exclusion Criteria, 3	The Criterion 3 list was re-lettered from 3a – e to 3a – f.	Added a criterion.
[REDACTED]	[REDACTED]	[REDACTED]
4.4 Exclusion Criteria, 4	The Criterion 4 list was re-lettered from 4a–e to 4a-c	Removed criteria.
4.4 Exclusion Criteria; [REDACTED]	[REDACTED]	[REDACTED]
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4.5.3 Special Activities	Deleted finasteride information.	See rationale above.
5.2 Control Treatments	Deleted finasteride information.	See rationale above.
5.3 Methods for Masking/Blinding	Deleted information about unblinded finasteride subjects/site staff and blinded investigator to perform efficacy assessments.	See rationale above.

Section	Revision	Rationale
5.4 Treatment Allocation Ratio and Stratification	Deleted finasteride arm. Changed number of [REDACTED] subjects from 175 to 140.  Changed the randomization ratio for [REDACTED] subjects from 2:2:1 (setipirant:placebo:finasteride) to 1:1 (setipirant:placebo). Added non-PK subjects to be stratified by age, 18 -34 and 35 – 49 years.	To be consistent with Section 4.1
5.5 Method for Assignment to Treatment Groups/Randomization	Deleted finasteride arm (n = 35). Changed number of [REDACTED] subjects from 175 to 140. Changed [REDACTED] randomization ratio from 2:2:1 (setipirant:placebo:finasteride) to 1:1 (setipirant:placebo).	To be consistent with Sections 4.1 and 5.4.
5.6 Treatment Regimen and Dosing	Added subjects assigned to finasteride prior to protocol Amendment 1 should continue treatment until they complete the study.  Deleted information about finasteride regimen.	For clarification.
5.7 Storage of Study Drugs	Deleted information about finasteride risk to pregnant or potentially pregnant women	See rationale above.
5.9 Treatment Administration	Deleted finasteride packaging, dosing, and open-label information.	See rationale above.
6.1 Efficacy Measures	Deleted finasteride blinding information.	See rationale above.
[REDACTED]	[REDACTED]	[REDACTED]
7.3 Hypothesis and Methods of Analysis	Deleted pairwise comparison of finasteride and placebo.  Added that finasteride subjects will be summarized alone.	Finasteride arm was removed.  To address how data from subjects treated with finasteride prior to protocol Amendment 1 will be analyzed.
7.3.1 Primary Efficacy Analyses	Added finasteride subject data will be summarized alone.	See rationale above.
[REDACTED]	[REDACTED]	[REDACTED]

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Section	Revision	Rationale
7.5 Sample Size Calculation	Deleted finasteride arm (n = 35) and related text.  Deleted Finasteride versus Placebo column from Table 2.	Removed finasteride arm.
8.3 Procedures for Final Study Entry	Changed time subject has entered the study from time of randomization (Day 1) to screening.	Correction as informed consent form is signed at screening.
8.4 Instructions for the Subjects	Deleted instructions for finasteride group.	Removed finasteride arm.
8.6 Compliance With Protocol	Deleted finasteride bottle information.	See rationale above.
10.5.1 Labeling/Packaging	Deleted finasteride information.	See rationale above.

# ALLERGAN

Protocol 1922-201-002 Amd 1

Date (DD/MMM/YYYY)/Time (PT)

[REDACTED]

Signed by:

[REDACTED]

Justification

[REDACTED]