STATISTICAL ANALYSIS PLAN

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose, 6-Week, In-Patient Study to Assess Efficacy and Safety of HP-3070 in Subjects Diagnosed with Schizophrenia
Version Number & Date of SAP:	Final V6, 18 January 2018
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STATISTICAL ANALYSIS PLAN

Protocol Number: HP-3070-GL-04 Version 3 Amendment 2

A Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose, 6-Week, In-Patient Study to Assess Efficacy and Safety of HP-3070 in Subjects Diagnosed with Schizophrenia

Author: Amanda Schwab

Version Number and Date: **Final V6, 18JAN2018**

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Final V6.0 (Dated 18JAN2018) for Protocol HP-3070-GL-04.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ACS	Abnormal, Clinically Significant
AE	Adverse Event
AIC	Akaike's Information Criterion
AIMS	Abnormal Involuntary Movement Scale
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
ANCS	Abnormal, Not Clinically Significant
AR(1)	Autoregressive (1)
ARH(1)	Autoregressive, Heterogeneous (1)
AST	Aspartate Transaminase
BARS	Barnes Akathisia Rating Scale
BMI	Body Mass Index
CDSS	Calgary Depression Scale for Schizophrenia
CGI-S	Clinical Global Impression – Severity of Illness Scale
CGI-I	Clinical Global Impression - Improvement Scale
CI	Confidence Interval
CMH	Cochran Mantel Haenszel
C-SSRS	Columbia-Suicide Severity Rating Scale
CS	Compound Symmetry
CSH	Compound Symmetry, Heterogeneous
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EPS	Extrapyramidal Symptoms
ET	Early Termination
FA0(q)	No Diagonal Factor Analytic covariance structure (with q equal to the number of time points)
FAS	Full Analysis Set
FDA	Food and Drug Administration
ISSR	Interim Sample Size Recalculation
ITT	Intent-to-Treat
IVRS	Interactive Voice-Activated Response System
IWRS	Interactive Web-based Response System
LSM	Least Squares Mean
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo

MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not at Random
MSQ	Medication Satisfaction Questionnaire
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PANSS	Positive and Negative Syndrome Scale
PAS	Pharmacokinetic Analysis Set
PK	Pharmacokinetic
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
SAS®	Statistical Analysis Software
SBP	Systolic Blood Pressure
SD	Standard Deviation
SI	Standard International
SL	Sublingual
SOC	System Organ Class
SSR	Sample Size Recalculation
TEAE	Treatment-Emergent Adverse Event
TOEP	Toeplitz (covariance structure)
TOEPH	Toeplitz, Heterogeneous (covariance structure)
ULN	Upper Limit Of Normal
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol HP-3070-GL-04. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 3 dated 21 November 2016.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of the study is to evaluate efficacy of HP-3070 compared with placebo for the treatment of schizophrenia as evaluated by Positive and Negative Syndrome Scale (PANSS) total score.

2.2. KEY SECONDARY OBJECTIVES

Key Secondary Efficacy Objective:

- Clinical Global Impression – Severity of Illness Scale (CGI-S)

2.3. OTHER SECONDARY OBJECTIVES

Other Secondary Efficacy Objectives: To evaluate the efficacy of HP-3070 using the following measures:

- PANSS total score at each timepoint
- Clinical Global Impression – Severity of Illness Scale (CGI-S) at each timepoint
- Clinical Global Impression – Improvement Scale (CGI-I) at each timepoint
- Proportion of CGI-I responders at each timepoint
- Positive, negative, and general pathology subscores of PANSS
- Proportion of PANSS responders; At each time point (Weeks 1 – 6), subjects having a 30% or greater improvement from baseline in PANSS total score will be defined as responders
- Calgary Depression Scale for Schizophrenia (CDSS)
- Medication Satisfaction Questionnaire (MSQ) score

2.4. SAFETY OBJECTIVES

Safety objectives are to evaluate the safety and tolerability of HP-3070 compared with placebo, including:

- Adverse events (AEs), including treatment-emergent AEs (TEAEs), AEs leading to discontinuation from the study drug, serious adverse events (SAEs), and deaths
- Change from Baseline in clinical laboratory results (including prolactin, fasting glucose, and lipids), ECG results, body weight, and vital signs
- Results of C-SSRS, BARS, AIMS, and SAS
- Dermal safety

2.5. EXPLORATORY OBJECTIVES

Exploratory objectives are to assess the impact of covariates on asenapine exposure using a model-based approach and to explore the exposure-response relationship with relevant endpoints.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase 3, randomized, double-blind, placebo-controlled, in-patient, safety, and efficacy study to evaluate HP-3070 for the treatment of schizophrenia.

This study will consist of a Screening/placebo Run-in Period of 3 to 14 days, a 6-week double-blind Treatment Period and a 30 day Follow-up Period.

Subjects will be hospitalized at the Screening Visit and will remain hospitalized during the study. The subject may leave the hospital study for necessary personal business. Any subject who leaves the site must have an alcohol breathalyzer and urine drug tests when they return to the site.

After obtaining informed consent, each subject will be assigned a unique subject number. Eligible subjects will be hospitalized for the duration of the study. While undergoing screening procedures and waiting for results of laboratory tests, ECGs, and other assessments, the subject will start treatment with the single-blind placebo patch. The subject must have the single-blind placebo patch applied for a minimum of 3 days prior to being randomized into the double-blind Treatment Period. In addition, current antipsychotic and other prohibited medications will be washed out during the run-in period and must be completed prior to randomization into the double-blind treatment period. Details in regard to wash-out periods for specific drugs are summarized in Protocol Section 5.10.1. Subjects who have a decrease in PANSS total score ≥20% from Screening to Baseline or a PANSS total score <80 at Screening or Baseline will be discontinued from the study and will not enter the double-blind Treatment Period.

Subjects eligible for randomization into the double-blind Treatment Period will be randomly assigned to HP-3070 9.0 mg, HP-3070 18.0 mg, or placebo in a 1:1:1 ratio stratified by country. Subjects will receive treatment with study medication daily for 6 weeks.

The study will evaluate 9.0mg (HP-3070 9.0 mg) and 18.0 mg (HP-3070 18.0 mg) of HP-3070 transdermal patches versus placebo transdermal patches. Patches will be applied by site personnel at approximately the same time daily and each patch will be worn for 24 hours. Every day, 24 hours (±15 minutes) after patch application, site personnel will remove previous day's patches and apply new patches.

All subjects will have a follow-up contact (site visit or telephone call, at the discretion of the Investigator) 30 days after the last patch is removed. This contact will be used to collect information about any Adverse Events (AEs) or Serious Adverse Events (SAEs) that may have occurred since discharge and to follow-up on any Adverse Events (AEs) that were on-going at discharge.

Assuming an effect size of 0.35 on the change in PANSS total score from baseline to Week 6 for the two pairwise comparisons between each active HP-3070 treatment arm and placebo, the power for detecting a statistically significant HP-3070 advantage will be approximately 0.90 having 204 evaluable subjects per each treatment arm, using a two-sided alpha level of 0.025 for each comparison. A two-sided overall type I error is equal to 0.05. Having three treatment arms, the total number of subjects randomized in the trial and included in primary analysis set will be approximately 612.

The effect size of 0.35 (difference between means equal to 7 and common standard deviation (SD) equal to 20) was chosen based on the lowest effect size observed in results from the studies conducted with sublingual (SL) asenapine and approved by the Food and Drug Administration (FDA) (Sycrest®/SAPHRIS® [Study 041004, and Study 041023]).

A sample size recalculation (SSR) will be conducted as described in Section 4.2 on the blinded data after approximately 50% of the originally planned number of subjects have been randomized and completed up to 6 weeks of study treatment.

3.2. SCHEDULE OF EVENTS

In this study, efficacy will be evaluated using widely accepted, standard questionnaires. These include the PANSS, CGI-S, CGI-I, CDSS and MSQ.

In addition to standard safety measures (AEs, clinical laboratory assessments, vital signs, weight, electrocardiogram [ECG] results), this study will also include assessments of extrapyramidal symptoms (EPS) symptoms using the Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS). Suicidality will be monitored using the Columbia-Suicide Severity Rating Scale (C-SSRS). Patch adhesion will be assessed at specified timepoints. Dermal safety will be assessed by daily evaluation of irritation at the site of patch application and by a review of any dermal reactions reported as AEs.

The schedule of study procedures and assessments is presented in Protocol Table 1.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

There are no changes to analysis from protocol.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Blinded Sample Size Recalculation
- Final Analysis

4.1. DATA MONITORING COMMITTEE (DMC)

There will be no DMC for this study.

4.2. BLINDED SAMPLE SIZE RECALCULATION

Sample size recalculation (SSR) will be conducted on the blinded data after approximately 50% of the desired number of patients have been randomized and completed up to 6 weeks of study treatment. This SSR will be directed and conducted by an independent statistician from IQVIA, who is not involved in the trial conduct other than this SSR.

The purpose of this SSR is to assess the assumption regarding the standard deviation made for sample size calculation for the primary endpoint. No other information will be generated as part of the SSR.

This SSR will not be conducted with an intention of decreasing the original sample size or stopping the trial early.

An assumed treatment effect size of 0.35 which served as basis for the original sample size calculation corresponds to an assumption of mean difference of 7 in the change in PANSS total score from Baseline to Week 6 between each HP-3070 treatment group and placebo and a common standard deviation of 20. The independent statistician will estimate a pooled standard deviation from blinded data at the time of SSR analysis as follows:

$$SD_{pooled} = \sqrt{\frac{1}{N_{SSR} - 1}\left[\sum_{i=1}^{N_{SSR}} (x_i - \bar{x})^2\right]}$$

where N_{SSR} is the total number of subject with change in PANSS total score from Baseline to Week 6 available at the time of SSR analysis, x_i are the changes from baseline values of these subjects, and $\bar{x}$ is the grand mean of the pooled sample. Based on the re-estimated SD_{pooled} and using the same assumptions for all other aspects of sample size calculation as postulated for the original sample size estimation, the independent statistician will

recommend either to keep the original sample size or to increase it in order to maintain a desired level of power. The final decision with regard to sample size will be at the discretion of the Sponsor upon review of the independent statistician's recommendation based on the estimated pooled standard deviation and its impact on the power of the study. The decision will be reported in a separate document.

The table below provides examples of different scenarios corresponding to various estimated values of SD_{pooled} and possible corresponding sample size increases.

SD_{pooled}	Sample Size per Arm*	Sample Size Increase per Arm**	Power if Original Sample Size Maintained
20.0	204	Not applicable (Original)	90%
20.5	215	**11**	88%
21.0	225	**21**	86%
21.5	236	**32**	85%
22.0	247	**43**	83%
22.5	258	**54**	81%
23.0	270	**66**	79%
23.5	282	**78**	77%
24.0	294	**90**	75%
24.5	306	**102**	73%
25.0	318	**114**	71%
25.5	331	**127**	69%
26.0	344	**140**	68%
26.5	358	**154**	66%
27.0	371	**167**	64%

* Sample size (per arm) required to attain 90% power.

** Sample size increase (per arm) required to maintain 90% power.

Note: Sample size calculations are based on assumed mean difference of 7 between each HP-3070 treatment group and placebo and a 2-sided t-test at the 0.025 significance level.

With the procedure for re-estimation of pooled standard deviation and re-calculation of sample size in a blinded manner, no Type I Error adjustment is necessary (Kieser and Friede, 2003).

4.2.1. SAMPLE SIZE RECALCULATION DOCUMENTATION

Additional details of the sample size recalculation can be found in the SSR SAP version 1, dated July 7th, 2017. The sample size recalculation was conducted according to the SSR SAP on July 10th, 2017. The conclusion of the sample size recalculation analysis is documented in the Interim Sample Size Recalculation (ISSR) Study report dated July 27th, 2017.

4.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this Statistical Analysis Plan, Database Lock, Sponsor Authorization of Analysis Sets and Unblinding of Treatment. The final analysis will include a set of patient profiles to be presented in the final report as patient narratives. These profiles will be included for subjects who reported serious adverse events, treatment emergent adverse events leading to study discontinuation, or adverse events of EPS.

5. ANALYSIS SETS

Sponsor agreement and authorization of subjects included/ excluded from each analysis set will be obtained prior to the unblinding of the study.

5.1. ALL SUBJECTS SCREENED SET

The all subjects screened set will contain all subjects who provide informed consent for this study. This analysis set will be used for run-in period demographic and disposition summaries and will be based on data collected in the Interactive Voice Activated Response System (IVRS)/Interactive Web-based Response System (IWRS).

5.2. INTENT-TO-TREAT ANALYSIS SET

Intent-to-Treat (ITT) Analysis Set includes all consented and randomized subjects. Regardless of any protocol deviations, analyses performed on the ITT set will be based on the randomized treatment assignment and all available data.

5.3. FULL ANALYSIS SET

Full Analysis Set (FAS) includes all randomized subjects who have had at least 1 patch of double-blind study medication applied and who have a Baseline PANSS total score and at least 1 post-Baseline assessment of the primary efficacy measure (PANSS total score). The FAS will be used as the primary set for analysis of efficacy endpoints based on randomized treatment assignment.

5.4. SAFETY ANALYSIS SET

The Safety Analysis Set (SAF) includes all subjects who have had at least 1 patch of double-blind study medication applied and who have at least 1 post-dose safety measurement during the double-blind treatment period. In the unlikely event that errors may have occurred in treatment arm assignments, then analyses using the SAF will

be based on treatment actually received. The SAF will be used for the analysis of dermal evaluations and safety endpoints.

5.5. PHARMACOKINETIC ANALYSIS SET

The Pharmacokinetic Analysis Set (PAS) includes all subjects who have at least one dose of study medication during the double blind treatment period and have at least one blood sample for pharmacokinetic (PK) assessment. Subjects may be excluded from the PAS set if they significantly violate inclusion or exclusion criteria, significantly violate the protocol in a way that may influence the PK analysis, if any unexpected error occurs during the study that may influence the PK analysis (e.g., early detachment of transdermal systems, apparent sample switching, etc.) or if their data are unavailable or incomplete. The PAS will be used for the analysis with model based approach as well as for the presentation of descriptive summaries of PK data. Excluded cases will be documented together with the reason for exclusion.

Analysis dataset for pharmacokinetic assessments will be created by Metrum Research Group, LLC.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day during the run-in period and during the double blind treatment period will be calculated from the reference start date, and will be used to show start/ stop day of assessments and events.

Reference start date during the double blind treatment period is defined as the day of the first dose of study medication, (Day 1 is the day of the first dose of double-blind study medication), and will appear in every listing where an assessment date or event date appears.

Reference start date during the run-in period is defined as the day of the first dose of study medication during the run-in period.

- If the date of the event is on or after the reference date then:

Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date then:

Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to or on the date of first dose of double-blind study medication (including unscheduled assessments). For assessments done on the date of first double-blind study medication dose, if time of measurement is available, it will be compared to the date and time of the first double-blind dose of study medication to determine if the measurement is pre-dose (baseline) or post-dose (post-baseline).

6.3. DERIVED TIME POINTS

Early Termination (ET) visit information that is collected post-Baseline will be assigned to the next scheduled visit. This will apply to all data points used in efficacy and safety analysis. For each type of assessment, the ET visit data will be assigned to the next scheduled visit when that type of assessment is planned to be collected. The purpose for this derivation is to include ET assessments in the summary tables and listings.

6.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be included in analysis. Unscheduled measurements will not be included in by-visit summaries, but will contribute to the worst case value where required (e.g., shift tables).

In the case of a retest (same visit number assigned), the latest available measurement for that visit will be used for by-visit summaries.

Subject data listings will present all available data: scheduled, unscheduled, retest, and ET visit data.

6.5. WINDOWING CONVENTIONS

There will be no visit windowing for this protocol. All data will be organized and analysed according to the scheduled times as outlined in the protocol and by the visit denoted on the electronic Case Report Form (eCRF). Early termination visit information will be handled as described in Section 6.3.

6.6. STATISTICAL TESTS

All statistical tests of treatment effects will be performed at a 2 sided significance level of 0.05, unless otherwise stated. Confidence intervals will be 95%, unless otherwise specified in the description of the analyses.

For primary analysis and analysis of the key secondary endpoint, both unadjusted and adjusted p-values will be reported.

6.7. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as Test Value at Visit X – Baseline Value.

Continuous variables will be summarized by descriptive statistics (sample size [n], mean, standard deviation [SD], median, minimum, and maximum). Categorical variables will be summarized in frequency tables (n, frequencies, and percentages).

6.8. SOFTWARE VERSION

All analyses will be conducted using SAS® version 9.2 or higher.

Details for software to be used for model based analysis will be described in a standalone modeling and simulation plan.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following covariates and factors are used in the analyses. For details of their inclusion in the models, see the specific analysis section.

- Country
- Baseline value corresponding to the parameter being analyzed

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers internationally. Randomization to treatment arms will be stratified by country. Country will be used as a factor in statistical analyses.

7.3. MISSING DATA

In the calculation of total and subscale scores, missing individual items used in the derivations of aggregate scores will be handled as described in the sections defining the corresponding variables, in accordance with a scoring manual for each scale.

Missing endpoint values in this study may result from patients discontinuing from the study prematurely or

missing intermediate assessments while remaining on study. For primary analysis of the primary endpoint and other efficacy endpoints, missing observations will not be imputed. The primary analysis method for continuous endpoints will be based on a mixed model with repeated measures (MMRM) which utilizes all available data (complete and partial) from subjects included in an analysis set. The MMRM-based approach assumes that data are missing at random (MAR). MAR refers to a missingness mechanism that is independent of missing responses, conditionally on observed response history and covariates. This assumption inherently implies that the treatment effect is similar for those who discontinue prematurely and for those who complete the study in their respective treatment arms.

Sensitivity analyses to investigate robustness to missing data will be performed for the primary endpoint as described in Section 15.1.4, and key secondary endpoint as described in Section 15.2.3.

For analysis of categorical efficacy endpoints, such as PANSS responders based on percent improvement from baseline, subjects discontinuing from the study prematurely or missing intermediate measurements will be considered as non-responders.

Missing safety data will not be imputed.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

The primary and key secondary efficacy hypotheses will be grouped into two hierarchical families.

- Family 1 is the HP-3070 9mg versus placebo (Hypothesis 1) and the HP-3070 18 mg versus placebo (Hypothesis 2), based on the primary endpoint of change from baseline in PANSS total score at Week 6.
- Family 2 is the HP-3070 9mg versus placebo (Hypothesis 3) and the HP-3070 18 mg versus placebo (Hypothesis 4), based on the key secondary endpoint of change from baseline in CGI-S at Week 6.

A matched parallel gatekeeping procedure (Chen, *et al.*, 2005, Dmitrienko, *et al.*, 2007, Dmitrienko, *et al.*, 2008) will be used to control the overall Type I error rate in a strong sense at the level of 0.05. The hypothesis testing used in this gatekeeping procedure will be based on truncated and regular Hochberg procedure (see Appendix 2 for details) as follows:

1. The comparisons for the primary endpoint (hypotheses 1 and 2) are performed using a truncated Hochberg procedure with a truncation parameter γ=0.9.
2. The comparisons for CGI-S (hypotheses 3 and 4) corresponding to the doses that were significant in step 1 are performed using a regular Hochberg procedure.

The family F1 serves as a gatekeeper for F2 such that F2 will be examined only when the gatekeeper F1 has been successfully passed (i.e., at least one of the hypotheses in the F1 family is rejected). The matched gatekeeper procedure utilizes the special logical relationship between the primary and the key secondary parameters to enhance the power of statistical testing. The significance in the key secondary endpoint for a dose level cannot be claimed unless its corresponding primary hypothesis is found significant. In other words, the key secondary endpoint can be restricted to the doses where the primary endpoint is significant to account for logical relationships among the multiple comparisons. The subsequent Family will be tested for the hypothesis that corresponds with the dose of the hypothesis in previous Family that demonstrated significant effect over placebo. Multiplicity adjustment will be applied to the analysis of the primary and key secondary endpoints

performed on the Full Analysis Set. There will be no multiplicity adjustments made for analysis on the ITT Analysis set or for the other secondary endpoints.

7.5. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted primary and key secondary endpoints on the Full Analysis Set. It should be noted that the study is not designed to detect treatment differences within subgroups.

The following subgroups will be assessed and described within the exploratory analysis sections:

- Gender:
  - Female
  - Male
- Age (years):
  - < 55
  - ≥ 55
- Race in 2 categories:
  - Black/African American
  - All other races combined (American Indian/Alaska Native, Asian, Native Hawaiian/Other Pacific Islanders, or White)
- Severity at baseline
  - < 90 PANSS Total Score
  - ≥ 90 PANSS Total Score
- Region
  - United States
  - Russia
  - Rest of World
- BMI (kg/m^2)
  - < 25
  - ≥ 25 to < 30
  - ≥ 30
- Age of onset (years)
  - < 25

- ≥ 25

- Disease duration (years)
  - < 5
  - ≥ 5 to < 10
  - ≥ 10 to < 20
  - ≥ 20

Additional sub-groups may be added after reviewing the data.

8. OUTPUT PRESENTATIONS

Descriptive summaries and statistical analyses will be provided for assessments performed during the double-blind treatment period and follow-up period. In general, data collected during the screening and single-blind placebo run-in periods will be presented in subject listings only, with the exception of calculated Baseline values which will be summarized and used in analyses as appropriate.

Appendix 1 describes some conventions for presentation of data in outputs.

The templates provided in addition to this SAP will describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by IQVIA Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study. Subject disposition will be presented by treatment group and overall, as appropriate.

Number and percentage of subjects randomized will be summarized by country.

Number and percentage of subjects included in each Analysis Set (as defined in Section 5) will be summarized.

Number and percentage of subjects who completed or discontinued the study prematurely will be summarized for the double-blind treatment period overall. Reasons for study discontinuation during the double-blind period will be summarized for the ITT, FAS, safety and PK analysis sets. Reasons for study discontinuations during the single-blind period will be listed for all subjects screened.

A Kaplan-Meier plot of time to discontinuation during the double-blind period will be presented for the ITT analysis set by treatment group, where time-to-event will be computed in days as [date of last dose of double-blind study medication – date of randomization]. For subjects who were randomized but did not receive any double-blind study medication, time-to-event will be equal to 0. Subjects who complete the entire 6 weeks of double-blind treatment will be censored on the date of their last dose of double-blind study medication.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be summarized descriptively for the ITT Analysis Set.

No statistical testing will be carried out for demographic or other baseline characteristics.

Subject characteristics may include, but are not limited to:

- Age (years) - calculated relative to date of informed consent
- Gender
- Race
- Ethnicity
- Region
- Weight (kg)
- Height (cm)
- Body Mass Index (BMI) (kg/m^2)
- Schizophrenia Diagnosis
    - Time since first diagnosis of Schizophrenia (years)
    - Time since start of current exacerbated episode (weeks)
- Schizophrenia Baseline Efficacy
    - Baseline PANSS total score (< 90, >= 90), Baseline MSQ score
- Age (years) of first diagnosis of schizophrenia
- Antipsychotics treatment before current episode (yes/no)

10.1. DERIVATIONS

- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$
- Time since first diagnosis of Schizophrenia (years) =

(Date of first dose of double-blind study medication – date of first diagnosis)/365.25

- Time since start of current exacerbated episode (weeks) =

(Date of first dose of double-blind study medication – start date of current exacerbated episode)/7

11. MEDICAL HISTORY

Medical History information will be presented in listings only.

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

12. STUDY MEDICATION EXPOSURE

To ensure treatment compliance, patches will be applied and removed by designated qualified staff. The exact times of patch application and removal will be recorded on the eCRF. The date of first and last doses of double-blind study medication administration will be taken from the eCRF.

The date and time of first dose of double-blind study medication will correspond to the date and time when the first double-blind patch is applied for each subject. The date and time of the last dose of double-blind study medication will correspond to the date and time when the last patch of double-blind study medication is removed.

Exposure to study medication will be summarized in terms of duration of exposure (days) to the double-blind study medications for the Safety analysis set by treatment group.

Duration of exposure to the double-blind study medication will be summarized by treatment group as a continuous variable. Additionally, duration of exposure to the double-blind study medication will be summarized in terms of the number and percentage of subjects with exposure for less than 1 week, and at least 1, 2, 3, 4, 5, and 6 weeks. The total number of patches applied will also be summarized for the double-blind period and by week.

12.1. DERIVATIONS

Duration of exposure (days) to the double-blind study medication will be calculated as (date of last dose of double-blind study medication) – (date of first dose of double-blind study medication) + 1.

13. STUDY MEDICATION COMPLIANCE

Compliance with study medication during the double-blind period will be summarized for the ITT analysis set.

During the double-blind Treatment Period (Day 1 through Day 42) site personnel will apply 2 patches once daily to subjects as randomized. Patches will be applied by site personnel at approximately the same time every day and each patch will be worn for 24 hours.

If both patches are detached completely then 2 new patches from the subject's kit should be applied immediately, provided that there is at least 6 hours of time remaining before the next dose. If only one patch detaches completely, then the other patch should also be removed and 2 new patches from the subject's kit should be applied immediately, provided that there is at least 6 hours of time remaining before the next dose.

Number and percentage of subjects who are compliant (defined as using ≥ 80% and ≤ 120% of study medication) and noncompliant (defined as using less than 80% or more than 120% of study medication) during any evaluation period will be presented.

Compliance will be summarized for periods between every double-blind treatment period visit (Weeks 1 through 6) and double-blind period overall.

13.1. DERIVATIONS

Compliance with study medication (based on the drug accountability and patch application and removal data) will be calculated as the number of patches applied divided by the prescribed number of patches over a given period, expressed as a percentage.

Patches are prescribed once daily, 2 patches per administration, on the days while the subject remains on study treatment during the double-blind treatment period.

The number of patches that needed to be replaced due to detachment more than 6 hours before the next dose (as described in Section 13) will be counted in the number of patches prescribed. Similarly, the number of patches that were applied as a result of such detachment will be counted in the total number of patches applied.

14. MEDICATIONS

Medications taken from 6 months prior to the Screening visit through the End of Study (including follow-up period) must be recorded and will be summarized for the Safety analysis set as either prior, concomitant, or post-treatment medications.. All medications will be coded using World Health Organization Drug Dictionary (WHO-DD) version 19.

Prior medications are medications which started and stopped prior to the first dose of double-blind study medication. Prior medications that stopped within the six months prior to screening medication will be summarized. All medications reported on the eCRF will be included in the listing.

Concomitant medications are medications which are administered to the subject during the period of time starting at the date of first dose of double-blind study medication up to 1 day after the date of last dose of study medication. They include medications which:

- started on, or after the first dose of double-blind study medication (no later 1 day following the date of last dose of study medication), and
- ended on or after the date of first dose of double-blind study medication or were ongoing at the end of the study.

Post-treatment medications are medications which started more than 1 day after the date of last dose of double-blind study medication.

In the case where it is not possible to define a medication as prior, concomitant, or post-treatment, the medication will be classified as concomitant.

Number of subjects with concomitant medications will be summarized by WHO-DD Preferred Term, overall and by treatment group for the Safety Analysis Set. Multiple occurrences of medications coded to the same PT in a subject will be counted only once within the PT.

The following algorithm will apply to partial dates. Imputed dates will NOT be presented in the listings but may be used to determine the category of medications (prior, concomitant, or post-treatment).

If a medication, as reported on the eCRF, has a partially or completely missing start or end date, use the following algorithm to impute missing components of the date(s). Imputed dates will be used in order to determine prior/concomitant/post-treatment status of a therapy.

Let CMSTDTC represent the medication start date and CMENDTC represent the medication stop date.

If a therapy has some missing components in both the start and end dates, first impute the end date as follows (only if the therapy is not ongoing):

1. If CMENDTC contains only year and month – impute the missing day to the last day of the corresponding month (e.g., 31 for January, or 30 for April).
2. If CMENDTC contains only year – impute the missing day and month to the 31st of December of the corresponding year.
3. If CMENDTC is completely missing impute to the date of the last contact with the subject.

Note: The end date should remain null for medications that are ongoing.

After having imputed the end date (if needed), impute the therapy start date if it is partial or missing as follows:

1. If CMSTDTC contains only year and month – impute the missing day to the 1st day of the corresponding month.
2. If CMSTDTC contains only year – impute the missing day and month to the 1st of January of the corresponding year.

If CMSTDTC is completely missing impute to the date of informed consent or to the medication end date (previously imputed if needed), whichever is earlier.

15. EFFICACY OUTCOMES

15.1. PRIMARY EFFICACY

15.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy endpoint is the change in PANSS total score between Baseline and Week 6.

The PANSS consists of 3 subscales containing a total of 30 items. For each item, severity is rated on an anchored 7-point scale, with a score of 1 indicating the absence of symptoms and a score of 7 indicating extremely severe

symptoms.

The PANSS total score is the sum of all 30 items. The score ranges from 30 through 210, with higher values representing greater severity of illness.

If one or more items are missing at a given assessment, the total score will be set to missing.

15.1.2. Missing Data Methods for Primary Efficacy Variable

Missing PANSS total scores will not be imputed for primary analysis. The primary analysis method, MMRM, will utilize all data available during the double-blind treatment period (complete and partial) from subjects included in the analysis set.

Analysis of sensitivity to missing data for the primary endpoint will be performed as described in Section 15.1.4.

Missing data patterns will be described graphically by plotting mean changes from baseline in PANSS total score, positive, negative and general psychopathology subscales across visits by treatment group and subgroups of subjects that either completed the double-blind treatment period or discontinued early. Subjects who discontinued early will be grouped by week at which they discontinued (1 through 6).

15.1.3. Primary Analysis of Primary Efficacy Variable

The primary efficacy analysis will be performed for the Full Analysis Set.

The estimand in the primary analysis for efficacy for each dose is the difference between treatments groups (HP-3070 dose group vs. placebo) in the change from Baseline to Week 6 in PANSS total score in all subjects as randomized, under the assumption that all randomized patients remain on their randomized treatment throughout the trial. PANSS scores obtained 24 hours after removal of the double-blind study medication on Day 42 or PANSS scores obtained more than 24 hours after discontinuation of double-blind study medication and the subject switched to an approved antipsychotic treatment will be excluded as outliers. Outliers will be defined *a priori* as (i) PANSS total scores obtained more than 24 hours after removal of double-blind study medication on Day 42; or (ii) PANSS total scores obtained more than 24 hours after discontinuation of double-blind study medication and the subject switched to an approved antipsychotic treatment. Non-compliance/non-adherence to study treatment may lead to poor outcomes and introduce variability. The terminal half-life of asenapine from Saphris/Sycrest is 24 hours and the mean half-life of asenapine from HP-3070 patch ranged from 29.7 hours to 31.3 hours for all the application sites.

Considerable efforts will be made during the study conduct to prevent outliers. For example: site personnel will be instructed to not issue a day pass to patients on Day 41 (last day of double-blind patch application) and patients will be allowed to leave the clinic only after all Day 42 (Week 6) assessments are complete. Subjects without PANSS total score at Week 6 will be modeled as similar to those with data conditional on observed response history and covariates. All discontinued subjects will be assessed with PANSS total score at the time of treatment discontinuation.

The primary efficacy variable, change from Baseline to Week 6 in the PANSS total score for each of the 3 treatment arms, will be analyzed using an MMRM analysis. The MMRM model will include change from Baseline

in PANSS total score as the repeated dependent variable, with country, treatment (HP-3070 9 mg, HP-3070 18 mg, and placebo), visit (Weeks 1, 2, 3, 4, 5, and 6), treatment by visit interaction, and the Baseline PANSS total score as covariates. An unstructured covariance matrix will be assumed. In the event the convergence cannot be attained with the unstructured correlation matrix, the following alternative structures will be attempted in the specified order (from least restrictive to most restrictive): heterogeneous Toeplitz structure (TOEPH), heterogeneous autoregressive(1) (ARH(1)), heterogeneous compound symmetry (CSH), No Diagonal Factor Analytic (FA0(q), with q equal to the number of time points), Toeplitz structure (TOEP), autoregressive(1) (AR(1)), and compound symmetry (CS). The first structure in this list with which the model converges will be used. If either ARH(1) or AR(1) structure is used, a random subject intercept will also be included in the model. The Restricted Maximum Likelihood (REML) method will be used for the estimation of the covariance parameters. The Kenward-Rogers method will be used to estimate the denominator degrees of freedom. The treatment-by-time interaction term allows for comparisons of the treatment groups at each time point. Treatment comparisons of each HP-3070 dose to placebo at Week 6 will be used for the primary analysis.

SAS procedure MIXED will be used to perform this analysis as follows:

```
proc mixed data=<analysis dataset>;
                class TRT COUNTRY VISIT SUBJID;
                model CHG = TRT COUNTRY VISIT TRT*VISIT BASE / ddfm=kr;
                repeated VISIT / type=un subject=SUBJID;
                lsmeans TRT*VISIT / cl pdiff=all;
        run;
```

The following statistics will be reported based on the MMRM analysis: least squares mean (LSM) estimates for change from baseline in PANSS score at Week 6, standard errors and 95% confidence intervals (CIs) for LSMs by treatment group. LSM differences between treatment groups (i.e., HP-3070 9 mg vs. placebo and HP-3070 18 mg vs. placebo), the corresponding standard errors, 95% CIs, and p-values will be presented for Week 6. P-values corresponding to Week 6 comparisons will be used for inferential purposes of the primary analysis and the comparisons between each of the two HP-3070 doses versus placebo will be adjusted for multiplicity as described in Section 7.4.

Observed values and change from Baseline to Week 6 will also be summarized descriptively.

An MMRM model with heterogeneous variances will be fitted (using a GROUP=<treatment> option in the REPEATED statement of SAS PROC MIXED) and the Akaike's Information Criterion (AIC) from this model will be compared to the AIC value from the primary analysis model. If the AIC value for the model with heterogeneous variances is smaller, the results from this model will be presented.

Residuals and influence diagnostics will be performed for the primary MMRM, and if there is an indication that the normality assumption is violated and/or extremely influential observations are identified.

Model diagnostics will be performed through examination of graphical displays of studentized residuals versus predicted mean, a quantile-quantile plot of studentized residuals, fixed effects influence diagnostics and covariance parameter influence diagnostics. These diagnostic plots will be produced using the ODS GRAPHICS functionality of SAS PROC MIXED (using options RESIDUAL and INFLUENCE(ITER=5 EFFECT=<subject>).

15.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The following three patterns will be considered to separate informative (treatment failures) versus non-informative cases based on the reason(s) of discontinuation when imputation of missing values performed for subjects discontinued early:

Pattern 1: Discontinuation for any of the reasons: An adverse event, death, non-compliance, lack of efficacy, subject required treatment with a prohibited medication, pregnancy, physician decision, study terminated by investigator, study terminated by sponsor, subject withdrew consent, or other is informative;

Pattern 2: Discontinuation due to lack of efficacy, adverse event, or death is informative and discontinuations due to all other reasons are non-informative;

Pattern 3: Discontinuation due to lack of efficacy is informative and discontinuations due to all other reasons are non-informative.

The following sensitivity analyses will be performed for the primary efficacy variable:

Scenario #1: A pattern-mixture model (PMM) approach. Sensitivity analysis will consider a Missing Not At Random (MNAR) mechanism for the missing data, where it will be assumed that subjects who discontinue early from the HP-3070 treatment will follow the trajectory of outcomes similar to the one in the placebo arm after discontinuation of the HP-3070 treatment, taking into account observed values prior to discontinuation (Little and Yau, 1996; Ratitch et al., 2013). Subjects discontinuing early from the placebo arm will be assumed to have unobserved outcomes similar to placebo subjects who remain on placebo treatment. The assumption that efficacy profiles of dropouts after discontinuation of active treatment are similar to those of placebo subjects provides an estimate of efficacy attributable to the active treatment if received through the time point of interest, while limiting efficacy after early discontinuation to that of the placebo and trial effect. A pattern-mixture model approach using a placebo-based multiple imputation will be used for this analysis.

Intermittent missing data will be multiply imputed using the MAR assumption within each treatment arm. Monotone missing data (data missing after an early discontinuation) for all subjects (from placebo and HP-3070 treatment arms) will be multiply imputed using a placebo-based imputation model. The steps to implement this sensitivity analysis are detailed in Appendix 3.

PMM analysis may also be performed according to patterns 2 and 3. For these analyses, only the discontinuation reasons considered as informative will be imputed using the placebo-based imputation model; discontinuations for non-informative reasons will be multiply imputed using the MAR assumption within each treatment arm. PMM analyses for pattern 2 and/or pattern 3 may only be performed if dropout is considered high.

Scenario #2: A continuous responder analysis based on improvement from baseline in PANSS total score will also be performed as described in Section 15.3.1.9.

Scenario #3: Time-to-failure analysis will combine two types of missing data (missing at random and missing not at random). Time-to-failure analysis will be performed treating informative missing data as failures following pattern 1, 2, and 3, and using censoring rules for non-informative cases. Time to failure will be calculated from the first PANSS score after baseline that is <20% improvement from baseline if there is never an improvement in PANSS score >=20% during the study or from the first PANSS score that is <20% improvement from baseline after a timepoint with >=20% improvement.

Scenario #4: Analysis of Covariance (ANCOVA) on rank-transformed data at Week 6, adjusted for baseline and country, will be also performed as sensitivity analysis.

In order to perform an ANCOVA on rank-transformed data, changes from Baseline to Week 6 in the PANSS total score will be transformed to ranks as described in Appendix 4. Before performing the rank transformation, subjects with missing data at Week 6 will be imputed with a change from baseline equal to the worst (largest) change from baseline in observed data plus 1 for informative cases following pattern 1, so that these subjects would have the worst (highest) rank after the transformation. (It should be noted that with an assignment of the highest rank to subjects with missing data, the rank-based ANCOVA, contrary to the primary analysis, does not assume a MAR mechanism, but rather implies the worst outcome for all early discontinued subjects regardless of treatment arm). The details of the rank-based ANCOVA are described in Appendix 4.

Sensitivity analysis to investigate impact of outliers on primary efficacy: To investigate the impact of outliers on the primary efficacy analysis, a sensitivity analysis will be performed by including outliers.

15.2. KEY SECONDARY EFFICACY

15.2.1. KEY SECONDARY EFFICACY VARIABLES & DERIVATIONS

15.2.1.1. Change in CGI-S Score Between Baseline and Week 6

The severity of illness for each subject will be rated using the CGI-S. To perform this assessment, the rater or Investigator will answer the following question: "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" Response choices include: 0 = not assessed; 1 = normal, not at all ill, 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill subjects.

Numerical values 1 through 7 corresponding to each response category (except "not assessed" category) will be used in analysis. The category of "not assessed" will be treated as a missing numerical value for analysis.

15.2.2. MISSING DATA METHODS FOR KEY SECONDARY EFFICACY VARIABLES

Missing data for the key secondary endpoint of change in CGI-S score between baseline and Week 6 will be treated in the same way as for the primary efficacy endpoint.

15.2.3. ANALYSIS OF KEY SECONDARY EFFICACY VARIABLES

Analysis of the key secondary efficacy endpoint will be performed for the Full Analysis Set with multiplicity adjustment as described in Section 7.4.

Change from Baseline in CGI-S score at Week 6 will be analyzed in the same way as described in Section 15.1.3 for the primary endpoint, with the only difference that the MMRMs will use Baseline value of CGI-S as covariate instead of Baseline PANSS total score.

Sensitivity analysis of the key secondary endpoint will be performed in the same way as described in Section 15.1.4 for the primary endpoint.

15.3. OTHER SECONDARY EFFICACY

15.3.1. EXPLORATORY EFFICACY VARIABLES & DERIVATIONS

15.3.1.1. Change from Baseline in PANSS Total Score at Weeks 1 through 5

PANSS total score will be calculated for each subject and time point as described in Section 15.1.1.

15.3.1.2. Change from Baseline in CGI-S Score at Weeks 1 through 5

CGI-S scores at each time point will be assessed as described in Section 15.2.1.1.

15.3.1.3. CGI-I Responder at Weeks 1 through 6

The efficacy of trial medication will be rated for each subject using the CGI-I. The rater or Investigator will rate the subject's total improvement whether or not it is due entirely to drug treatment. All responses will be compared to the subject's condition at Baseline prior to the first dose of double-blind study drug. Response choices include: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. The category of "not assessed" will be treated as a missing numerical value for analysis. CGI-I responders are defined as subjects who have a score of 1 (very much improved) or a score of 2 (much improved).

15.3.1.4. CGI-I Score at Weeks 1 through 6

Numerical values 1 through 7 corresponding to each CGI-I response category as described in Section 15.3.1.3 (except "not assessed" category) will be used in analysis. The category of "not assessed" will be treated as a missing numerical value for analysis. CGI-I score at each week will be analyzed in the same way as described in Section 15.1.3 for the primary endpoint, with the only difference that the MMRM will use Baseline value of CGI-S as covariate instead of Baseline PANSS total score.

15.3.1.5. Change from Baseline in PANSS Positive Subscale at Weeks 1 through 6

PANSS Positive Subscale is a sum of 7 positive items: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility.

If one or more items in the subscale are missing at a given assessment, the subscale score will be set to missing.

15.3.1.6. Change from Baseline in PANSS Negative Subscale at Weeks 1 through 6

PANSS Negative Subscale is a sum of 7 negative items: blunted affect, emotional withdrawal, poor rapport,

passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking.

If one or more items in the subscale are missing at a given assessment, the subscale score will be set to missing.

15.3.1.7. Change from Baseline in PANSS General Psychopathology Subscale at Weeks 1 through 6

PANSS General Psychopathology Subscale is a sum of 16 items: somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance.

If one or more items in the subscale are missing at a given assessment, the subscale score will be set to missing.

15.3.1.8. PANSS Responder Based on ≥30% Improvement from Baseline in PANSS total score at Weeks 1 through 6

At each time point, subjects having a 30% or greater improvement from baseline in PANSS total score will be defined as "responders".

The PANSS total score percentage change will be defined as (Value at Week X – Baseline value) X 100 / (Baseline value).

The responder indicator will be set to 1 if the percentage change is less than or equal to -30% and set to 0 if the percentage change is greater than -30% or missing.

15.3.1.9. PANSS Responder Based on >=X% Improvement from Baseline in PANSS total score at Week 6

At Week 6, responder status will be derived in a similar way as described in section 15.3.1. 8 at different levels of required percent improvement from baseline where X=5% to 100% with 5% increments.

A continuous responder analysis will be performed based on these derivations as described in Section 15.3.3.3.

15.3.1.10. Change from Baseline in CDSS Score at Weeks 1 through 6

The CDSS is a nine-item scale designed for assessment of the level of depression in patients with schizophrenia. Each of the 9 items is rated on a 4-point scale, scored from 0-3. The first 8 items are rated on the basis of responses during a semi-structured interview conducted by a qualified clinician. The ninth item (Observed Depression) is rated by evaluating signs and symptoms over the course of the interview.

The total score is derived by adding each of the 9 items together. Totals scores of 6 or more identifies the presence of treatment emergent depression predictive of major depressive episodes. If one or more items are missing at a given assessment, the total score will be set to missing.

15.3.1.11. MSQ Subscale Scores at Weeks 2, 4, and 6

The MSQ is a single-item questionnaire used to assess the level of patient's satisfaction or dissatisfaction with the medication they are taking. Responses can range from Extremely Dissatisfied (1) to Extremely Satisfied (7).

15.3.2. MISSING DATA METHODS FOR OTHER SECONDARY EFFICACY VARIABLES

For continuous variables, missing data will be handled in the same way as for the primary efficacy endpoint.

For responder-type endpoints, subjects with missing data at a given time point will be classified as non-responders at that time point.

15.3.3. ANALYSIS OF OTHER SECONDARY EFFICACY VARIABLES

All other secondary efficacy endpoints will analysed for the Full Analysis Set.

15.3.3.1. Other Secondary Efficacy Endpoints Based on Continuous Variables

All endpoints based on continuous variables (all except PANSS responder endpoints based on percentage improvement) will be analyzed in the same way as described in Section 15.1.3 for the primary endpoint, with the only difference in that the MMRM models will use Baseline value of the corresponding efficacy variable as covariate instead of Baseline PANSS total score.

15.3.3.2. Other Secondary Efficacy Endpoints Based on Binary (Responder) Variables

Effect of treatment on the proportion of PANSS responders from Baseline in PANSS total score as well as on the proportion of CGI-I responders at Weeks 1 through 6 will be tested using the Cochran Mantel Haenszel (CMH) method stratified by country. The hypothesis test will be based on the General Association statistic.

Descriptive summaries will be provided for the number and percentage of responders at Weeks 1 through 6 by treatment group. Also, estimates of the proportion of responders in each treatment group and differences of proportions (risk difference) between the treatment groups will be provided using the standard method based on the binomial distribution. Two-sided 95% CIs for proportion estimates based on the Wilson method and 2-sided 95% CIs for risk differences based on the Newcombe method will be reported.

15.3.3.3. PANSS Continuous Responder Analysis at Week 6

A continuous responder analysis will be performed based on definition of responder at multiple levels of percent improvement from Baseline, from 5% to 100% with 5% increments. Results will be reported by means of a graph with response threshold on the X-axis and proportion of responders in each treatment group on the Y-axis. Corresponding data will be presented in a summary table.

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified within the relevant section.

16.1. TREATMENT EMERGENT ADVERSE EVENTS

Adverse events will be coded using MedDRA central coding dictionary, version 20.1 . Severity for AEs is classified in the eCRF as 'mild', 'moderate', or 'severe'.

Treatment Emergent Adverse Events (TEAEs) are defined as AEs that first occurred or worsened in severity after the first administration of the study drug.

TEAEs during the double-blind treatment period is defined as an AE with a start date on or after the date of first dose of double-blind study medication through the 30 day follow-up period. The same rule applies for Run-in Period (for those enrolled in the double-blind period)

SAEs that occur within 30 days after last dose of double-blind study medication will be reported.

In the case where it is not possible to define an AE as treatment-emergent or not, the AE will be classified by the worst case i.e. treatment-emergent.

Adverse event summaries will include numbers of events and subject incidence (number and percentage of subjects with at least one event) by treatment group and further categorization as described below.

An overview of AEs within each of the categories described below will be provided:

- AEs (for those who enrolled in the double-blind period) which occurred during the single-blind run-in or double-blind period
- TEAEs
- TEAEs by highest severity
- TEAEs by strongest relationship to study medication (Not Related, Related)
- TEAEs leading to study medication discontinuation
- Serious TEAEs
- Serious TEAEs by strongest relationship to study medication (Not Related, Related)
- TEAEs leading to death
- Commonly occurring TEAEs (defined as those which occur in 5% or more of the subjects in any treatment arm)
- TEAEs at the patch application site

Multiple occurrences of the same category of AEs will be counted once for each subject, at the highest severity and strongest relationship to study medication as appropriate.

Listings will include all AEs (TEAEs and non-TEAEs) collected on the eCRF for each study period based on the onset date.

The following algorithm will apply to partial dates. Imputed dates will NOT be presented in the listings but may be used to determine treatment-emergent status of AEs and category of medications (prior, concomitant, or post-treatment).

If an adverse event, as reported on the eCRF, has a partially or completely missing event start or end date, use the following algorithm to impute missing components of the date(s). Imputed dates will be used in order to determine treatment-emergent status of an AE as well as to assign the AE to one of the treatment periods.

Let AESTDTC represent the AE start date and AEENDTC represent the AE stop date.

If an AE has some missing components in both the start and end dates, first impute the end date as follows (only if AE is not ongoing):

1. If AEENDTC contains only year and month – impute the missing day to the last day of the corresponding month (e.g., 31 for January, or 30 for April).
2. If AEENDTC contains only year – impute the missing day and month to the 31st of December of the corresponding year.
3. If AEENDTC is completely missing impute to the date of the last contact with the subject.

Note: AE end date should remain null for AEs that are ongoing.

After having imputed the AE end date (if needed), impute the AE start date if it is partial or missing as follows:

1. If AESTDTC contains only year and month
   - 1.1 If AESTDTC = year-month part of the first dose date of study medication:
     - 1.1.1 If AE is not ongoing – impute to the earlier of the first dose date of double-blind study medication and AE end date (previously imputed if needed).
     - 1.1.2 If AE is ongoing – impute to the first dose date of double-blind study medication.
   - 1.2 If AESTDTC ≠ year-month part of the first dose date of double-blind study medication, impute the missing day to the first day of the month.
2. If AE start date contains only year
   - 2.1 If AESTDTC = year part of the first dose date of double-blind study medication:
     - 2.1.1 If AE is not ongoing – impute to the earlier of the first dose date of double-blind study medication and AE end date (previously imputed if needed).
     - 2.1.2 If AE is ongoing – impute to the first dose date of double-blind study medication.
   - 2.2 If AESTDTC ≠ year part of the first dose date of double-blind study medication impute to January 1st of the year in AESTDTC.
3. If AE start date is completely missing
   - 3.1 If AE is not ongoing – impute to the earlier of the first dose date of double-blind study medication and AE end date (previously imputed if needed).

If AE is ongoing – impute to the first dose date of double-blind study medication.

16.1.1. ALL AEs

Incidence of TEAEs will be presented by SOC and PT and also broken down further by maximum severity and relationship to study medication. Summaries will be sorted by incidence: by SOC and by PT within SOC.

16.1.1.1. TEAEs by Relationship to Study Medication and Severity

Relationship, as indicated by the Investigator, is classed as ”Unrelated”, “Unlikely”, “Possible”, and “Probable” (increasing severity of relationship). A ”Related” TEAE is defined as a TEAE with a relationship to study medication as ”Possible” or ”Probable”. TEAEs with a missing relationship to study medication will be regarded “Related”. If a subject reports the same AE more than once within a SOC/PT, the AE with the worst case relationship to study medication will be used in the corresponding summary.

Severity will be presented within Relationship. Severity is classed as mild/ moderate/ severe (increasing severity). TEAEs starting after the first dose of study medication with a missing severity will be classified as severe. If a subject reports a TEAE more than once within a SOC/PT at the worst relationship level, the AE with the worst severity will be used in the corresponding summary.

16.1.2. TEAEs LEADING TO DISCONTINUATION OF STUDY MEDICATION

TEAEs leading to permanent discontinuation of study medication will be identified by using the category of “Drug Withdrawn (Drug Discontinued)” from the eCRF fields “Action Taken in Regard to Study Drug” on the “Adverse Events” eCRF page.

For TEAEs leading to discontinuation of study medication, summaries by SOC and PT will be prepared. A subject data listing for TEAEs leading to discontinuation of study medication will be provided.

16.1.3. SERIOUS ADVERSE EVENTS

Serious adverse events are those events recorded as “Serious” on the Adverse Events page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared. A subject data listing for all SAEs will be provided.

16.1.4. ADVERSE EVENTS LEADING TO DEATH

TEAEs leading to death are those events which are recorded as “Fatal” on the Adverse Events page of the eCRF. A summary of TEAEs leading to death by SOC and PT will be prepared. A subject data listing for TEAEs leading to death will be provided.

16.1.5. COMMONLY OCCURRING TEAEs

Commonly occurring TEAEs are defined as those which occur in 5% or more of the subjects in any treatment arm. A summary of commonly occurring TEAEs by SOC and PT will be prepared. A subject data listing for commonly occurring TEAEs will be provided.

16.1.6. AEs AT PATCH APPLICATION SITE

Spontaneous complaints of dermal reactions (skin irritation, discomfort) will be recorded as AEs. Spontaneous reports might include but are not limited to the following: initial dermal response and exacerbation of an existing response. AEs at the patch application site will be summarized by PT and severity for the events occurring during the double-blind period. A subject data listing of AEs at the patch application site will be provided.

16.2. DEATHS

If any subjects die during the study, the information will be presented in a subject data listing.

16.3. LABORATORY EVALUATIONS

A central laboratory designated by the Sponsor will be used for all laboratory assessments during the trial. If an immediate result is required, a sample should be sent to both the local and central laboratory.

Laboratory assessments will include standard measures of hematology, clinical chemistry [including prolactin levels], urinalysis, urine drug screen, and some additional tests as per protocol, Section 6.3. Pregnancy testing will be done for women of child-bearing capacity.

The central laboratory will not report prolactin levels to the sites, Sponsor, or other personnel involved in the study conduct until the overall study unblinding at final analysis, because this could potentially result in unblinding the treatment.

Urine drug screens may be done at the Investigator's discretion. If the subject is allowed to leave the hospital during study, an alcohol breathalyzer and urine drug tests must be done when the subject returns.

Summary tables will summarize laboratory data for each scheduled time point based on the visits at which samples were collected. Unscheduled evaluations will be presented in subject listings, but will not be summarized in tables. Unscheduled evaluations will be used in the determination of baseline values.

All available laboratory data will be presented in subject listings.

Presentations will use standard international (SI) Units for all laboratory tests.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification, or "> X", i.e. above the upper limit of quantification, will be converted to X for the purpose of quantitative summaries, but will be presented as originally recorded, i.e. as "< X" or "> X" in the subject listings.

Laboratory findings will be classified as Low, Normal, and High relative to the laboratory. Central laboratories will also provide a classification of Clinically Significant or Not Clinically Significant abnormalities. Hematology and serum chemistry laboratory findings will also be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria, version 4.03, as applicable.

The following descriptive summaries will be provided for hematology, serum chemistry, and urinalysis data by treatment group:

- Actual and change from baseline by visit for quantitative measurements
- Shift from baseline to the worst on-treatment result for each category of result for categorical measurements. Worst on-treatment result is defined as the worst result occurring after the administration of the first dose of double-blind study medication.
- Number and percentage of subjects with an absolute neutrophil count of <1000 per mm3 by visit
- Number and percentage of subjects who meet the definition of potential Hy's Law cases at any point during the study. Potential Hy's Law cases are determined based on the FDA Guidance for Industry on Drug Induced Liver Industry, July 2009.
    - Alanine transaminase (ALT) or Aspartate transaminase (AST) >3x upper limit of normal (ULN) and
    - Alkaline phosphatase (ALP) <2x ULN and
    - Increase in bilirubin ≥2x ULN

    Hy's Law evaluation based on the above

    - (ALP) ≤2x ULN [for subjects that meet the criteria of ALP≤2, present ALT or AST elevations with ≥3x ULN]
    - ALT ≥3x ULN
    - AST ≥3x ULN

    Ranges of Interest

    - Creatine kinase ≥3x ULN
    - Prolactin ≥4x ULN
    - Bilirubin ≥2x ULN
- Shift from baseline to the worst on-treatment result based on classification of Low, Normal, and High relative to the laboratory reference ranges (see Section 16.3.1). Worst on-treatment result is defined as the worst result occurring after the administration of the first dose of double-blind study medication.
- Shift from baseline to the worst on-treatment result based on classification of clinically significant and not clinically significant. If at least one laboratory finding is clinically significant, the subject will be counted in the clinically significant category. Worst on-treatment result is defined as the worst result occurring after the administration of the first dose of double-blind study medication.
- Shift from baseline to the worst on-treatment result based on NCI CTCAE grades. Worst on-treatment

result is defined as the worst result occurring after the administration of the first dose of double-blind study medication.

A subject listing of subjects with Clinically Significant or NCI CTCAE Grade ≥ 3 abnormal post-baseline measurements will be provided. This listing will include all available results (normal and abnormal) from laboratory tests for which a subject had at least one Clinically Significant or NCI CTCAE Grade ≥ 3 abnormal post-baseline value.

Results of urine drug screens and pregnancy testing will be presented in subject listings only.

16.3.1. Laboratory Reference Ranges and Markedly Abnormal Criteria

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

In addition to the high and low quantitative laboratory assignments (as identified by means of the laboratory reference ranges), laboratory assessments will also be graded in accordance with the predefined criteria as presented in NCI CTCAE criteria, version 4.03 (Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.03, DCTD, NCI, NIH, DHHS; (http://ctep.cancer.gov), Publish Date: June 14, 2010)

16.4. ECG Evaluations

Twelve-lead ECGs will be recorded at Screening and at each visit during the double-blind treatment period and at the time the subject discontinues the study early. A central ECG service will be utilized for reading all ECGs in order to standardize interpretations for the safety analysis. In addition, ECG results will be evaluated at the investigational site to monitor safety during the trial. The Investigator or designee will note whether or not any abnormal results are of clinical significance.

The following ECG parameters will be reported for this study:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTc Interval (msec)
- QTcF Interval (msec)
- QTcB Interval (msec)
- HR (bpm)
- Overall assessment of ECG (Investigator's judgment):
  - Normal
  - Abnormal, Not Clinically Significant (ANCS)

- Abnormal, Clinically Significant (ACS)

The following summaries will be provided for ECG data:

- Actual and change from baseline by visit for quantitative measurements
- Number and percentage of subjects with each category of overall assessment (Investigator's judgement) by visit
- Shift from baseline to worst on-treatment category of overall assessment of ECG. Worst on-treatment result is defined as the worst result occurring after the administration of the first dose of double-blind study medication.
- Number and percentage of subjects with markedly abnormal ECG results (see Section 16.4.2) by visit and incidence of markedly abnormal ECG results for study overall (post-Baseline)

A listing of subjects with at least one post-Baseline markedly abnormal ECG result will be presented and will include all available ECG data for such subjects.

16.4.1. ECG Specific Derivations

No derivations will be necessary. All parameters will be provided directly by the central ECG reading center.

16.4.2. ECG Markedly Abnormal Criteria

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following criteria:

- Absolute values for QT interval, QTc interval, QTcB interval and QTcF will be classified as:
  - > 450 msec
  - > 480 msec
  - > 500 msec
- Change from Baseline for QT interval, QTc interval, QTcB interval and QTcF will be classified as:
  - ≥30 msec increase from baseline
  - ≥60 msec increase from baseline
- Other abnormal values:
  - HR (bpm) ≥ 100 bpm
  - PR interval (msec) ≥ 210 msec
  - QRS interval (msec) ≥ 120 msec

16.5. Vital Signs

The following Vital Signs measurements will be reported for this study at each visit:

- Sitting, supine, and standing Systolic Blood Pressure [SBP] (mmHg)
- Sitting, supine, and standing Diastolic Blood Pressure [DBP] (mmHg)
- Sitting, supine, and standing Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (^{o}C)
- Weight (kg)

Height (cm) will measured at Screening only.

Subjects with a decrease of ≥30 mmHg in SBP and/or a decrease of ≥20 mmHg in DBP after ≥3 minutes standing compared to the previous supine blood pressure will be classified as having orthostatic hypotension.

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit
- Number and percentage of subjects with orthostatic hypotension by visit
- Incidence of markedly abnormal values (see Section 16.5.1) by visit

16.5.1. VITAL SIGNS MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the following criteria:

Variable	Unit	Low	High
SBP	mmHg	≤ 90 mmHg AND change from baseline ≤ -20 mmHg	≥ 180 mmHg AND change from baseline ≥ 20 mmHg
DBP	mmHg	≤ 50 mmHg AND change from ≤ -15 mmHg	≥ 105 mmHg AND change from baseline ≥ 15 mmHg
Heart rate	bpm	≤ 50 bpm AND change from baseline ≤ -15 bpm	≥ 120 bpm AND change from baseline ≥ 15 bpm
Body temperature	˚C	NA	≥ 38.3 ˚C AND change from baseline ≥ 1.1 ˚C
Weight	Kg	percentage change from baseline ≤ -7.0 %	percentage change from baseline ≥ 7.0 %

16.6. PHYSICAL EXAMINATION

A complete physical examination including examination of the head, neck, ears and throat, thorax, abdomen, urogenital, extremities, neurological, and skin and mucosae will be performed at Screening. Abnormal physical examination findings during screening will be recorded as medical history and abnormal physical examination findings at subsequent visits will be recorded as adverse events.

16.7. OTHER SAFETY ASSESSMENTS

16.7.1. SIMPSON ANGUS SCALE

The SAS consists of a list of 10 symptoms of Parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Each item will be rated on a 5-point scale, with a score of 0 (zero) representing absence of symptoms, and a score of 4 representing a severe condition.

The SAS total score is the sum of the scores for all 10 items and ranges between 0 and 40. Lower values of the SAS total score indicate milder symptoms. If one or more items are missing at a visit the SAS total score will be set to missing.

Descriptive summaries of actual and change from baseline in SAS total scores by visit will be provided for each treatment group.

All data, including individual items and SAS total score, will be presented in a subject listing.

16.7.2. ABNORMAL INVOLUNTARY MOVEMENT SCALE

The AIMS assessment consists of 10 items describing symptoms of dyskinesia. Facial and oral movements (items 1 through 4), extremity movements (items 5 and 6), and trunk movements (item 7) will be observed unobtrusively while the subject is at rest (e.g., in the waiting room), and the Investigator will also make global judgments on the subject's dyskinesias (items 8 through 10). Each item will be rated on a 5-point scale, with a score of 0 representing absence of symptoms (for item 10, no awareness), and a score of 4 indicating a severe condition (for item 10, awareness, severe distress). For this scale, the subject is to be sitting on a hard, firm chair. In addition, the AIMS includes 2 yes/no questions that address the subject's dental status.

The global severity score is the response to "Severity of abnormal movements" found within the global judgments section.

The AIMS Movement Rating Score is defined as the sum of items 1 through 7 (i.e., items 1 through 4, facial and oral movements; items 5 and 6, extremity movements; and item 7, trunk movements). The possible range for the total AIMS score is 0 to 28. Higher values of the total AIMS score indicate increased severity in abnormal movement. If one or more of the AIMS total score items are missing at a visit, the score will be set to missing.

Descriptive summaries of actual and change from baseline in the global severity score and AIMS total score by

visit will be provided for each treatment group.

All data, including individual items and AIMS total score, will be presented in a subject listing.

16.7.3. BARNES AKATHISIA RATING SCALE

The BARS consists of 4 items related to akathisia. These include objective observation of akathisia by the Investigator, subjective feelings of restlessness by the subject, subjective distress due to akathisia, and global clinical assessment of akathisia. The first 3 items will be rated on a 4-point scale, with a score of 0 representing absence of symptoms and a score of 3 representing a severe condition. The global clinical evaluation will be made on a 6-point scale, with 0 (zero) representing absence of symptoms and a score of 5 representing severe akathisia.

The BARS Global Score is defined as the global clinical assessment of akathisia.

The BARS total score is the sum of items 1 through 3 and ranges from 0 to 9. Higher values of the BARS total score indicate akathisia is higher in severity. If one or more items at a visit are missing the total will not be calculated.

Descriptive summaries of actual and change from baseline in the BARS Global Score and total score by visit will be provided for each treatment group.

All data, including individual items and BARS total score, will be presented in a subject listing.

16.7.4. SUICIDALITY: COLUMBIA-SUICIDE SEVERITY RATING SCALE

Suicidality will be monitored during the trial using the C-SSRS. This trial will use the "Baseline/Screening" and "Since Last Visit" versions of the scale. The "Baseline/Screening" version, which assesses the lifetime experience of the subject with suicide events and suicidal ideation and the occurrence of suicide events and/or ideation within a specified time period prior to entry into the trial, will be completed for all subjects at the Screening visit to determine eligibility. The "Since Last Visit" C-SSRS form will be completed at Baseline to confirm eligibility (prior to the first dose) and at all post-Baseline visits.

Suicidal Ideation is rated on a 6-point scale from 0="No ideation present" to 5="Active ideation with plan and intent". A score of 4 or 5 on this scale indicates serious suicidal ideation. Any score greater than 0 will be counted as having suicidal ideation.

The Ideation Intensity total score is the sum of five items from the Ideation Intensity scale: frequency, duration, controllability, deterrents, and reasons for ideation. The possible range for the Intensity total score is 0 to 25. If a subject did not endorse any suicidal ideation, a score of 0 for the intensity total score will be given.

Suicidal Behavior is collected as actual attempt, interrupted attempt, and aborted attempt. Any attempt will be defined as suicidal behavior.

The following summaries will be presented:

- Suicidal ideation:

- The number and percentage of subjects with each type of suicidal ideation or any suicidal ideation will be summarized by visit
- The number and percentage of subjects with any suicidal ideation and by their most severe suicidal ideation type during each study period (Baseline/Screening and Double-Blind Treatment Period)
- The number and percentage of subjects with no suicidal ideation at Baseline/Screening, and any type of suicidal ideation post-Baseline
- The number and percentage of subjects with worsening of suicidal ideation (most severe suicidal ideation post-Baseline was more severe than it was at Baseline/Screening)

- Suicidal behavior:
  - The number and percentage of subjects by their most severe suicidal behavior type during each study period (Baseline/Screening and Double-Blind Treatment Period)
  - The number and percentage of subjects with any suicidal behavior and those completing suicide will be summarized by visit and overall by study period
  - The number and percentage of subjects with no suicidal behavior at Baseline/Screening, and any type of suicidal behavior post-Baseline
- Suicidality: Suicidality is defined as having at least one occurrence of suicidal ideation or at least one occurrence of suicidal behavior. At each visit, the suicidality indicator will be set to 1 if the subject exhibits suicidality, 0 if the subject does not exhibit suicidality, and missing otherwise.
  - The number and percentage of subjects with suicidality will be summarized overall by study period (Baseline/Screening and Double-Blind Treatment Period)
  - The number and percentage of subjects with no suicidality at Baseline, and any suicidality post-Baseline
  - The number and percentage of subjects with at least one occurrence of suicidal ideation and at least one occurrence of suicidal behavior post-Baseline
  - The number and percentage of subjects without both suicidal ideation and suicidal behavior at Baseline with at least one occurrence of suicidal ideation and at least one occurrence of suicidal behavior post-Baseline

All C-SSRS data will be presented in a subject listing.

16.7.5. Evaluations of Patch and Dermal Assessments

Each subject will wear 2 patches simultaneously; both patches will be applied to 1 application site in close proximity without overlapping. Dermal assessments for both patches will be assessed but only the worse of the 2 scores will be recorded.

The actual time of all scheduled and unscheduled evaluations will be recorded.

16.7.5.1. Skin irritation at patch application site

Irritation assessed at the patch application site each day after patch removal will be recorded using the descriptors provided in the Berger and Bowman scale and any irritation observed will be recorded as an AE. In addition, spontaneous reports of skin irritation by the subject will be recorded as an AE. If a subject reports skin irritation, then site personnel will conduct visual inspection of the skin at the application site and will record the description of the observed skin irritation using the descriptors provided in the Berger and Bowman scale. The maximum results from the Berger and Bowman scale results will be summarized for each study week and over the entire double-blind treatment period. Scale results will be combined in the following ways:

1. By concatenating the 2 scores (i.e., 0N, 1N, 2N, 2A, 2B, 3N, 3A, 3B, 3C, 3F, etc.).
2. By summation of the dermal response scale score and a numeric equivalent for the other effects observations scale. The character grades will be converted to numerical equivalents in the following way: N=0, A=0, B=1, C=2, F=3, G=3 and H=3. By the summation, a combined score is obtained for each patch at each evaluation time point (e.g., 2C=2+2=4). If no grade was assigned for the other effects observations (N) scale the combined score will consist of the dermal response scale score only.

Dermal response scale:

Score	Skin Appearance
0	No evidence of irritation
1	Minimal erythema (barely perceptible)
2	Definite erythema, readily visible; minimal edema or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test (application) site

Other Effects:

Score (numeric equivalent)	Letter Grade
A (0)	Slightly glazed appearance
B (1)	Marked glazing
C (2)	Glazing with peeling and cracking
F (3)	Glazing with fissures
G (3)	Film of dried serous exudate covering all or part of the patch site
H (3)	Small petechial erosions and/or scabs

16.7.5.2. Discomfort at patch application site

Report of discomfort at the patch application site will be recorded as an AE. If a subject reports discomfort at the patch application site, the site personnel will ask the subject to rate the discomfort as mild, moderate, or severe, and will ask the subject to describe the discomfort. The description of discomfort as reported by the subject should be recorded verbatim.

These data will be summarized as part of AEs and AEs at patch application site summaries as described in Section 16.1.

16.7.5.3. Patch Adhesion and Adhesive Residue

Patch adhesion will be assessed by site personnel at the time points defined in the Protocol Schedule of Events. In addition to patch adhesion assessments by site personnel at specified time points, subjects should be instructed to check adhesion of the patch throughout the day and report to site personnel immediately if patch detaches completely or if partial patch detachment is observed.

Adhesion will be evaluated according to Yes/No questions as follows:

1. Is the patch fully attached to the skin? Yes/No
2. If 'No', did the patch detach completely? Yes/No

The following variables will be derived for each subject for the evaluation of adhesion:

- Any occurrence of complete detachment for each study week and over the entire double-blind treatment period
- Any occurrence of partial detachment for each study week and over the entire double-blind treatment period

Descriptive summaries of the above variables will be presented. All adhesion data collected during the single-blind run-in and double-blind period will be presented in subject listings.

Immediately after the removal of a patch, the amount of adhesive residue remaining at the application site will be examined by the Investigator or designee and graded as described below.

Adhesive Residue	
Score	**Definition**
0	None
1	Light
2	Medium
3	Heavy

The following variable will be derived for each subject for the evaluation of adhesive residue:

- Any occurrence of medium or heavy adhesive residue for each study week and over the entire double-blind treatment period

Descriptive summaries of the above variable will be presented. All adhesive residue data collected during the single-blind run-in and double-blind period will be presented in subject listings.

17. PHARMACOKINETICS

At least 3 blood samples will be collected at 2, 14, and 22 hours after application of the patch with ± 2 hour-window on Day 21 and 42.

Individual plasma concentrations will be presented in subject listings and descriptive statistics for plasma concentration will also be summarized. Actual sampling time after doing will be used for the analysis.

A model-based approach will be used to assess the impact of covariates on asenapine exposure (population pharmacokinetics) and to explore the exposure-response relationship of relevant endpoints. These analysis will be done by Metrum Research Group LLC.

These analysis will be conducted using standard population nonlinear mixed effects modeling methods. Details for model based analysis (such as the choice of studies/data to be included for analysis, covariates to be tested, data handling, model development, model validation) is not covered by this statistical analysis plan and will be described in a stand-alone modeling and simulation plan prior to database lock.

18. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Site/investigator Comments

19. REFERENCES

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Dmitrienko A, Temhane AC. Gatekeeping procedures with clinical trial applications. *Pharmaceutical Statistics* 2007; 6(3):171–180.

Dmitrienko A, Temhane AC, Wiens BL. General Multistage Gatekeeping Procedures. *Biometrical Journal* 2008; 50(5):667–677.Kieser M, Friede T. Simple procedures for blinded sample size adjustment that do not affect the type I error rate. *Statistics in Medicine* 2003; 22:3571–3581.

Little R, Yau L. Intent-to-treat analysis for longitudinal studies with drop-outs. *Biometrics* 1996; 52:1324–1333.

Ratitch B, O'Kelly M, Tosiello R. DataMissing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. *Pharmaceutical Statistics* 2013; 12(6):337-347.

U.S. Department of Health and Human Services Food and Drug Administation. Guidance for industry. Drug-induced Livery injury: premarketing clinical evaluation 2009; July.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

Presentation of Treatment Groups

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group	For Tables, Listings, and Graphs
HP-3070 18.0 mg	HP-3070 18.0 mg
HP-3070 9.0 mg	HP-3070 9.0 mg
Placebo	Placebo

APPENDIX 2. MULTIPLICITY ADJUSTMENT: REGULAR AND TRUNCATED HOCHBERG DETAILS

Consider a general problem of testing m null hypotheses denoted by $H_1,\ldots,H_m$. Let $p_1,\ldots,p_m$ denote the associated raw (unadjusted) p-values. Further, let $p_{(1)}<\ldots<p_{(m)}$ denote the ordered p-values and $H_{(1)},\ldots,H_{(m)}$ denote the hypotheses corresponding to the ordered p-values. Finally, let α denote the overall Type I error rate.

The regular Hochberg procedure is based on the following testing algorithm:

- Step 1: If $p_{(m)} > \alpha$, accept $H_{(m)}$ and go to Step 2, otherwise reject all null hypotheses and stop.
- Step i = 2,…,m-1: If $p_{(m-i+1)} > \alpha/i$, accept $H_{(m-i+1)}$ and go to Step i+1, otherwise reject all remaining null hypotheses and stop.
- Step m: If $p_{(1)} > \alpha/m$, accept $H_{(1)}$, otherwise reject $H_{(1)}$.

The truncated Hochberg procedure is defined as a convex combination of the Bonferroni procedure and regular Hochberg procedure based on a pre-specified truncation parameter $0 \le \gamma < 1$ (Dmitrienko, *et al.*; 2008). The truncated Hochberg procedure is based on the following testing algorithm:

- Step 1: If $p_{(m)} > (\gamma+(1-\gamma)/m)\alpha$, accept $H_{(m)}$ and go to Step 2, otherwise reject all null hypotheses and stop.
- Step i = 2,…,m-1: If $p_{(m-i+1)} > (\gamma/i+(1-\gamma)/m)\alpha$, accept $H_{(m-i+1)}$ and go to Step i+1, otherwise reject all remaining null hypotheses and stop.
- Step m: If $p_{(1)} > \alpha/m$, accept $H_{(1)}$, otherwise reject $H_{(1)}$.

APPENDIX 3. PATTERN MIXTURE MODEL WITH PLACEBO-BASED MULTIPLE IMPUTATION

- Step 1: In order to impute missing data for a given efficacy variable (e.g., PANSS total score), 500 datasets will be generated where missing data at intermediate visit(s) will be imputed based on non-missing data at baseline and all double-blind treatment period time points of the corresponding variable from all subjects within each treatment group using a multivariate normal distribution model and a Markov chain Monte Carlo (MCMC) imputation method. Country will be incorporated in the imputation model using dummy-coding of each classification level for the country by a binary (yes/no) variable. This imputation step will be implemented using the MCMC statement in the SAS® PROC MI procedure and the IMPUTE=MONOTONE option to obtain partial imputation where each imputed dataset will have intermittent missing values imputed, while monotone missing data will remain not imputed. An option to use multiple chains in the MCMC method will be used (option CHAIN=MULTIPLE in MCMC statement). Random number generator seed of 873465 will be used at this step.
- Step 2: For each dataset from Step 1, monotone missing data will be imputed based on information from the placebo group. As a result, 500 imputed complete datasets will be generated. This will be implemented by using SAS v9.4 PROC MI, statement MNAR MODEL (<variable to impute> / MODELOBS=(<treatment variable>=’<placebo level>’)). The imputation model will include baseline value and all post baseline time points prior to the one being imputed. Random number generator seed of 12676854 will be used at this step.
- Change from Baseline to each post-Baseline time point will be computed based on observed and imputed data from Step 2. Each imputed complete dataset will be analysed with the same MMRM model as used for the primary analysis.
- Estimates obtained from the MMRM analysis applied to each imputed dataset will be combined using SAS MIANALYZE procedure.

APPENDIX 4. ANCOVA ON RANK-TRANSFPORMED DATA

ANCOVA on rank-transformed data to compare changes from baseline at a specific time point between treatment groups, adjusting for baseline and country, will be carried out based on the methodology described in Koch et al. (1982, 1990) and Stokes et al. (2012) as follows.

First the values of the change from baseline variable as well as baseline covariate will be transformed to standardized ranks within each country, using fractional ranks and mean method for ties:

```
proc rank nplus1 ties=mean out=RANKED_DATA;
        by <COUNTRY>;
        var <BASELINE> <CHANGE_FROM_BASELINE>;
run;
```

Then, separate regression models will be fit for each country using a regression model for change from baseline with baseline as predictor. Residuals from this regression model will be captured for further testing of differences between treatment groups:

```
proc reg DATA=<RANKED_DATA>;
        by <COUNTRY>;
        model <CHANGE_FROM_BASELINE> = <BASELINE>;
        output out=RESUDUALS r=RESID;
run;
```

Finally, the stratified (for country) Cochran-Mantel-Haenszel test based on the Row Mean Score Differ statistic using the values of the residuals as scores will be used to compare treatment groups in a pairwise fashion (including one HP-3070 dose group and placebo at a time):

```
proc freq DATA=RESIDUALS;
        tables <COUNTRY> * <TREATMENT> * RESID / CMH2;
run;
```

IMS Health & Quintiles are now IQVIA™

STATISTICAL ANALYSIS PLAN

Protocol Number: HP-3070-GL-04 Version 3 Amendment 2

A Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose, 6-Week, In-Patient Study to Assess Efficacy and Safety of HP-3070 in Subjects Diagnosed with Schizophrenia

Author: Amanda Schwab

Version Number and Date: Draft V3 (SAP V6), 18Jan2018

OUTPUT TEMPLATES SIGNATURE PAGE

Output Templates V3.0 (Dated 18JAN2018) for Protocol HP-3070-GL-04.

	Name	Signature	Date
Author:	Amanda Schwab		18 Jan 2018 2:00pm EST
Position:	Senior Biostatistician		
Company:	IQVIA		

Upon review of this document, the undersigned approves this version of the Output Templates, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:	Marina Komaroff		
Position:	Director, Biostatistics		18 Jan 2018 3:07pm EST
Company:	Noven, Inc.		
Approved By:	Alex Park		18JAN 2018 2:55pm EST
Position:	Executive Director – Regulatory Affairs and Pharmacovigilance		
Company:	Noven, Inc.		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0 (SAP Draft V4)	06OCT2016	Lauren Dobson Murray	Not Applicable – First Version
2.0 (SAP Draft V5)	12JAN2018	Amanda Schwab	Review Comments Implemented Key changes: Coordinated with SAP updates to reflect updated protocol Removed sensitivity for secondary efficacy Added disposition and demographic summaries from IVRS/IWRS Added additional information on screening to Analysis sets table Updated table formatting Removed disposition during run-in table Reorganized Analysis Sets, Disposition and Randomization Tables Added new figures by PANSS subscales Added table and listing for PK Updated skin irritation table to include combined and concatenated scores Updated presentation of region to North America, Russia and Rest of the World

3.0 (SAP Draft V6)	18JAN2018	Amanda Schwab	Removed ATC coding for concomitant medications Removed analysis using ITT population for primary efficacy variable Added sensitivity analysis for secondary efficacy variable

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OUTPUT CONVENTIONS

General:
- The first row in the body of the table or listing should be blank
- The left hand column should start in column 1. No indenting or centering of the output should occur.
- Rounding should be done with the SAS function ROUND.
- Numbers in tables should be rounded, not truncated.
- Alphanumeric output should be left aligned.
- Numbers should be decimal point aligned.
- Whole numbers should be right aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized
- Listings of adverse events, concomitant medications, medical histories etc. should be sorted in chronological order, with earliest adverse event, medication or history coming first.
- All listing outputs should be sorted (preferably by Treatment, Site Number and Subject Number).
- Do not use superscripts and subscripts
- Exponentiation will be expressed using a double asterisk, i.e., mm^3 will be written as mm**3.

Univariate Statistics:
- Statistics should be presented in the same order across tables (i.e., n, Mean, SD, Median, Minimum, Maximum)
- Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up. If the minimum and maximum are output on one line as Minimum, Maximum then the comma should line up with the decimal point.
- If the original data has N decimal places, then the summary statistics should have the following decimal places:
  Minimum and maximum: N
  Mean, median and CV%: N + 1
  SD: N + 2

Frequencies and percentages (n and %):
- Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:
  77 (100.0)
  50 (64.9)
  0 (0.0)
- Percentages will be reported to one decimal place, except percents <100.0% but >99.9% will be presented as '>99.9%' (e.g., 99.99% is presented as >99.9%); and percents < 0.1% will be presented as '<0.1%' (e.g., 0.08% is presented as <0.1%). Rounding will be applied after the <0.1% and >99.9% rule.
  E.g. (<0.1%)
  (6.8%)
  (>99.9%)
  Percentages may be reported to 0 decimal places as appropriate (for example, where the

denominator is relatively small).
• Where counts are zero, percentages of 0.0% should appear in the output.

Confidence Intervals:
• As a rule confidence intervals are output to one place more than the raw data, and standard deviations and standard errors to two places more than the raw data
• Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up".
• Boundary values of confidence intervals should be separated by a comma.
• Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.
• An example is given below:
(-0.12, -0.10)
(9.54, 12.91)

P-values:
• P-values should be reported to three decimal places, except values <1.000 but >0.999 will be presented as '>0.999' (e.g., 0.9998 is presented as >0.999); and values <0.001 will be presented as '<0.001' (e.g., 0.0009 is presented as <0.001). Rounding will be applied after the <0.001 and >0.999 rule

Ratios:
• Ratios should be reported to one more decimal place than the original data.

Spacing:
• There must be a minimum of 1 blank space between columns (preferably 2)

Denominators:
• If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "N".
• Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

Missing values
• A "0" should be used to indicate a zero frequency.
• A blank will be used to indicate missing data in an end-of-text table or subject listing.

• Figures should be provided in RTF files using the SAS Output Delivery System (ODS), as Computer Graphics Metafile (CGM) formatted graphical output generated by SAS.
• The CGM file itself should contain the title and footer.
• The image should be clear and of high quality when viewed in the Word document, and when printed.
• In general, boxes around the figures should be used.

Footers should be defined as follows:

- A continuous line of underscores ('_') will follow the body of the table or listing prior to any footnotes at the bottom of the page
- Table footnotes should be defined using compute statements in the proc report, and should appear directly after the body of the table
- The program path and name and version number (if applicable), and the date/time stamp, should appear in the last footnote at the bottom of the page

- Footnotes should be left-aligned.
- Footnotes should be in sentence case.
- Only "typewriter" symbols are permitted – e.g. "*", "$", "#", "@", "&" and "+".
- The choice of footnote symbols should be consistent. E.g. if you have the footnote "# indicates last observation carried forward" for one table, the same symbol and footnote should indicate LOCF for all tables.
- If text wraps across more than one line (for a note), the first letter for all lines of text after the first one will be indented to align beneath the first letter of the text in the first line.
- The page identification in the format Page X of Y (where Y is the total number of pages for the output) should appear in the header line, right aligned

Ordering of footnotes should be as follows:

1.) Abbreviations
2) Definitions
3.) Formulae
4.) P-value significance footnote
5.) Symbols
6.) Specific notes

- Common notes from table to table should appear in the same order.
- The symbols should appear in the same order as what they are defined in the table or listing, from left to right.

1. TABLES AND FIGURES

1.1 Disposition, Demographics, and Baseline Characteristics

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Protocol HP-3070-GL-04

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Table 14.1.1 Analysis Sets

	Statistic	HP-3070 18.0 mg	HP-3070 9.0 mg	Placebo	Overall
Number of Subjects Screened in Run-in	N	xxx	xxx	xxx	xxx
Number of Subjects Randomized in Double-blind	N	xxx	xxx	xxx	xxx
Number of Subjects in the ITT Analysis Set	N	xxx	xxx	xxx	xxx
Reasons for Exclusion from the ITT Analysis Set:	n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Not Consented	n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Not Randomized	n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Protocol Deviation	n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Number of Subjects in the Full Analysis Set	n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Reasons for Exclusion from the Full Analysis Set:	n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No Double-Blind Study Medication Applied	n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No Baseline Assessment of PANSS Total Score	n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No Post-Baseline Assessment of PANSS Total Score	n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Note: ITT = Intent-to-treat, PK = Pharmacokinetic, IVRS = Interactive Voice Activated Response System, IWRS = Interactive Web-based Response System.
Note: The all subjects screened set contains all subjects who provided informed consent for this study. This analysis set and the reasons for screening/run-in failure are based on data collected in the IVRS/IWRS. Some subjects in this analysis set do not have data recorded in the eCRF.
Note: The ITT analysis set includes all consented and randomized subjects.
Note: The Full analysis set includes all randomized subjects who have at least one patch of double-blind study medication applied, who have a baseline PANSS total score, and who have at least one post-baseline assessment of the PANSS total score.
Note: The Safety analysis set includes all subjects who have had at least one patch of double-blind study medication applied and who have at least one post-dose safety measurement during the double-blind treatment period.
Note: The PK analysis set includes all subjects who have at least one dose of double-blind study medication and have at least one blood sample for PK assessment. Subjects may be excluded from the PK analysis set if they significantly violate inclusion or exclusion criteria, significantly violate the protocol in a way that may influence the PK analysis, if any unexpected error occurs during the study that may influence the PK analysis (e.g., early detachment of transdermal systems, apparent sample switching, etc.), or if their data are unavailable or incomplete.
Note: Percentages for Full analysis set, Safety analysis set, and PK analysis set are calculated out of the total ITT analysis set. Percentages for reasons for exclusion are out of the total number of subjects excluded from the given analysis set.

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Table 14.1.1 Analysis Sets

	Statistic	HP-3070 18.0 mg	HP-3070 9.0 mg	Placebo	Overall
Number of Subjects in the Safety Analysis Set	n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Reasons for Exclusion from the Safety Analysis Set:	n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No Double-Blind Study Medication Applied	n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No Post-Dose Safety Measurements	n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Number of Subjects in the PK Analysis Set	n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Reasons for Exclusion from the PK Analysis Set:	n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
No study medication HP-3070 9.0mg or 18.0mg applied	n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Significant protocol or inclusion/exclusion criteria violation	n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unexpected errors that may influence the PK analysis	n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unavailable/incomplete data	n (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Note: ITT = Intent-to-treat, PK = Pharmacokinetic, IVRS = Interactive Voice Activated Response System, IWRS = Interactive Web-based Response System.
Note: The all subjects screened set contains all subjects who provided informed consent for this study. This analysis set and the reasons for screening/run-in failure are based on data collected in the IVRS/IWRS. Some subjects in this analysis set do not have data recorded in the eCRF.
Note: The ITT analysis set includes all consented and randomized subjects.
Note: The Full analysis set includes all randomized subjects who have at least one patch of double-blind study medication applied, who have a baseline PANSS total score, and who have at least one post-baseline assessment of the PANSS total score.
Note: The Safety analysis set includes all subjects who have had at least one patch of double-blind study medication applied and who have at least one post-dose safety measurement during the double-blind treatment period.
Note: The PK analysis set includes all subjects who have at least one dose of double-blind study medication and have at least one blood sample for PK assessment. Subjects may be excluded from the PK analysis set if they significantly violate inclusion or exclusion criteria, significantly violate the protocol in a way that may influence the PK analysis, if any unexpected error occurs during the study that may influence the PK analysis (e.g., early detachment of transdermal systems, apparent sample switching, etc.), or if their data are unavailable or incomplete.
Note: Percentages for Full analysis set, Safety analysis set, and PK analysis set are calculated out of the total ITT analysis set. Percentages for reasons for exclusion are out of the total number of subjects excluded from the given analysis set.

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Table 14.1.2 Randomization by Country
ITT Analysis Set

Region / Country	HP-3070 18.0 mg (N=xxx) n (%)	HP-3070 9.0 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)	Overall (N=xxx) n (%)
Rest of the World				
Bulgaria	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Serbia	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ukraine	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Russia	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
North America	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
United States	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: ITT = Intent-to-treat, N = number of subjects in the ITT analysis set by treatment group.
Note: Percentages are calculated as (n/N)*100.

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Table 14.1.3 Disposition During the Double-Blind Period
All Analysis Sets

	HP-3070 18.0 mg (N=xxx) n (%)	HP-3070 9.0 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)	Overall (N=xxx) n (%)
ITT Analysis Set				
Number of Subjects who Completed the Study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Subjects who Discontinued the Study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Primary reason for early discontinuation				
Adverse event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Non-compliance	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lack of efficacy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject requires treatment with a prohibited medication	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pregnancy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Physician decision	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study terminated by investigator	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study terminated by sponsor	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject withdrew consent	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: ITT = Intent-to-treat, PK = Pharmacokinetic, N = number of subjects in the ITT analysis set by treatment group.
Note: Percentages are calculated as (n/N)*100.
Note: This summary is based on data recorded in the eCRF.

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Table 14.1.3 Disposition During the Double-Blind Period
All Analysis Sets

	HP-3070 18.0 mg (N=xxx) n (%)	HP-3070 9.0 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)	Overall (N=xxx) n (%)
Full Analysis Set				
Number of Subjects who Completed the Study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Subjects who Discontinued the Study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Primary reason for early discontinuation				
Adverse event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Non-compliance	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lack of efficacy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject requires treatment with a prohibited medication	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pregnancy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Physician decision				
Study terminated by investigator				
Study terminated by sponsor	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject withdrew consent	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: ITT = Intent-to-treat, PK = Pharmacokinetic, N = number of subjects in the ITT analysis set by treatment group.
Note: Percentages are calculated as (n/N)*100.
Note: This summary is based on data recorded in the eCRF.

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Table 14.1.3 Disposition During the Double-Blind Period
All Analysis Sets

	HP-3070 18.0 mg (N=xxx) n (%)	HP-3070 9.0 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)	Overall (N=xxx) n (%)
Safety Analysis Set				
Number of Subjects who Completed the Study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Subjects who Discontinued the Study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Primary reason for early discontinuation				
Adverse event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Non-compliance	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lack of efficacy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject requires treatment with a prohibited medication	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pregnancy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Physician decision	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study terminated by investigator	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study terminated by sponsor	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject withdrew consent	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: ITT = Intent-to-treat, PK = Pharmacokinetic, N = number of subjects in the ITT analysis set by treatment group.
Note: Percentages are calculated as (n/N)*100.
Note: This summary is based on data recorded in the eCRF.

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Table 14.1.3 Disposition During the Double-Blind Period
All Analysis Sets

	HP-3070 18.0 mg (N=xxx) n (%)	HP-3070 9.0 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)	Overall (N=xxx) n (%)
PK Analysis Set				
Number of Subjects who Completed the Study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Subjects who Discontinued the Study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Primary reason for early discontinuation				
Adverse event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Non-compliance	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lack of efficacy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject requires treatment with a prohibited medication	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pregnancy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Physician decision	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study terminated by investigator	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study terminated by sponsor	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject withdrew consent	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: ITT = Intent-to-treat, PK = Pharmacokinetic, N = number of subjects in the ITT analysis set by treatment group.
Note: Percentages are calculated as (n/N)*100.
Note: This summary is based on data recorded in the eCRF.

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Table 14.1.4 Time to Discontinuation During the Double-Blind Period
ITT Analysis Set

Time (Days)	HP-3070 18.0 mg (N=xxx) %	HP-3070 9.0 mg (N=xxx) %	Placebo (N=xxx) %	Overall (N=xxx) %
Day 0	xx	xx	xx	xx
Day 7	xx	xx	xx	xx
Day 14	xx	xx	xx	xx
Day 21	xx	xx	xx	xx
Day 28	xx	xx	xx	xx
Day 35	xx	xx	xx	xx
Day 42	xx	xx	xx	xx

Note: ITT = Intent-to-treat, N = number of subjects in the ITT analysis set by treatment group.
Note: Percents are based on Kaplan Meier failure rates at each week.
Note: Time to discontinuation is computed as date of last dose of double-blind study medication – date of randomization.

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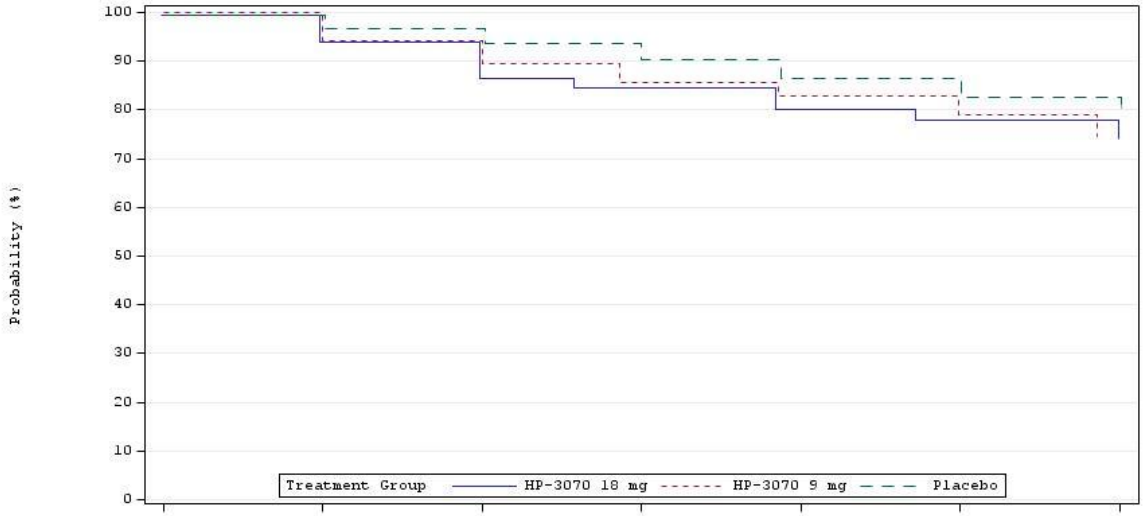
Figure 14.1.4 Time to Discontinuation During the Double Blind Period, Kaplan Meier Plot
ITT Analysis Set



Note: ITT = Intent-to-treat.
Note: Time to discontinuation is computed as date of last dose of double-blind study medication - date of randomization.
Note: Reference Table 14.1.4

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Table 14.1.5 Demographic Characteristics
ITT Analysis Set

	Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)	Overall (N=xxx)
Age (years)	n	xx	xx	xx	xx
	Mean	x.x	x.x	x.x	x.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	x.x	x.x	x.x	x.x
	Min	x	x	x	x
	Max	x	x	x	x
< 55	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>= 55	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Gender					
Male	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Female	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race					
American Indian or Alaska Native	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black or African American	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian or Other Pacific Islanders	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
White	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity					
Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Region					
Rest of the World	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Russia	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
North America	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: ITT = Intent-to-treat, BMI = Body Mass Index, N = number of subjects in the ITT analysis set by treatment group.
Note: Rest of the World includes Bulgaria, Serbia and Ukraine.
Note: Percentages are calculated as (n/N)*100.
Note: A subject may select more than one race in the eCRF.

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Table 14.1.5 Demographic Characteristics
ITT Analysis Set

	Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)	Overall (N=xxx)
Baseline Height (cm)	n	xx	xx	xx	Xx
	Mean	x.x	x.x	x.x	x.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	x.x	x.x	x.x	x.x
	Min	x	x	x	X
	Max	x	x	x	X
Baseline Weight (kg)	n	xx	xx	xx	Xx
	Mean	x.x	x.x	x.x	x.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	x.x	x.x	x.x	x.x
	Min	x	x	x	X
	Max	x	x	x	X
Baseline BMI (kg/m2)	n	xx	xx	xx	Xx
	Mean	x.x	x.x	x.x	x.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	x.x	x.x	x.x	x.x
	Min	x	x	x	x
	Max	x	x	x	x
< 25	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>= 25 to < 30	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>= 30	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: ITT = Intent-to-treat, BMI = Body Mass Index, N = number of subjects in the ITT analysis set by treatment group.
Note: Rest of the World includes Bulgaria, Serbia and Ukraine. North America includes the United States.
Note: Percentages are calculated as (n/N)*100.
Note: A subject may select more than one race in the eCRF.

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Table 14.1.6 Baseline Psychiatric Characteristics
ITT Analysis Set

	Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)	Overall (N=xxx)
Time Since First Diagnosis of Schizophrenia (years)	n	xx	xx	xx	xx
	Mean	x.x	x.x	x.x	x.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	x.x	x.x	x.x	x.x
	Min	x	x	x	x
	Max	x	x	x	x
< 5	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>= 5 to < 10	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>= 10 to < 20	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>= 20	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Time Since Current Exacerbated Episode (weeks)	n	xx	xx	xx	xx
	Mean	x.x	x.x	x.x	x.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	x.x	x.x	x.x	x.x
	Min	x	x	x	x
	Max	x	x	x	x
Baseline PANSS Total Score					
< 90	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>= 90	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: ITT = Intent-to-treat, PANSS = Positive and Negative Syndrome Scale, MSQ = Medication Satisfaction Questionnaire, N = number of subjects in the ITT analysis set by treatment group.

Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Percentages are calculated as (n/N)*100.
Note: Time since is calculated as date of first dose of double blind medication – current exacerbated episode or first diagnosis of schizophrenia
Note: The MSQ is a single-item questionnaire used to assess the level of patient's satisfaction or dissatisfaction with the medication they are taking. Responses can range from Extremely Dissatisfied (1) to Extremely Satisfied (7).

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Table 14.1.6 Baseline Psychiatric Characteristics
ITT Analysis Set

	Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)	Overall (N=xxx)
Age of First Diagnosis of Schizophrenia (years)	n	xx	xx	xx	xx
	Mean	x.x	x.x	x.x	x.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	x.x	x.x	x.x	x.x
	Min	x	x	x	x
	Max	x	x	x	x
< 25	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>= 25	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Antipsychotic Treatment Before Current Episode					
Yes	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Baseline MSQ Score	n	xx	xx	xx	xx
	Mean	x.x	x.x	x.x	x.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	x.x	x.x	x.x	x.x
	Min	x	x	x	x
	Max	x	x	x	x

Note: ITT = Intent-to-treat, PANSS = Positive and Negative Syndrome Scale, MSQ = Medication Satisfaction Questionnaire, N = number of subjects in the ITT analysis set by treatment group.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Percentages are calculated as (n/N)*100.
Note: Time since is calculated as date of first dose of double blind medication - current exacerbated episode or first diagnosis of schizophrenia
Note: The MSQ is a single-item questionnaire used to assess the level of patient's satisfaction or dissatisfaction with the medication they are taking. Responses can range from Extremely Dissatisfied (1) to Extremely Satisfied (7).

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Table 14.1.7 Exposure to Double Blind Study Medication
Safety Analysis Set

		HP-3070 18.0 mg (N=xxx)		HP-3070 9.0 mg (N=xxx)		Placebo (N=xxx)		Overall (N=xxx)	
	Statistic	Subjects	Patches	Subjects	Patches	Subjects	Patches	Subjects	Patches
Exposed to Double-Blind Study Medication	n (%)	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Duration of Exposure (days)	Mean	x.x		x.x		x.x		x.x	
	SD	x.xx		x.xx		x.xx		x.xx	
	Median	x.x		x.x		x.x		x.x	
	Min	x		x		x		x	
	Max	x		x		x		x	
Week 1	n (%)	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Week 2	n (%)	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Week 3	n (%)	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Week 4	n (%)	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Week 5	n (%)	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Week 6	n (%)	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

Note: N = the number of subjects in the safety analysis set by treatment group.
Note: Percentages are calculated as (n/N)*100.

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Table 14.1.8 Study Medication Compliance
Safety Analysis Set

Visit/Abnormality	Statistic	HP-3070 18.0 mg (N=XXX)	HP-3070 9.0 mg (N=XXX)	Placebo (N=XXX)	Overall (N=XXX)
Overall Double-Blind Period	N	xxx	xxx	xxx	xxx
Compliant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Noncompliant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<80%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>=120%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Period from Day 0 to Week 1 Visit	N	xxx	xxx	xxx	xxx
Compliant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Noncompliant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<80%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>=120%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Period from Week 1 to Week 2 Visit	N				
Compliant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Noncompliant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<80%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>=120%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Period from Week 2 to Week 3 Visit	N	xxx	xxx	xxx	xxx
Compliant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Noncompliant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<80%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>=120%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: Compliant is defined as using >=80% and <=120% of study medication during the evaluation period. Noncompliant is defined as using <80% or >120% of study medication during the evaluation period.
Note: Compliance with study medication is calculated as the number of patches applied divided by the prescribed number of patches over a given period.
Note: Percentages are calculated as (n/N)*100 where N is the number of subjects for the period being summarized.

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Table 14.1.8 Study Medication Compliance
Safety Analysis Set

Visit/Abnormality	Statistic	HP-3070 18.0 mg (N=XXX)	HP-3070 9.0 mg (N=XXX)	Placebo (N=XXX)	Overall (N=XXX)
Period from Week 3 to Week 4 Visit	N	xxx	xxx	xxx	xxx
Compliant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Noncompliant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<80%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>=120%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Period from Week 4 to Week 5 Visit	N	xxx	xxx	xxx	xxx
Compliant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Noncompliant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<80%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>=120%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Period from Week 5 to Week 6 Visit	N	xxx	xxx	xxx	xxx
Compliant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Noncompliant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<80%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
>=120%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: Compliant is defined as using >=80% and <=120% of study medication during the evaluation period. Noncompliant is defined as using <80% or >120% of study medication during the evaluation period.
Note: Compliance with study medication is calculated as the number of patches applied divided by the prescribed number of patches over a given period.
Note: Percentages are calculated as (n/N)*100 where N is the number of subjects for the period being summarized.

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Table 14.1.9 Prior Medications
ITT Analysis Set

Preferred Term	HP-3070 18.0 mg (N=xxx) n (%)	HP-3070 9.0 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)	Overall (N=xxx) n (%)
Number of Subjects with at Least One Prior Medication	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred Term>>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred Term>>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred Term>>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred Term>>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred Term>>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred Term>>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred Term>>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
...				

Note: N = number of subjects in the ITT analysis set by treatment group. Overall includes all subjects in the safety analysis set.
Note: Prior medications are medications which started and stopped prior to the first dose of double-blind study medication. Medications taken from 6 months prior to screening are included.
Note: Percentages are calculated as (n/N)*100.
Note: At each level of summarization, subjects reporting more than one medication are counted once.
Note: Medications are coded using World Health Organization Drug Dictionary (WHO-DD) Version xx.x.

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Table 14.1.10 Concomitant Medications
Safety Analysis Set

Preferred Term	HP-3070 18.0 mg (N=xxx) n (%)	HP-3070 9.0 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)	Overall (N=xxx) n (%)
Number of Subjects with at Least One Concomitant Medication	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred Term>>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred Term>>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred Term>>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred Term>>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred Term>>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred Term>>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<<Preferred Term>>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
...				

Note: N = number of subjects in the safety analysis set by treatment group. Overall includes all subjects in the safety analysis set.
Note: Concomitant medications are medications which started prior to, on, or after the first dose of double-blind study medication and no later than 1 day following the date of last study medication patch application, and ended on or after the date of first dose of study medication or were ongoing at the end of the study.
Note: Percentages are calculated as (n/N)*100.
Note: Prefered Terms are presented in order of decreasing frequency.
Note: Medications are coded using World Health Organization Drug Dictionary (WHO-DD) Version xx.x.

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1.2 Efficacy

Table 14.2.1.1.1 Treatment Comparison of Change from Baseline in PANSS Total Score at Week 6
Full Analysis Set

	Treatment Group			Treatment Group Comparison (Active - Placebo)	
Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)
Baseline					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		
Week 6					
Observed					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		

Note: PANSS = Positive and Negative Syndrome Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. If one or more items are missing at a given assessment, the total score is set to missing.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.
Note: Adjusted p-values are calculated according to the truncated Hochberg procedure with a truncation factor γ=0.9. Adjustment for multiple comparisons uses a parallel gatekeeping procedure. Adjusted p-values are presented for the secondary endpoint CGI-S Score change from baseline only if at least one of the primary hypotheses for the primary endpoint PANSS total score change from baseline are rejected.

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Table 14.2.1.1.1 Treatment Comparison of Change from Baseline in PANSS Total Score at Week 6
Full Analysis Set

	Treatment Group			Treatment Group Comparison (Active - Placebo)	
Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)
Week 6					
Change from Baseline to Week 6					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		
LSM estimate	x.x	x.x	x.x	x.x	x.x
SE	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
95% CI	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
p-value				x.xxx	x.xxx
Adjusted p-value				x.xxx	x.xxx

Note: PANSS = Positive and Negative Syndrome Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. If one or more items are missing at a given assessment, the total score is set to missing.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.
Note: Adjusted p-values are calculated according to the truncated Hochberg procedure with a truncation factor γ=0.9. Adjustment for multiple comparisons uses a parallel gatekeeping procedure. Adjusted p-values are presented for the secondary endpoint CGI-S Score change from baseline only if at least one of the primary hypotheses for the primary endpoint PANSS total score change from baseline are rejected.

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Programming note: If unstructured covariance model does not converge, modify footnote to specify the actual covariance structure used in the final model. If AIC from heterogeneous variances is smaller, update accordingly. Same notes apply to similar outputs below.

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Table 14.2.1.1.2 Treatment Comparison of Change from Baseline in PANSS Total Score at Week 6
ITT Analysis Set

	Treatment Group			Treatment Group Comparison (Active - Placebo)	
Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Place\(N=xxx)	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)
Baseline					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		
Week 6 Observed					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		

Note: ITT = Intent-to-Treat, PANSS = Positive and Negative Syndrome Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the ITT analysis set by treatment group.
Note: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. If one or more items are missing at a given assessment, the total score is set to missing.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

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Table 14.2.1.1.2 Treatment Comparison of Change from Baseline in PANSS Total Score at Week 6
ITT Analysis Set

	Treatment Group			Treatment Group Comparison (Active - Placebo)	
Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)
Change from Baseline to Week 6					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		
LSM estimate	x.x	x.x	x.x	x.x	x.x
SE	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
95% CI	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
p-value				x.xxx	x.xxx

Note: ITT = Intent-to-Treat, PANSS = Positive and Negative Syndrome Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the ITT analysis set by treatment group.
Note: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. If one or more items are missing at a given assessment, the total score is set to missing.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

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Table 14.2.1.2.1.1 Treatment Comparison of Change from Baseline in PANSS Total Score at Week 6 – Pattern-Mixture Model
Full Analysis Set

This table will be similar to 14.2.1.1.2.
Footnotes will be:
Note: PANSS = Positive and Negative Syndrome Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. If one or more items are missing at a given assessment, the total score is set to missing.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: A pattern-mixture model approach using a placebo-based multiple imputation has been used for this analysis.
Note: Imputed datasets are analyzed with the mixed linear repeated measures model including treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

Table 14.2.1.2.1.2 Treatment Comparison of Change from Baseline in PANSS Total Score at Week 6 – Pattern-Mixture Model for Dropout Pattern 2
Full Analysis Set

This table will be similar to 14.2.1.1.2.
Footnotes will be:
Note: PANSS = Positive and Negative Syndrome Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. If one or more items are missing at a given assessment, the total score is set to missing.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: A pattern-mixture model approach using a placebo-based multiple imputation for discontinuation due to lack of efficacy, adverse event, or death has been used for this analysis.
Note: Imputed datasets are analyzed with the mixed linear repeated measures model including treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

Table 14.2.1.2.1.3 Treatment Comparison of Change from Baseline in PANSS Total Score at Week 6 – Pattern-Mixture Model for Dropout Pattern 3
Full Analysis Set

This table will be similar to 14.2.1.1.2.
Footnotes will be:
Note: PANSS = Positive and Negative Syndrome Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.

Note: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. If one or more items are missing at a given assessment, the total score is set to missing.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: A pattern-mixture model approach using a placebo-based multiple imputation for discontinuation due to lack of efficacy has been used for this analysis.
Note: Imputed datasets are analyzed with the mixed linear repeated measures model including treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

Table 14.2.1.2.3 Time-to-Failure Based on Change from Baseline in PANSS Total Score and Dropout Pattern 1
Full Analysis Set

Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)
Failures, n (%)	xx (x.xx)	xx (x.xx)	xx (x.xx)
Time to Failure (Days)			
25th Percentile	x.xx	x.xx	x.xx
Median	x.xx	x.xx	x.xx
75th Percentile	x.xx	x.xx	x.xx
Log Rank p-value	x.xxx	x.xxx	x.xxx
Probability of Failure at			
Week 1	x.xx	x.xx	x.xx
Week 2	x.xx	x.xx	x.xx
Week 3	x.xx	x.xx	x.xx
Week 4	x.xx	x.xx	x.xx
Week 5	x.xx	x.xx	x.xx
Week 6	x.xx	x.xx	x.xx

Note: PANSS = Positive and Negative Syndrome Scale, N = number of subjects in the full analysis set by treatment group.
Note: a subject is considered to have failed if there is never an improvement in PANSS score >=20% during the study or if there is an improvement >=20% during the study but a subsequent change from baseline <20%, or if the subjectdiscontinues for any reason.
Note: Time to Failure is calculated based on Kaplan-Meier methodology.
Note: Percentages are calculated as (n/N)*100.

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Table 14.2.1.2.4 Time-to-Failure Analysis Based on Change from Baseline in PANSS Total Score and Dropout Pattern 2
Full Analysis Set

This table will be similar to 14.2.1.2.3.
Second Footnote will be:
Note: a subject is considered to have failed if there is never an improvement in PANSS score >=20% during the study or if there is an improvement >=20% during the study but a subsequent change from baseline <20%, or if the subject discontinues due to lack of efficacy, adverse event, or death. Discontinuations for other reasons are censored at discontinuation date.

Table 14.2.1.2.5 Time-to-Failure Analysis Based on Change from Baseline in PANSS Total Score and Dropout Pattern 3
Full Analysis Set

This table will be similar to 14.2.1.2.3.
Second Footnote will be:
Note: a subject is considered to have failed if there is never an improvement in PANSS score >=30% during the study or if there is an improvement >=30% during the study but a subsequent change from baseline <30%, or if the subject discontinues due to lack of efficacy. Discontinuations for other reasons are censored at discontinuation date.

Table 14.2.1.2.6 ANCOVA on Rank-Transformed PANSS Total Score Data at Week 6
Full Analysis Set

	Treatment Group			Treatment Group Comparison (Active - Placebo)	
Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)
Rank-Transformed Change from Baseline to Week 6					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		
LSM estimate	x.x	x.x	x.x		
SE	x.xxx	x.xxx	x.xxx		
p-value				x.xxx	x.xxx

Note: ANCOVA = Analysis of Covariance, PANSS = Positive and Negative Syndrome Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. If one or more items are missing at a given assessment, the total score is set to missing.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: The values of the change from baseline variable as well as baseline covariate are transformed to standardized ranks within each country, using fractional ranks and mean method for ties. Before performing the rank transformation, subjects with missing data at Week 6 due to discontinuation for any reason are imputed with a change from baseline equal to the largest change from baseline in observed data plus 1, so that these subjects have the highest rank after the transformation.
Note: Separate regression models are fit for each country using a regression model for change from baseline with baseline as predictor.
Note: P-value is based on the Cochran-Mantel-Haenszel test, controlling for country. The hypothesis tested is the Row Mean Score Differ statistic, using the values of the residuals as scores.

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Table 14.2.2.1 Treatment Comparison of Change from Baseline in CGI-S Score at Week 6
Full Analysis Set

This table will be similar to 14.2.1.1.1.
Footnotes will be:
Note: CGI-S = Clinical Global Impression – Severity of Illness Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: CGI-S score is determined by answering the question "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" on a scale of 0-7, with 0 indicating not assessed and 7 indicating the most extremely ill subjects.
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.
Note: Adjusted p-values are calculated according to the Hochberg procedure. Adjustment for multiple comparisons uses a parallel gatekeeping procedure. Adjusted p-values are presented for the secondary endpoint CGI-S Score change from baseline only if at least one of the primary hypotheses for the primary endpoint PANSS total score change from baseline are rejected.

Table 14.2.2.2 Treatment Comparison of Change from Baseline in CGI-S Score at Week 6 – Pattern-Mixture Model
Full Analysis Set

This table will be similar to 14.2.1.1.2.
Footnotes will be:
Note: CGI-S = Clinical Global Impression – Severity of Illness Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: CGI-S score is determined by answering the question "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" on a scale of 0-7, with 0 indicating not assessed and 7 indicating the most extremely ill subjects.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: A pattern-mixture model approach using a placebo-based multiple imputation has been used for this analysis.
Note: Imputed datasets are analyzed with the mixed linear repeated measures model including treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

Table 14.2.2.3 Treatment Comparison of Change from Baseline in CGI-S Score at Week 6 – Pattern-Mixture Model for Dropout Pattern 2
Full Analysis Set

This table will be similar to 14.2.1.1.2.
Footnotes will be:
Note: CGI-S = Clinical Global Impression – Severity of Illness Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.

Note: CGI-S score is determined by answering the question "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" on a scale of 0-7, with 0 indicating not assessed and 7 indicating the most extremely ill subjects.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: A pattern-mixture model approach using a placebo-based multiple imputation for discontinuation due to lack of efficacy, adverse event, or death has been used for this analysis.
Note: Imputed datasets are analyzed with the mixed linear repeated measures model including treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

Table 14.2.2.4 Treatment Comparison of Change from Baseline in CGI-S Score at Week 6 – Pattern-Mixture Model for Dropout Pattern 3
Full Analysis Set

This table will be similar to 14.2.1.1.2.
Footnotes will be:
Note: CGI-S = Clinical Global Impression - Severity of Illness Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: CGI-S score is determined by answering the question "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" on a scale of 0-7, with 0 indicating not assessed and 7 indicating the most extremely ill subjects.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: A pattern-mixture model approach using a placebo-based multiple imputation for discontinuation due to lack of efficacy has been used for this analysis.
Note: Imputed datasets are analyzed with the mixed linear repeated measures model including treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

Table 14.2.2.5 Time-to-Failure Analysis Based on Change from Baseline in CGI-S Score and Dropout Pattern 1
Full Analysis Set

This table will be similar to 14.2.1.2.3.
Footnotes will be:
Note: CGI-S = Clinical Global Impression - Severity of Illness Scale, N = number of subjects in the full analysis set by treatment group.
Note: CGI-S score is determined by answering the question "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" on a scale of 0-7, with 0 indicating not assessed and 7 indicating the most extremely ill subjects.
Note: a subject is considered to have failed if there is never an improvement in CGI-S score >=20% during the study or if there is an improvement >=20% during the study but a subsequent change from baseline <20%, or if the subject discontinues for any reason.
Note: Time to Failure is calculated based on Kaplan-Meier methodology.
*Note: Percentages are calculated as (n/N)*100.*

Table 14.2.2.6 Time-to-Failure Analysis Based on Change from Baseline in CGI-S Score and Dropout Pattern 2
Full Analysis Set

This table will be similar to 14.2.1.2.3.
Footnotes will be:
Note: CGI-S = Clinical Global Impression – Severity of Illness Scale, N = number of subjects in the full analysis set by treatment group.
Note: CGI-S score is determined by answering the question "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" on a scale of 0-7, with 0 indicating not assessed and 7 indicating the most extremely ill subjects.
Note: a subject is considered to have failed if there is never an improvement in CGI-S score >=20% during the study or if there is an improvement >=20% during the study but a subsequent change from baseline <20%, or if the subject discontinues due to lack of efficacy, adverse event, or death. Discontinuations for other reasons are censored at discontinuation date.
Note: Time to Failure is calculated based on Kaplan-Meier methodology.
*Note: Percentages are calculated as (n/N)*100.*

Table 14.2.2.7 Time-to-Failure Analysis Based on Change from Baseline in CGI-S Score and Dropout Pattern 3
Full Analysis Set

This table will be similar to 14.2.1.2.3.
Footnotes will be:
Note: CGI-S = Clinical Global Impression – Severity of Illness Scale, N = number of subjects in the full analysis set by treatment group.
Note: CGI-S score is determined by answering the question "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" on a scale of 0-7, with 0 indicating not assessed and 7 indicating the most extremely ill subjects.
Note: a subject is considered to have failed if there is never an improvement in CGI-S score >=30% during the study or if there is an improvement >=30% during the study but a subsequent change from baseline <30%, or if the subject discontinues due to lack of efficacy. Discontinuations for other reasons are censored at discontinuation date.
Note: Time to Failure is calculated based on Kaplan-Meier methodology.
*Note: Percentages are calculated as (n/N)*100.*

Table 14.2.2.8 ANCOVA on Rank-Transformed CGI-S Score Data at Week 6
Full Analysis Set

This table will be similar to 14.2.1.2.6.
Footnotes will be:
Note: ANCOVA = Analysis of Covariance, CGI-S = Clinical Global Impression – Severity of Illness Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: CGI-S score is determined by answering the question "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" on a scale of 0-7, with 0 indicating not assessed and 7 indicating the most extremely ill subjects.

Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: The values of the change from baseline variable as well as baseline covariate are transformed to standardized ranks within each country, using fractional ranks and mean method for ties. Before performing the rank transformation, subjects with missing data at Week 6 due to discontinuation for any reason are imputed with a change from baseline equal to the largest change from baseline in observed data plus 1, so that these subjects have the highest rank after the transformation.
Note: Separate regression models are fit for each country using a regression model for change from baseline with baseline as predictor.
Note: P-value is based on the Cochran-Mantel-Haenszel test, controlling for country. The hypothesis tested is the Row Mean Score Differ statistic, using the values of the residuals as scores.

Table 14.2.3.1.1 Treatment Comparison of Change from Baseline in PANSS Total Score at Weeks 1 - 6
Full Analysis Set

	Treatment Group			Treatment Group Comparison (Active - Placebo)	
Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)
Baseline					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		
Week 1					
Observed					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		

Note: PANSS = Positive and Negative Syndrome Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. If one or more items are missing at a given assessment, the total score is set to missing.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

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Table 14.2.3.1.1 Treatment Comparison of Change from Baseline in PANSS Total Score at Weeks 1 - 6
Full Analysis Set

	Treatment Group			Treatment Group Comparison (Active - Placebo)	
Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)
Change from Baseline to Week 1					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		
LSM estimate	x.x	x.x	x.x	x.x	x.x
SE	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
95% CI	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
p-value				x.xxx	x.xxx

Note: PANSS = Positive and Negative Syndrome Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. If one or more items are missing at a given assessment, the total score is set to missing.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

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Programming note: Repeat for weeks 2-6

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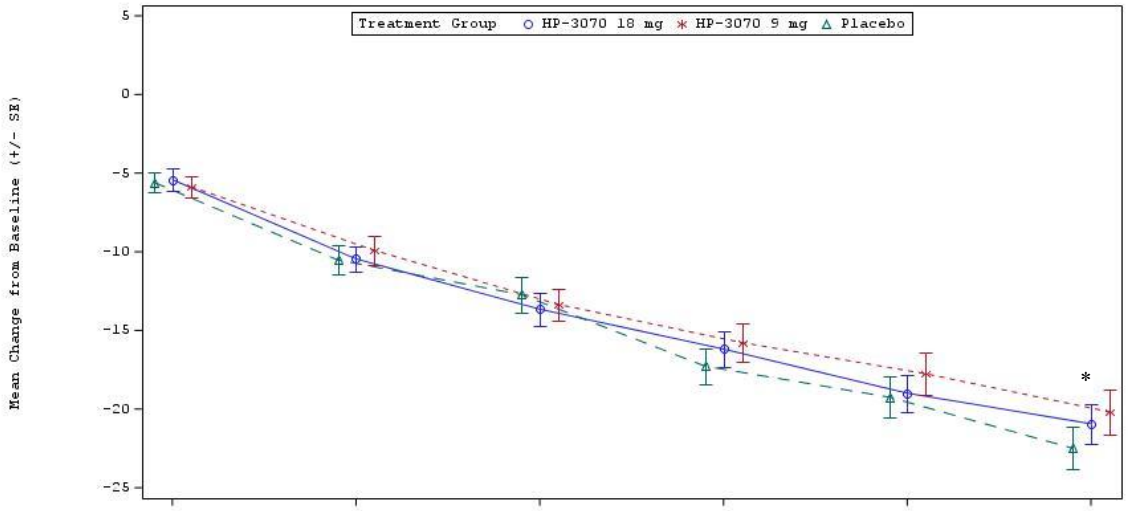
Figure 14.2.3.1.1 Mean Changes from Baseline in PANSS Total Score Across Visits
Full Analysis Set



HP-3070 18 mg	152	143	132	130	124	119
HP-3070 9 mg	142	136	128	123	121	114
Placebo	147	141	136	130	127	118

Note: PANSS = Positive and Negative Syndrome Scale.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. If one or more items are missing at a given assessment, the total score is set to missing.
Note: '*' represents a statistically significant p-value<0.05 for the comparison of HP-3070 9.0mg to placebo at that week. '**' represents a statistically significant p-value<0.05 for the comparison of HP-3070 18.0mg to placebo at that week.
Note: Reference table 14.2.3.1.1

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Table 14.2.3.1.2 Treatment Comparison of Change from Baseline in PANSS Positive Subscale at Weeks 1 - 6
Full Analysis Set

This table will be similar to 14.2.3.1.1.
Second Footnote will be:
Note: The PANSS positive subscale is the sum of 7 items: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility

Figure 14.2.3.1.2 Mean Changes from Baseline in PANSS Positive Subscale Across Visits
Full Analysis Set

This figure will be similar to 14.2.3.1.1
Third Footnote will be:
Note: The PANSS positive subscale is the sum of 7 items: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility

Table 14.2.3.1.3 Treatment Comparison of Change from Baseline in PANSS Negative Subscale at Weeks 1 - 6
Full Analysis Set

This table will be similar to 14.2.3.1.1.
Second Footnote will be:
Note: The PANSS negative subscale is the sum of 7 items: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking.

Figure 14.2.3.1.3 Mean Changes from Baseline in PANSS Negative Subscale Across Visits
Full Analysis Set

This figure will be similar to 14.2.3.1.1
Third Footnote will be:
Note: The PANSS negative subscale is the sum of 7 items: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking.

Table 14.2.3.1.4 Treatment Comparison of Change from Baseline in PANSS General Psychopathology Subscale at Weeks 1 - 6
Full Analysis Set

This table will be similar to 14.2.3.1.1.
Second Footnote will be:
Note: The PANSS general psychopathy subscale is the sum of 16 items: somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance.

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Figure 14.2.3.1.4 Mean Changes from Baseline in PANSS General Psychopathology Subscale Across Visits
Full Analysis Set

This figure will be similar to 14.2.3.1.1

Third Footnote will be:

Note: The PANSS general psychopathy subscale is the sum of 16 items: somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance.

Table 14.2.3.1.5 Treatment Comparison of Change from Baseline in PANSS Total Score at Weeks 1 – 6 by Completion Status
Full Analysis Set

	Treatment Group			Treatment Group Comparison (Active - Placebo)	
Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)
Subjects who Completed the Study					
Baseline					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		
Week 1					
Observed					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		

Note: PANSS = Positive and Negative Syndrome Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. If one or more items are missing at a given assessment, the total score is set to missing.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

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Table 14.2.3.1.5 Treatment Comparison of Change from Baseline in PANSS Total Score at Weeks 1 – 6 by Completion Status Full Analysis Set

	Treatment Group			Treatment Group Comparison (Active - Placebo)	
Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)
Change from Baseline to Week 1					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		
LSM estimate	x.x	x.x	x.x	x.x	x.x
SE	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
95% CI	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
p-value				x.xxx	x.xxx

Note: PANSS = Positive and Negative Syndrome Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group and completion status.
Note: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. If one or more items are missing at a given assessment, the total score is set to missing.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

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Programming note: Repeat for weeks 2-6, then repeat for subjects who discontinued the study.

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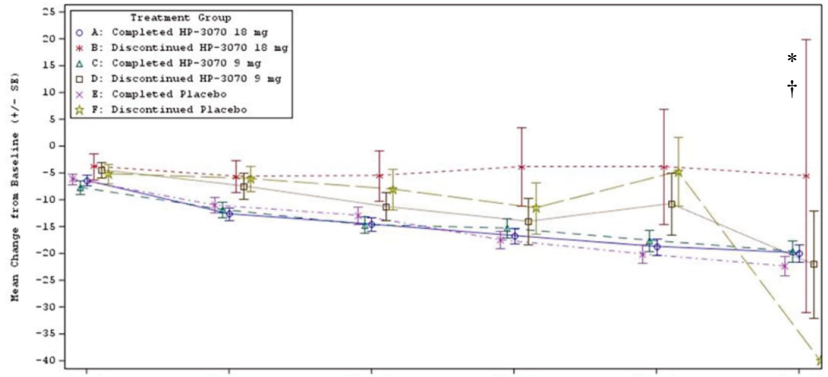
Figure 14.2.3.1.5 Mean Changes From Baseline in PANSS Total Score Across Visits by Completion Status
Full Analysis Set

Missing data patterns will be described graphically by plotting mean changes from baseline in PANSS total score across visits by treatment group and subgroups of subjects that either completed the double-blind treatment period or discontinued early. Subjects who discontinued early will be grouped by week at which they discontinued (0 through 6).



Note: PANSS = Positive and Negative Syndrome Scale, N = number of subjects in the full analysis set by treatment group and completion status.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. If one or more items are missing at a given assessment, the total score is set to missing.
Note: N's for each week represent the number of subjects in the full analysis set by treatment group and completion status.
Note: '*' represents a statistically significant p-value<0.05 for the comparison of HP-3070 9.0mg to placebo at that week for subjects who completed the study. '**' represents statistical significance for the comparison of HP-3070 18.0mg to placebo for subjects who completed the study. '†' represents statistical significance for the comparison of HP-3070 9.0mg to placebo for subjects who discontinued the study. '††' represents statistical significance for the comparison of HP-3070 18.0mg to placebo for subjects who discontinued the study.
Note: Reference table 14.2.3.1.5

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Table 14.2.3.1.6 Treatment Comparison of Change from Baseline in PANSS Positive Subscale at Weeks 1 – 6 by Completion Status

Full Analysis Set

This table will be similar to 14.2.3.1.5.
Second Footnote will be:
Note: The PANSS positive subscale is the sum of 7 items: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility.

Figure 14.2.3.1.6 Mean Changes From Baseline in PANSS Positive Subscale Across Visits by Completion Status

Full Analysis Set

This figure will be similar to 14.2.1.2.2
Third Footnote will be:
Note: The PANSS positive subscale is the sum of 7 items: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility.

Table 14.2.3.1.7 Treatment Comparison of Change from Baseline in PANSS Negative Subscale at Weeks 1 – 6 by Completion Status

Full Analysis Set

This table will be similar to 14.2.3.1.5.
Second Footnote will be:
Note: The PANSS negative subscale is the sum of 7 items: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking.

Figure 14.2.3.1.7 Mean Changes From Baseline in PANSS Negative Subscale Across Visits by Completion Status

Full Analysis Set

This figure will be similar to 14.2.1.2.2
Third Footnote will be:
Note: The PANSS negative subscale is the sum of 7 items: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking.

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Table 14.2.3.1.8 Treatment Comparison of Change from Baseline in PANSS General Psychopathology Subscale at Weeks 1 – 6 by Completion Status
Full Analysis Set

This table will be similar to 14.2.3.1.5.
Second Footnote will be:
Note: The PANSS general psychopathy subscale is the sum of 16 items: somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance.

Figure 14.2.3.1.8 Mean Changes From Baseline in PANSS General Psychopathology Subscale Across Visits by Completion Status
Full Analysis Set

This figure will be similar to 14.2.1.2.2
Third Footnote will be:
Note: The PANSS general psychopathy subscale is the sum of 16 items: somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance.

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Table 14.2.3.2 Treatment Comparison of Change from Baseline in CGI-S Score at Weeks 1 - 6
Full Analysis Set

This table will be similar to 14.2.3.1.

Footnotes will be:

Note: CGI-S = Clinical Global Impression – Severity of Illness Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.

Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.

Note: CGI-S score is determined by answering the question "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" on a scale of 0-7, with 0 indicating not assessed and 7 indicating the most extremely ill subjects.

Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

Table 14.2.3.3 Treatment Comparison of CGI-I Responders
Full Analysis Set

	Treatment Group			Treatment Group Comparison (Active - Placebo)	
Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)
Week 1					
Responders, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)		
Estimate	x.xx	x.xx	x.xx	x.xx	x.xx
SE	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
95% CI	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
p-value				x.xxx	x.xxx
Week 2					
Responders, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)		
Estimate	x.xx	x.xx	x.xx	x.xx	x.xx
SE	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
95% CI	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
p-value				x.xxx	x.xxx

Note: CGI-I = Clinical Global Impression – Improvement Scale, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: CGI-I responders are defined as subjects who have a score of 1 (very much improved) or a score of 2 (much improved.)
Note: Percentages are calculated as (n/N)*100.
Note: Estimates of the proportion of responders in each treatment group and differences of proportions between the treatment groups are based on the standard method based on the binomial distribution. 95% CIs for proportion estimates are based on the Wilson method. 95% CIs for the differences of proportions are based on the Newcombe method.
Note: P-value is based on the Cochran-Mantel-Haenszel test, stratified by country. The hypothesis tested is the general association statistic.

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Programming Note: Repeat for weeks 3 through 6

Table 14.2.3.4 Treatment Comparison of CGI-I Score
Full Analysis Set

	Treatment Group			Treatment Group Comparison (Active - Placebo)	
Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)
Week 1					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		
LSM estimate	x.x	x.x	x.x	x.x	x.x
SE	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
95% CI	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
p-value				x.xxx	x.xxx
Week 2					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		
LSM estimate	x.x	x.x	x.x	x.x	x.x
SE	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
95% CI	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
p-value				x.xxx	x.xxx

Note: CGI-I = Clinical Global Impression – Improvement Scale, CGI-S = Clinical Global Impression – Severity Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value of CGI-S as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.
Note: To perform this assessment, the rater or Investigator rates the subject's total improvement whether or not it is due entirely to drug treatment. Lower values represent greater improvement.
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Programming Note: Repeat for weeks 3 through 6

Programming Note: Repeat for weeks 3 through 6

Table 14.2.3.5 Treatment Comparison of PANSS Responders Based on >= 30% Improvement from Baseline
Full Analysis Set

This table will be similar to 14.2.3.3.
Footnotes will be:
Note: PANSS = Positive and Negative Syndrome Scale, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: PANSS responders are defined as subjects who have >= 30% improvement from baseline.
Note: Estimates of the proportion of responders in each treatment group and differences of proportions between the treatment groups are based on the standard method based on the binomial distribution. 95% CIs for proportion estimates are based on the Wilson method. 95% CIs for the differences of proportions are based on the Newcombe method.
Note: P-value is based on the Cochran-Mantel-Haenszel test, stratified by country. The hypothesis tested is the general association statistic.

Table 14.2.3.6 Treatment Comparison of PANSS Responders Based on >= 30% Improvement from Baseline
ITT Analysis Set

This table will be similar to 14.2.3.3.
Footnotes will be:
Note: ITT = Intent-to-Treat, PANSS = Positive and Negative Syndrome Scale, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the ITT analysis set by treatment group.
Note: PANSS responders are defined as subjects who have >= 30% improvement from baseline.
Note: Estimates of the proportion of responders in each treatment group and differences of proportions between the treatment groups are based on the standard method based on the binomial distribution. 95% CIs for proportion estimates are based on the Wilson method. 95% CIs for the differences of proportions are based on the Newcombe method.
Note: P-value is based on the Cochran-Mantel-Haenszel test, stratified by country. The hypothesis tested is the general association statistic.

Table 14.2.3.7 Treatment Comparison of PANSS Responders Based on >= X% Improvement at Week 6
Full Analysis Set

	Treatment Group			Treatment Group Comparison (Active - Placebo)	
Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)
>= 5% Improvement					
Responders, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)		
Estimate	x.x	x.x	x.x	x.x	x.x
SE	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
95% CI	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
>= 10% Improvement					
Responders, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)		
Estimate	x.x	x.x	x.x	x.x	x.x
SE	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
95% CI	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx

Note: PANSS = Positive and Negative Syndrome Scale, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: PANSS responders are defined as subjects who have >= X% improvement from baseline.
Note: Percentages are calculated as (n/N)*100. N includes subjects who have a baseline and at least one post-baseline measurement.
Note: Estimates of the proportion of responders in each treatment group and differences of proportions between the treatment groups are based on the standard method based on the binomial distribution. 95% CIs for proportion estimates are based on the Wilson method. 95% CIs for the differences of proportions are based on the Newcombe method.

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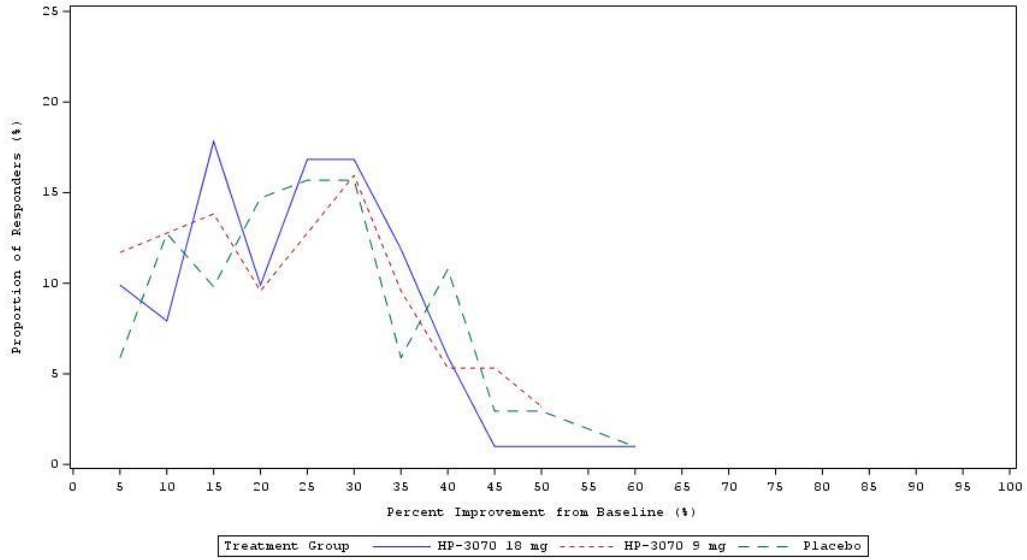
Programming Note: Repeat by 5% Increments up to 100%

Figure 14.2.3.7 Continuous Responder Analysis Based on Change from Baseline in PANSS Total Score at Week 6 Full Analysis Set

A continuous responder analysis will be performed based on definition of responder at multiple levels of percent improvement from Baseline, from >=5% to 100% with 5% increments. Results will be reported by means of a graph with response threshold on the X-axis and proportion of responders in each treatment group on the Y-axis.



Note: PANSS = Positive and Negative Syndrome Scale.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: PANSS responders are defined as subjects who have >=X% improvement from baseline
Note: Reference Table 14.2.3.7

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Table 14.2.3.8 Treatment Comparison of PANSS Responders Based on >= X% Improvement at Week 6
ITT Analysis Set

This table will be similar to 14.2.3.10.
Footnotes will be:
Note: ITT = Intent-to-Treat, PANSS = Positive and Negative Syndrome Scale, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the ITT analysis set by treatment group.
Note: PANSS responders are defined as subjects who have >= X% improvement from baseline.
*Note: Percentages are calculated as (n/N)*100.*
Note: Estimates of the proportion of responders in each treatment group and differences of proportions between the treatment groups are based on the standard method based on the binomial distribution. 95% CIs for proportion estimates are based on the Wilson method. 95% CIs for the differences of proportions are based on the Newcombe method.

Figure 14.2.3.8 Continuous Responder Analysis Based on Change from Baseline in PANSS Total Score at Week 6
ITT Analysis Set

This figure will be similar to figure 14.2.1.2.1.1.
First footnote will be:
Note: PANSS = Positive and Negative Syndrome Scale, SE = Standard Error, CI = Confidence Interval, ITT = Intent-to-Treat, N = number of subjects in the ITT analysis set by treatment group.

Table 14.2.3.9 Treatment Comparison of Change from Baseline in CDSS Total Score
Full Analysis Set

This table will be similar to 14.2.3.5.
Footnotes will be:
Note: CDSS = Calgary Depression Scale for Schizophrenia, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the ITT analysis set by treatment group.
Note: The CDSS is a nine-item scale designed for assessment of the level of depression in patients with schizophrenia.The CDSS total score is the sum of all 9 items.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

Table 14.2.3.10 Treatment Comparison of MSQ Score
Full Analysis Set

	Treatment Group			Treatment Group Comparison (Active - Placebo)	
Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)
Week 2					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		
LSM estimate	x.x	x.x	x.x	x.x	x.x
SE	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
95% CI	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
p-value				x.xxx	x.xxx
Week 4					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		
LSM estimate	x.x	x.x	x.x	x.x	x.x
SE	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
95% CI	x.xx, x.xx	x.xx, x.xx	x.xx, x,xx	x.xx, x.xx	x.xx, x.xx
p-value				x.xxx	x.xxx

Note: MSQ = Medication Satisfaction Questionnaire, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: The MSQ is a single-item questionnaire used to assess the level of patient's satisfaction or dissatisfaction with the medication they are taking. Responses can range from Extremely Dissatisfied (1) to Extremely Satisfied (7).
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

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Table 14.2.3.10 Treatment Comparison of MSQ Score
Full Analysis Set

	Treatment Group			Treatment Group Comparison (Active - Placebo)	
Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)
Week 6					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		
LSM estimate	x.x	x.x	x.x	x.x	x.x
SE	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
95% CI	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx
p-value				x.xxx	x.xxx

Note: MSQ = Medication Satisfaction Questionnaire, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: The MSQ is a single-item questionnaire used to assess the level of patient's satisfaction or dissatisfaction with the medication they are taking. Responses can range from Extremely Dissatisfied (1) to Extremely Satisfied (7).
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

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Table 14.2.4.1 Treatment Comparison of Change from Baseline in PANSS Total Score at Week 6 by Gender
Full Analysis Set

	Treatment Group			Treatment Group Comparison (Active - Placebo)	
Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)
Female, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)		
Baseline					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		
Week 6					
Observed					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		

Note: PANSS = Positive and Negative Syndrome Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. If one or more items are missing at a given assessment, the total score is set to missing.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Percentages are calculated as (n/N)*100.
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

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Table 14.2.4.1 Treatment Comparison of Change from Baseline in PANSS Total Score at Week 6 by Gender
Full Analysis Set

	Treatment Group			Treatment Group Comparison (Active - Placebo)	
Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)
Change from Baseline to Week 6					
n	xx	xx	xx		
Mean	x.x	x.x	x.x		
SD	x.xx	x.xx	x.xx		
Median	x.x	x.x	x.x		
Min	x	x	x		
Max	x	x	x		
LSM estimate	x.x	x.x	x.x	x.x	x.x
SE	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
95% CI	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx	x.xx, x.xx

Note: PANSS = Positive and Negative Syndrome Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: The PANSS total score is the sum of all 30 items. Higher values represent greater severity of illness. If one or more items are missing at a given assessment, the total score is set to missing.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Percentages are calculated as (n/N)*100.
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

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Programming Note: Repeat for Male

Table 14.2.4.2 Treatment Comparison of Change from Baseline in CGI-S Score at Week 6 by Gender
Full Analysis Set

This table will be similar to 14.2.4.1.
Footnotes will be:
Note: CGI-S = Clinical Global Impression – Severity of Illness Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
*Note: Percentages are calculated as (n/N)*100.*
Note: CGI-S score is determined by answering the question "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" on a scale of 0-7, with 0 indicating not assessed and 7 indicating the most extremely ill subjects.
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

Table 14.2.4.3 Treatment Comparison of Change from Baseline in PANSS Total Score at Week 6 by Age
Full Analysis Set

This table will be similar to 14.2.4.1.
'Female' and 'Male' are replaced with 'Age < 55' and 'Age >= 55'.

Table 14.2.4.4 Treatment Comparison of Change from Baseline in CGI-S Score at Week 6 by Age
Full Analysis Set

This table will be similar to 14.2.4.1.
'Female' and 'Male' are replaced with 'Age < 55' and 'Age >= 55'.

Footnotes will be:
Note: CGI-S = Clinical Global Impression – Severity of Illness Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
*Note: Percentages are calculated as (n/N)*100.*
Note: CGI-S score is determined by answering the question "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" on a scale of 0-7, with 0 indicating not assessed and 7 indicating the most extremely ill subjects.
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

Table 14.2.4.5 Treatment Comparison of Change from Baseline in PANSS Total Score at Week 6 by Race
Full Analysis Set

This table will be similar to 14.2.4.1.
'Female' and 'Male' are replaced with 'Black/African American' and 'All Other Races Combined'.
Include the Footnote:
Note: All Other Races Combined includes: American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islanders, White and Other.

Table 14.2.4.6 Treatment Comparison of Change from Baseline in CGI-S Score at Week 6 by Race
Full Analysis Set

This table will be similar to 14.2.4.1.
'Female' and 'Male' are replaced with 'Black/African American' and 'All Other Races Combined'.

Footnotes will be:
Note: CGI-S = Clinical Global Impression – Severity of Illness Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
*Note: Percentages are calculated as (n/N)*100.*
Note: CGI-S score is determined by answering the question "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" on a scale of 0-7, with 0 indicating not assessed and 7 indicating the most extremely ill subjects.
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.
Note: All Other Races Combined includes: American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islanders, White and Other.

Table 14.2.4.7 Treatment Comparison of Change from Baseline in PANSS Total Score at Week 6 by Severity at Baseline
Full Analysis Set

This table will be similar to 14.2.4.1.
'Female' and 'Male' are replaced with 'PANSS Total Score < 90' and 'PANSS Total Score >= 90'.

Table 14.2.4.8 Treatment Comparison of Change from Baseline in CGI-S Score at Week 6 by Severity at Baseline
Full Analysis Set

This table will be similar to 14.2.4.1.
'Female' and 'Male' are replaced with 'PANSS Total Score < 90' and 'PANSS Total Score >= 90'.
Footnotes will be:

Note: CGI-S = Clinical Global Impression – Severity of Illness Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
*Note: Percentages are calculated as (n/N)*100.*
Note: CGI-S score is determined by answering the question "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" on a scale of 0-7, with 0 indicating not assessed and 7 indicating the most extremely ill subjects.
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

Table 14.2.4.9 Treatment Comparison of Change from Baseline in PANSS Total Score at Week 6 by Region
Full Analysis Set

This table will be similar to 14.2.4.1.
'Female' and 'Male' are replaced with 'North America' 'Rest of the World and 'Russia'.

Table 14.2.4.10 Treatment Comparison of Change from Baseline in CGI-S Score at Week 6 by Region
Full Analysis Set

This table will be similar to 14.2.4.1.
'Female' and 'Male' are replaced with 'North America, 'Rest of the World and 'Russia'.
Footnotes will be:
Note: CGI-S = Clinical Global Impression – Severity of Illness Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
*Note: Percentages are calculated as (n/N)*100.*
Note: CGI-S score is determined by answering the question "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" on a scale of 0-7, with 0 indicating not assessed and 7 indicating the most extremely ill subjects.
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

Table 14.2.4.11 Treatment Comparison of Change from Baseline in PANSS Total Score at Week 6 by BMI at Baseline
Full Analysis Set

This table will be similar to 14.2.4.1.
Instead of 2 categories of 'Female' and 'Male', there will be 3 categories of '< 25 kg/m2', '>= 25 to < 30 kg/m2', and '>= 30 kg/m2'.

Table 14.2.4.12 Treatment Comparison of Change from Baseline in CGI-S Score at Week 6 by BMI at Baseline
Full Analysis Set

This table will be similar to 14.2.4.1.

Instead of 2 categories of 'Female' and 'Male', there will be 3 categories of '< 25 kg/m2', '>= 25 to < 30 kg/m2', and '>= 30 kg/m2'.
Footnotes will be:
Note: CGI-S = Clinical Global Impression – Severity of Illness Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
*Note: Percentages are calculated as (n/N)*100.*
Note: CGI-S score is determined by answering the question "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" on a scale of 0-7, with 0 indicating not assessed and 7 indicating the most extremely ill subjects.
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

Table 14.2.4.13 Treatment Comparison of Change from Baseline in PANSS Total Score at Week 6 by Age of Onset Full Analysis Set

This table will be similar to 14.2.4.1.
'Female' and 'Male' are replaced with 'Onset Age < 25' and 'Onset Age >= 25'.

Table 14.2.4.14 Treatment Comparison of Change from Baseline in CGI-S Total Score at Week 6 by Age of Onset Full Analysis Set

This table will be similar to 14.2.4.1.
'Female' and 'Male' are replaced with 'Onset Age < 25' and 'Onset Age >= 25'.
Footnotes will be:
Note: CGI-S = Clinical Global Impression – Severity of Illness Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
*Note: Percentages are calculated as (n/N)*100.*
Note: CGI-S score is determined by answering the question "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" on a scale of 0-7, with 0 indicating not assessed and 7 indicating the most extremely ill subjects.
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.
Note: To perform this assessment, the rater or Investigator answers the following question: "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" Higher values represent greater severity of illness. The maximum score is 7.

Table 14.2.4.15 Treatment Comparison of Change from Baseline in PANSS Total Score at Week 6 by Disease Duration Full Analysis Set

This table will be similar to 14.2.4.1.
Instead of 2 categories of 'Female' and 'Male', there will be 4 categories of '< 5 years', '>= 5 to < 10 years', '>= 10 to < 20 years', and '>= 20 years'.

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Table 14.2.4.16 Treatment Comparison of Change from Baseline in CGI-S Score at Week 6 by Disease Duration
Full Analysis Set

This table will be similar to 14.2.4.1.
Instead of 2 categories of 'Female' and 'Male', there will be 4 categories of '< 5 years', '>= 5 to < 10 years', '>= 10 to < 20 years', and '>= 20 years'.
Footnotes will be:
Note: CGI-S = Clinical Global Impression – Severity of Illness Scale, LSM = Least Squares Mean, SE = Standard Error, CI = Confidence Interval, N = number of subjects in the full analysis set by treatment group.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: CGI-S score is determined by answering the question "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" on a scale of 0-7, with 0 indicating not assessed and 7 indicating the most extremely ill subjects.
*Note: Percentages are calculated as (n/N)*100.*
Note: The mixed linear repeated measures model includes treatment, country, visit, treatment by visit interaction, and baseline value as covariates, and subject as random effect. The correlation of repeated measures within a subject is estimated with an unstructured covariance matrix. The Kenward-Rogers method is used to estimate the denominator degrees of freedom.

1.3 Safety

Table 14.3.1.1 Overview of Adverse Events
Safety Analysis Set

		HP-3070 18.0 mg (N=xxx)		HP-3070 9.0 mg (N=xxx)		Placebo (N=xxx)	
	Statistic	Subjects [a]	Events [b]	Subjects [a]	Events [b]	Subjects [a]	Events [b]
Any AE	n (%)	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Any TEAE	n (%)	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Any Severe TEAE	n (%)	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Any Related TEAE	n (%)	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Any TEAE Leading to Discontinuation of Study Medication	n (%)	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Any Serious TEAE	n (%)	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Any Related Serious TEAE	n (%)	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Any TEAE Leading to Death	n (%)	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Any TEAE Occurring at Patch Application Site	n (%)	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

Note: AE = Adverse Event, TEAE = Treatment-Emergent Adverse Event, N = number of subjects in the safety analysis set by treatment group.
Note: TEAEs are defined as all AEs which start (or increase in severity) prior to, on or after the date of first dose of double-blind study medication through the 30 day follow-up period.
Note: Related is defined as any investigator assessment of possible or probable. TEAEs with missing relationship to study medication are counted as related.
Note: Percentages are calculated as (n/N)*100.
[a]: Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.
[b]: Multiple events for a subject that are in the same AE category are counted multiple times in that AE category. Multiple events belonging to more than one AE category are counted multiple times in each of those AE categories.

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Table 14.3.1.2 Treatment-Emergent Adverse Events During the Double-Blind Period by System Organ Class and Preferred Term
Safety Analysis Set

System Organ Class Preferred Term	HP-3070 18.0 mg (N=xxx) n (%)	HP-3070 9.0 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)
Total number of TEAE	xx	xx	xx
Subjects with any TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	xx (xx.x)	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: TEAE = Treatment-Emergent Adverse Event, AE = Adverse Event, N = number of subjects in the safety analysis set by treatment group.
Note: TEAEs are defined as all AEs which start (or increase in severity) prior to, on or after the date of first dose of double-blind study medication through the 30 day follow-up period.
Note: Percentages are calculated as (n/N)*100.
Note: Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.
Note: This summary is sorted by decreasing frequency of system organ class, and within system organ class, by decreasing frequency of preferred term in the HP-3070 18.0mg column.
Note: Adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version xx.x.

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Programming note: SOC should be displayed in all caps. Preferred Term should include lower case.

Table 14.3.1.3 Treatment-Emergent Adverse Events During the Double-Blind Period by System Organ Class, Preferred Term, Relationship to Study Medication, and Severity
Safety Analysis Set

System Organ Class Preferred Term	Relationship Severity	HP-3070 18.0 mg (N=XXX) Subjects [a]	 Events [b]	HP-3070 9.0 mg (N=XXX) Subjects [a]	 Events [b]	Placebo (N=XXX) Subjects [a]	 Events [b]
Subjects with any TEAE	Related	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
	Mild	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
	Moderate	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
	Severe	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
	Not Related	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
	Mild	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
	Moderate	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
	Severe	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
SYSTEM ORGAN CLASS 1	Related	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
	Mild	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
	Moderate	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
	Severe	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

Note: TEAE = Treatment-Emergent Adverse Event, AE = Adverse Event, N = number of subjects in the safety analysis set by treatment group.
Note: TEAEs are defined as all AEs which start (or increase in severity) prior to, on or after the date of first dose of double-blind study medication through the 30 day follow-up period.
Note: Related is defined as any investigator assessment of possible or probable. TEAEs with missing relationship to study medication are counted as related.
Note: TEAEs with a missing severity are counted as severe.
[a]: Subjects with more than one TEAE are counted once in each category. The worst case relationship is summarized, at the maximum severity.
[b]: Multiple events for a subject that are in the same AE category are counted multiple times in that AE category.
Note: Adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version xx.x.
Note: Percentages are calculated as (n/N)*100.

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Programming note: Repeat for all Related and Not Related options for every SOC and PT. SOC should be displayed in all caps. Preferred Term should include lower case.

Programming note: In the Subjects [a] column, each subject is counted once per SOC/PT. At a given SOC or PT level, identify the worst case relationship per subject, then within that relationship level identify the worst case severity. In the Events [b] column, all TEAEs meeting the relationship/severity condition should be counted. (A subject may contribute to the events count in a row where he/she is not counted at the subject level, if it is not the worst case event.)

Table 14.3.1.4 Treatment-Emergent Adverse Events During the Double-Blind Period Leading to Study Drug Discontinuation by System Organ Class and Preferred Term
Safety Analysis Set

This table will be similar to 14.3.1.2.
Programming note: Replace the first row with "Total number of TEAEs leading to study drug discontinuation" and the second row with "Subjects with any TEAE Leading to Study Drug Discontinuation".

Table 14.3.1.5 Treatment-Emergent Adverse Events During the Double-Blind Period Leading to Study Drug Discontinuation by Region and by System Organ Class and Preferred Term
Safety Analysis Set

System Organ Class Preferred Term	HP-3070 18.0 mg (N=xxx) n (%)	HP-3070 9.0 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)
Rest of the World			
Total number of TEAEs Leading to Study Drug Discontinuation	xx	xx	xx
Subjects with any TEAE Leading to Study Drug Discontinuation	xx (xx.x)	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	xx (xx.x)	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: TEAE = Treatment-Emergent Adverse Event, AE = Adverse Event, N = number of subjects in the safety analysis set by treatment group.
Note: TEAEs are defined as all AEs which start (or increase in severity) prior to, on or after the date of first dose of double-blind study medication through the 30 day follow-up period.
Note: Percentages are calculated as (n/N)*100.
Note: Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.
Note: This summary is sorted by decreasing frequency of system organ class, and within system organ class, by decreasing frequency of preferred term in the HP-3070 18.0mg column.
Note: Adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version xx.x.

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Programming note: SOC should be displayed in all caps. Preferred Term should include lower case. Repeat table for each region: Rest of

the World, Russia then North America.

Table 14.3.1.6 Serious Treatment-Emergent Adverse Events During the Double-Blind Period by System Organ Class and Preferred Term

Safety Analysis Set

This table will be similar to 14.3.1.2.

Programming note: Replace the first row with "Total number of serious TEAEs" and the second row with "Subjects with any Serious TEAE".

Table 14.3.1.7 Serious Treatment-Emergent Adverse Events During the Double-Blind Period by Region and by System Organ Class and Preferred Term

Safety Analysis Set

This table will be similar to 14.3.1.5.

Programming note: Replace the first row with "Total number of serious TEAEs" and the second row with "Subjects with any Serious TEAE".

Table 14.3.1.8 Serious Treatment-Emergent Adverse Events During the Double-Blind Period by System Organ Class, Preferred Term, Relationship to Study Medication, and Severity

Safety Analysis Set

This table will be similar to 14.3.1.3.

Programming note: Replace the first row with "Subjects with any Serious TEAE".

Table 14.3.1.9 Treatment-Emergent Adverse Events During the Double-Blind Period Leading to Death by System Organ Class and Preferred Term

Safety Analysis Set

This table will be similar to 14.3.1.2.

Programming note: Replace the first row with "Total number of TEAEs leading to death" and the second row with "Subjects with any TEAE Leading to Death".

Table 14.3.1.10 Commonly Occurring (>= 5%) Treatment-Emergent Adverse Events During the Double-Blind Period by System Organ Class and Preferred Term

Safety Analysis Set

This table will be similar to 14.3.1.2.

Add a footnote:

Note: Commonly Occurring TEAE is defined as any TEAE occurring in at least 5% of subjects in any treatment arm.

Table 14.3.1.11 Commonly Occurring (>= 5%) Treatment-Emergent Adverse Events During the Double-Blind Period by Region and by System Organ Class and Preferred Term
Safety Analysis Set
This table will be similar to 14.3.1.5.
Add a footnote:
Note: Commonly Occurring TEAE is defined as any TEAE occurring in at least 5% of subjects in any treatment arm.

Table 14.3.1.12 All Commonly Occurring (>= 5%) Adverse Events During the Double-Blind Period by Region and by System Organ Class and Preferred Term
Safety Analysis Set
This table will be similar to 14.3.1.5.
Add a footnote:
Note: Commonly Occurring AE is defined as any AE occurring in at least 5% of subjects in any treatment arm.

Table 14.3.1.13 Commonly Occurring (>= 2%) Treatment-Emergent Adverse Events During the Double-Blind Period by System Organ Class and Preferred Term
Safety Analysis Set
This table will be similar to 14.3.1.2.
Add a footnote:
Note: Commonly Occurring TEAE is defined as any TEAE occurring in at least 2% of subjects in any treatment arm.

Table 14.3.1.14 Treatment-Emergent Adverse Events at Patch Application Site During the Double-Blind Period by Preferred Term and Severity
Safety Analysis Set

Preferred Term Severity	HP-3070 18.0 mg (N=xxx) n (%)	HP-3070 9.0 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)
Total number of Dermal TEAEs	xx	xx	xx
Subjects with any Dermal TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	…	…	…

Note: TEAE = Treatment-Emergent Adverse Event, AE = Adverse Event, N = number of subjects in the safety analysis set by treatment group.
Note: TEAEs are defined as all AEs which start (or increase in severity) prior to, on or after the date of first dose of double-blind study medication through the 30 day follow-up period.
Note: TEAEs with a missing severity are counted as severe.
Note: Percentages are calculated as (n/N)*100.
Note: Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.
Note: This summary is sorted by decreasing frequency of preferred term in the HP-3070 18.0mg column.
Note: Adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version xx.x.

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Table 14.3.2.1 Clinical Laboratory Quantitative Results and Change from Baseline by Visit - Hematology
Safety Analysis Set

Laboratory Test (SI Unit)	Visit	Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)
Hemoglobin (g/dL)					
	Baseline	n	xx	xx	xx
		Mean	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx
		Median	xx	xx	xx
		Min	xx	xx	xx
		Max	xx	xx	xx
	Week 3	n	xx	xx	xx
		Mean	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx
		Median	xx	xx	xx
		Min	xx	xx	xx
		Max	xx	xx	xx
	Change from Baseline to Week 3	n	xx	xx	xx
		Mean	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx
		Median	xx	xx	xx
		Min	xx	xx	xx
		Max	xx	xx	xx

Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Unscheduled visits are not included in this summary.

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Programming note: Repeat at week 6 and for all tests planned in the protocol

Table 14.3.2.2 Clinical Laboratory Quantitative Results and Change from Baseline by Visit – Serum Chemistry
Safety Analysis Set

This table will be similar to 14.3.2.1.

Table 14.3.2.3 Clinical Laboratory Quantitative Results and Change from Baseline by Visit – Urinalysis
Safety Analysis Set

This table will be similar to 14.3.2.1.

Table 14.3.2.4 Clinical Laboratory Shifts from Baseline to Worst On-Treatment Result for Categorical Measurements
Safety Analysis Set

			Worst On-Treatment Result					
Laboratory Test	Treatment Group	Baseline Result	Negative n (%)	Trace n (%)	1+ n (%)	2+	3+	4+
Categorical Lab Test 1								
	HP-3070 18.0 mg (N=XX)	Negative	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Trace	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		…	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	HP-3070 9.0 mg (N=XX)	Negative	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Trace	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		…	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Placebo (N=XX)	Negative	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Trace	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		…	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: N is the number of subjects with both baseline and post-baseline assessments in a treatment group.
Note: Worst on-treatment result is defined as the worst result occurring after the administration of the first dose of double-blind study medication.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Percentages are calculated as (n/N)*100.

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Programming note: Repeat for all tests planned in the protocol

Table 14.3.2.5.1 Clinical Laboratory Shifts from Baseline to Maximum On-Treatment Result - Hematology
Safety Analysis Set

			Worst On-Treatment Result		
			Low	Normal	High
Laboratory Test	Treatment Group	Baseline Result	n (%)	n (%)	n (%)
Hemoglobin					
	HP-3070 18.0 mg (N=XX)	Low	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)
		High	xx (xx.x)	xx (xx.x)	xx (xx.x)
	HP-3070 9.0 mg (N=XX)	Low	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)
		High	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Placebo (N=XX)	Low	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)
		High	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: N is the number of subjects with both baseline and post-baseline assessments in a treatment group.
Note: Maximim on-treatment result is defined as the maximum result occurring after the administration of the first dose of double-blind study medication.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Percentages are calculated as (n/N)*100.
Note: Low is less than the normal low range value, Normal is inclusive of the normal low and high range values, and High is greater than the normal high range value.

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Programming note: Repeat for all tests planned in the protocol

Table 14.3.2.5.2 Clinical Laboratory Shifts from Baseline to Minimum On-Treatment Result – Hematology
Safety Analysis Set
This table will be similar to 14.3.2.5.1.

Table 14.3.2.6.1 Clinical Laboratory Shifts from Baseline to Maximum On-Treatment Result – Serum Chemistry
Safety Analysis Set
This table will be similar to 14.3.2.5.1.

Table 14.3.2.6.2 Clinical Laboratory Shifts from Baseline to Minimum On-Treatment Result – Serum Chemistry
Safety Analysis Set
This table will be similar to 14.3.2.5.1.

Table 14.3.2.7.1 Clinical Laboratory Shifts from Baseline to Maximum On-Treatment Result – Urinalysis
Safety Analysis Set
This table will be similar to 14.3.2.5.1.

Table 14.3.2.7.2 Clinical Laboratory Shifts from Baseline to Minimum On-Treatment Result – Urinalysis
Safety Analysis Set
This table will be similar to 14.3.2.5.1.

Table 14.3.2.8 Clinical Laboratory Shifts in NCI CTCAE Grades from Baseline to Worst On-Treatment Result
Safety Analysis Set

Laboratory Test (Upper or Lower Limit of Normal)	Treatment Group	Baseline Result	Worst On-Treatment Result 0	1	2	3	4
Hemoglobin (Low)							
	HP-3070 18.0 mg (N=XX)	0	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	HP-3070 9.0 mg (N=XX)	0	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Placebo (N=XX)	0	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: NCI = National Cancer Institute, CTCAE = Common Terminology Criteria for Adverse Events.
Note: N is the number of subjects with both baseline and post-baseline assessments in a treatment group.
Note: Worst on-treatment result is defined as the worst result occurring after the administration of the first dose of double-blind study medication.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Grade refers to the severity. As a general guideline: Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe or medically significant but not immediately life-threatening, and Grade 4 is life-threatening consequences.
Note: Percentages are calculated as (n/N)*100.
Note: Grades are assigned using CTCAE Version x.xx.

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Programming note: Repeat for all tests planned in the protocol. For tests with grades in both high and low directions, show each direction separately, with high or low indicated in the laboratory test column.

Table 14.3.2.9 Clinical Laboratory Neutrophil Results Below 1000 per Cubic Millimeter by Visit
Safety Analysis Set

Visit	Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)
Baseline	N	xx	xx	xx
	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 3	N	xx	xx	xx
	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 6	N	xx	xx	xx
	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Percentages are calculated as (n/N)*100, where N is the number of subjects with data at the given visit for each treatment group.
Note: Unscheduled visits are not included in this summary.

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Table 14.3.2.10 Clinical Laboratory Liver Function Abnormalities
Safety Analysis Set

Abnormality	HP-3070 18.0 mg (N=xxx) n (%)	HP-3070 9.0 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)
ALT > 3xULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
AST > 3xULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
ALP < 2xULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
Potential Hy's Law Cases	xx (xx.x)	xx (xx.x)	xx (xx.x)
ALP <= 2xULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
ALT >= 3xULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
AST >= 3xULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other Tests			
Creatine Kinase >= 3xULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
Prolactin >= 4xULN	xx (xx.x)	xx (xx.x)	xx (xx.x)
Total Bilirubin >= 2xULN	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: ALT = Alanine Transaminase, AST = Aspartate Transaminase, ALP = Alkaline Phosphatase, ULN = Upper Limit of Normal.
Note: Potential Hy's Law Cases are defined as subjects who at any point during the study meet the criteria of ALT or AST > 3xULN, ALP < 2xULN, and Total Bilirubin >= 2xULN.
Note: Percentages are calculated as (n/N)*100.
Note: Values for ALT >=3xULN and AST >=3xULN are only presented for subjects that meet the criteria of ALP<=2xULN.

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Table 14.3.3.1 12-Lead ECG Quantitative Results and Change from Baseline by Visit
Safety Analysis Set

Parameter (Unit)	Visit	Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)
PR Interval (msec)					
	Baseline	n	xx	xx	xx
		Mean	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx
		Median	xx	xx	xx
		Min	xx	xx	xx
		Max	xx	xx	xx
	Week 1	n	xx	xx	xx
		Mean	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx
		Median	xx	xx	xx
		Min	xx	xx	xx
		Max	xx	xx	xx
	Change from Baseline to Week 1	n	xx	xx	xx
		Mean	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx
		Median	xx	xx	xx
		Min	xx	xx	xx
		Max	xx	xx	xx

Note: ECG = Electrocardiogram.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Unscheduled visits are not included in this summary.

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Programming note: Repeat for all visits and all tests planned in the protocol.

Table 14.3.3.2 12-Lead ECG Overall Assessment by Visit
Safety Analysis Set

Visit/ Assessment	Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)
Baseline	N	xx	xx	xx
Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abnormal, Not Clinically Significant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abnormal, Clinically Significant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 1	N	xx	xx	xx
Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abnormal, Not Clinically Significant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abnormal, Clinically Significant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 2	N	xx	xx	xx
Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abnormal, Not Clinically Significant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abnormal, Clinically Significant	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: ECG = Electrocardiogram.
Note: Overall assessment of ECG is based on investigator's judgment.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Unscheduled visits are not included in this summary.
Note: Percentages are calculated as (n/N)*100, where N is the number of subjects with data at the given visit.

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Programming note: Repeat for all visits.

Table 14.3.3.3 12-Lead ECG Overall Assessment Shifts from Baseline to Worst On-Treatment Result
Safety Analysis Set

		Worst On-Treatment Result		
Treatment Group	Baseline Result	Normal n (%)	Abnormal, NCS n (%)	Abnormal, CS n (%)
HP-3070 18.0 mg (N=XX)	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal, NCS	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal, CS	xx (xx.x)	xx (xx.x)	xx (xx.x)
HP-3070 9.0 mg (N=XX)	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal, NCS	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal, CS	xx (xx.x)	xx (xx.x)	xx (xx.x)
Placebo (N=XX)	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal, NCS	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal, CS	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: ECG = Electrocardiogram, NCS = Not Clinically Significant, CS = Clinically Significant
Note: N is the number of subjects with both baseline and post-baseline assessments in a treatment group.
Note: Worst on-treatment result is defined as the worst result occurring after the administration of the first dose of double-blind study medication.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Percentages are calculated as (n/N)*100.

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Table 14.3.3.4 12-Lead ECG Markedly Abnormal Results by Visit
Safety Analysis Set

Visit/ Abnormality	Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)
Overall Post-baseline	N	xx	xx	xx
Any Marked Abnormality	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
QT Interval				
Result > 450 msec	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Result > 480 msec	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Result > 500 msec	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Change from Baseline >= 30 msec	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Change from Baseline >= 60 msec	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
QTcB Interval				
Result > 450 msec	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Result > 480 msec	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Result > 500 msec	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
CFB >= 30 msec	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
CFB >= 60 msec	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: ECG = Electrocardiogram, QTcB = QT interval corrected by Bazett's formula, QTcF = QT interval corrected by Fridericia's formula, HR = Heart Rate.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Percentages are calculated as (n/N)*100, where N is the number of subjects with data at the given visit.
Note: Unscheduled visits are not included in this summary.

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Table 14.3.3.4 12-Lead ECG Markedly Abnormal Results by Visit
Safety Analysis Set

Visit/ Abnormality	Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)
QTcF Interval				
Result > 450 msec	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Result > 480 msec	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Result > 500 msec	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Change from Baseline >= 30 msec	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Change from Baseline >= 60 msec	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
HR				
>= 100 bpm	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PR Interval				
>= 210 msec	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
QRS Interval				
>= 120 msec	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 1				
…				

Note: ECG = Electrocardiogram, QTcB = QT interval corrected by Bazett's formula, QTcF = QT interval corrected by Fridericia's formula, HR = Heart Rate,
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Percentages are calculated as (n/N)*100, where N is the number of subjects with data at the given visit.
Note: Unscheduled visits are not included in this summary.

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Programming note: Repeat for week 2 through 6.

Table 14.3.3.5 12-Lead ECG Markedly Abnormal Shifts from Baseline to Worst On-Treatment Result
Safety Analysis Set

			Worst On-Treatment Result	
Parameter	Treatment Group	Baseline Result	No Marked Abnormality n (%)	At Least One Marked Abnormality n (%)
Any Parameter	HP-3070 18.0 mg (N=XX)	No Marked Abnromality	xx (xx.x)	xx (xx.x)
		At Least One Marked Abnormality	xx (xx.x)	xx (xx.x)
	HP-3070 9.0 mg (N=XX)	No Marked Abnormality	xx (xx.x)	xx (xx.x)
		At Least One Marked Abnormality	xx (xx.x)	xx (xx.x)
	Placebo (N=XX)	No Marked Abnormality	xx (xx.x)	xx (xx.x)
		At Least One Marked Abnormality	xx (xx.x)	xx (xx.x)
QT Interval	HP-3070 18.0 mg (N=XX)	No Marked Abnormality	xx (xx.x)	xx (xx.x)
		At Least One Marked Abnormality	xx (xx.x)	xx (xx.x)

Note: ECG = Electrocardiogram, QTcB = QT interval corrected by Bazett's formula, QTcF = QT interval corrected by Fridericia's formula, HR = Heart Rate,
Note: N is the number of subjects with both baseline and post-baseline assessments in a treatment group.
Note: Worst on-treatment result is defined as the worst result occurring after the administration of the first dose of double-blind study medication.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Markedly abnormal is defined as an absolute value > 450 msec or a CFB >= 30 msec for parameters QT interval, QTcB interval, or QTcF interval; value >= 100 bpm for HR parameter; value >= 210 msec for PR interval parameter; >=120 msec for QRS interval.
Note: Percentages are calculated as (n/N)*100.

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Programming note: Repeat for all parameters and treatment groups.

Table 14.3.4.1 Vital Signs Results and Change from Baseline by Visit
Safety Analysis Set

Parameter (Unit)	Visit	Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)
Sitting Systolic Blood Pressure (mmHg)					
	Baseline	n	xx	xx	xx
		Mean	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx
		Median	xx	xx	xx
		Min	xx	xx	xx
		Max	xx	xx	xx
	Week 1	n	xx	xx	xx
		Mean	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx
		Median	xx	xx	xx
		Min	xx	xx	xx
		Max	xx	xx	xx
	Change from Baseline to Week 1	n	xx	xx	xx
		Mean	xx.x	xx.x	xx.x
		SD	xx.xx	xx.xx	xx.xx
		Median	xx	xx	xx
		Min	xx	xx	xx
		Max	xx	xx	xx

Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Unscheduled visits are not included in this summary.

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Programming note: Repeat for all visits and all measurements planned in the protocol.

Table 14.3.4.2 Orthostatic Hypotension by Visit
Safety Analysis Set

Visit	Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)
Baseline	N	xx	xx	xx
	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 1	N	xx	xx	xx
	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 2	N	xx	xx	xx
	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 3	N	xx	xx	xx
	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 4	N	xx	xx	xx
	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 5	N	xx	xx	xx
	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 6	N	xx	xx	xx
	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: Subjects with a decrease of >= 30 mmHg in Systolic Blood Pressure and/or a decrease of >= 20 mmHg in Diastolic Blood Pressure after >=3 minutes standing compared to the previous supine blood pressure are classified as having orthostatic hypotension.
Note: Percentages are calculated as (n/N)*100, where N is the number of subjects with data at the given visit.
Note: Unscheduled visits are not included in this summary.

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Table 14.3.4.3 Vital Signs Markedly Abnormal Results by Visit
Safety Analysis Set

Visit/ Abnormality	Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)
Overall Post-baseline	N	xx	xx	xx
Any Marked Abnormality	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Systolic Blood Pressure				
Result <= 90 mmHg and CFB <= -20 mmHg	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Result >= 180 mmHg and CFB >= 20 mmHg	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Diastolic Blood Pressure				
Result <= 50 mmHg and CFB <= -15 mmHg	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Result >= 105 mmHg and CFB >= 15 mmHg	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Heart Rate				
Result <= 50 bpm and CFB <= -15 bpm	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Result >= 120 bpm and CFB >= 15 bpm	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Body Temperature				
Result >= 38.3 C and CFB >= 1.1 C	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Weight				
CFB <= 7.0%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
CFB >= 7.0%	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: CFB = Change from baseline.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Percentages are calculated as (n/N)*100, where N is the number of subjects with data at the given visit.
Note: Unscheduled visits are not included in this summary.

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Programming note: Repeat for week 1 through week 6.

Table 14.3.5.1 SAS Total Score Results and Change from Baseline by Visit
Safety Analysis Set

Visit	Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)
Baseline	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx	xx	xx
	Min	xx	xx	xx
	Max	xx	xx	xx
Week 1	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx	xx	xx
	Min	xx	xx	xx
	Max	xx	xx	xx
Change from Baseline to Week 1	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx	xx	xx
	Min	xx	xx	xx
	Max	xx	xx	xx

Note: SAS = Simpson Angus Scale,
Note: The SAS total score is the sum of the scores for all 10 items and ranges between 0 and 40. If one or more items are missing at a visit the SAS total score is missing. Lower values of the SAS total score indicate milder symptoms.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.

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Programming note: Repeat for all visits.

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Table 14.3.5.2.1 AIMS Global Severity Score Results and Change from Baseline by Visit
Safety Analysis Set

This table will be similar to 14.3.5.1.
Footnotes will be:
Note: AIMS = Abnormal Movement Scale,
Note: The AIMS global severity score is the response to "Severity of abnormal movements" found within the global judgments section.
Note: The AIMSassessment consists of 10 items describing symptoms of dyskinesia. Each subject is observed unobtrusively while at rest (e.g., in the waiting room). Each item is rated on a 5-point scale, where 0 is the absence of symptoms and 4 is a severe condition. The AIMS Score is the sum of scored movements of the face, oral, extremities, trunk, and the Investigator's judgments.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.

Table 14.3.5.2.2 AIMS Total Score Results and Change from Baseline by Visit
Safety Analysis Set

This table will be similar to 14.3.5.1.
Footnotes will be:
Note: AIMS = Abnormal Movement Scale,
Note: The AIMS total score is the sum of the scores for all 7 items and ranges between 0 and 28. If one or more items are missing at a visit the AIMS total score is missing.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.

Table 14.3.5.3.1 BARS Global Score Results and Change from Baseline by Visit
Safety Analysis Set

This table will be similar to 14.3.5.1.
Footnotes will be:
Note: BARS = Barnes Akathisia Rating Scale,
Note: The BARS Global Score is defined as the global clinical assessment of akathisia and assesses extrapyramidal symptoms on a 6-point scale, whith 0 representing absence of symptoms and 5 representing severe akathesia.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.

Table 14.3.5.3.2 BARS Total Score Results and Change from Baseline by Visit
Safety Analysis Set

This table will be similar to 14.3.5.1.
Footnotes will be:
Note: BARS = Barnes Akathisia Rating Scale, Note: The BARS total score is the sum of the scores for the first 3 items and ranges between 0 and 9. If one or more items are missing at a visit the BARS total score is missing.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.

Table 14.3.5.4.1 C-SSRS Suicidal Ideation by Visit
Safety Analysis Set

Visit/ Assessment	Statistic	HP-3070 18.0 mg (N=xxx)	HP-3070 9.0 mg (N=xxx)	Placebo (N=xxx)
Baseline	N	xx	xx	xx
Subjects reporting at least one occurrence of suicidal ideation or behavior	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects reporting any type of suicidal behavior	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects reporting any type of sucicidal ideation	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 1	N	xx	xx	xx
Subjects reporting at least one occurrence of suicidal ideation or behavior	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects reporting any type of suicidal behavior	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects reporting any type of sucicidal ideation	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: C-SSRS = Columbia-Suicide Severity Rating Scale.
Note: Any Suicidal Ideation is defined as any score greater than 0.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Percentages are calculated as (n/N)*100, where N is the number of subjects with data at the given visit.

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Programming note: Repeat for all visits.

Table 14.3.5.4.2 C-SSRS Most Severe Suicidal Ideation and Suicidal Behavior
Safety Analysis Set

	HP-3070 18.0 mg (N=xxx) n (%)	HP-3070 9.0 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)
Any Suicidal Ideation During Screening/Baseline	xx (xx.x)	xx (xx.x)	xx (xx.x)
1: Wish to be Dead	xx (xx.x)	xx (xx.x)	xx (xx.x)
2: Non-Specific Active Suicidal Thoughts	xx (xx.x)	xx (xx.x)	xx (xx.x)
3: Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act	xx (xx.x)	xx (xx.x)	xx (xx.x)
4: Active Suicidal Ideation with Some Intent to Act, without Specific Plan	xx (xx.x)	xx (xx.x)	xx (xx.x)
5: Active Suicidal Ideation with Specific Plan and Intent	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Suicidal Behavior During Screening/Baseline	xx (xx.x)	xx (xx.x)	xx (xx.x)
Actual Attempt	xx (xx.x)	xx (xx.x)	xx (xx.x)
Interrupted Attempt	xx (xx.x)	xx (xx.x)	xx (xx.x)
Aborted Attempt	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preparatory Acts or Behavior	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed Suicide During Screening/Baseline	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Ideation or Behavior Suicidality During Screening/Baseline	xx (xx.x)	xx (xx.x)	xx (xx.x)
Both Ideation and Behavior Suicidality During Screening/Baseline	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: C-SSRS = Columbia-Suicide Severity Rating Scale.
Note: Any Suicidal Ideation is defined as any score greater than 0.
Note: Treatment-emergent suicidal ideation is defined as no suicidal ideation at baseline/screening and any suicidal ideation post-baseline.
Note: Worsening suicidal ideation is defined as most severe suicidal ideation post-baseline more severe than at baseline/screening.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Percentages are calculated as (n/N)*100.
Note: Subjects are counted only at their most severe suicidal ideation type and at their most severe behavior type.

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Table 14.3.5.4.2 C-SSRS Most Severe Suicidal Ideation and Suicidal Behavior
Safety Analysis Set

	HP-3070 18.0 mg (N=xxx) n (%)	HP-3070 9.0 mg (N=xxx) n (%)	Placebo (N=xxx) n (%)
Any Suicidal Ideation During Double-Blind Treatment Period	xx (xx.x)	xx (xx.x)	xx (xx.x)
1: Wish to be Dead	xx (xx.x)	xx (xx.x)	xx (xx.x)
2: Non-Specific Active Suicidal Thoughts	xx (xx.x)	xx (xx.x)	xx (xx.x)
3: Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act	xx (xx.x)	xx (xx.x)	xx (xx.x)
4: Active Suicidal Ideation with Some Intent to Act, without Specific Plan	xx (xx.x)	xx (xx.x)	xx (xx.x)
5: Active Suicidal Ideation with Specific Plan and Intent	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Suicidal Behavior During Double-Blind Treatment Period	xx (xx.x)	xx (xx.x)	xx (xx.x)
Actual Attempt	xx (xx.x)	xx (xx.x)	xx (xx.x)
Interrupted Attempt	xx (xx.x)	xx (xx.x)	xx (xx.x)
Aborted Attempt	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preparatory Acts or Behavior	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed Suicide During Double-Blind Treatment Period	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Ideation or Behavior Suicidality During Double-Blind Treatment Period	xx (xx.x)	xx (xx.x)	xx (xx.x)
Without Ideation or Behavior Suicidality During Screening/Baseline	xx (xx.x)	xx (xx.x)	xx (xx.x)
Both Ideation and Behavior Suicidality During Double-Blind Treatment Period	xx (xx.x)	xx (xx.x)	xx (xx.x)
Without Ideation and Behavior Suicidality During Screening/Baseline	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: C-SSRS = Columbia-Suicide Severity Rating Scale.
Note: Any Suicidal Ideation is defined as any score greater than 0.
Note: Treatment-emergent suicidal ideation is defined as no suicidal ideation at baseline/screening and any suicidal ideation post-baseline.
Note: Worsening suicidal ideation is defined as most severe suicidal ideation post-baseline more severe than at baseline/screening.
Note: Baseline is defined as the last non-missing measurement taken prior to first dose of double-blind study medication.
Note: Percentages are calculated as (n/N)*100.
Note: Subjects are counted only at their most severe suicidal ideation type and at their most severe behavior type.

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Table 14.3.6 Summary of Patch Adhesion, Adhesive Residue, and Skin Irritation
Safety Analysis Set

Visit/ Assessment	Statistic	HP-3070 18.0 mg	HP-3070 9.0 mg	Placebo
Over the Entire Double-Blind Treatment Period	N	xx	xx	xx
Any Complete Detachment	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Partial Detachment	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adhesive Residue				
0=None	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1=Mild	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2=Medium	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3=Heavy	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Occurrence of Medium or Heavy	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 1	N	xx	xx	xx
Any Complete Detachment	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Partial Detachment	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: N = number of subjects with data at the given visit.
Note: A subject's maximum adhesive residue score and maximum skin irritation score per visit are shown.
Note: Percentages are calculated as (n/N)*100.
Note: Patch adhesion is determined from the following yes/no questions: "Is the patch fully attached to the skin?" and "If 'No', did the patch detach completely?"
Note: Skin irritation combined score is the sum of the numerical scores from the skin irritation – dermal response score and the skin irritation – other effects scores, where N=0, A=0, B=1, C=2, F=3, G=3 and H=3 for the other effects score. If no grade was assigned for the other effects observations (N) score the combined score will consist of the dermal response scale score only.
Note: Skin irritation concatenated score is determined by concatenating the dermal response score and other effects score (i.e., 0N, 1N, 2N, 2A, 2B, 3N, 3A, 3B, 3C, 3F, etc.).

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Table 14.3.6 Summary of Patch Adhesion, Adhesive Residue, and Skin Irritation
Safety Analysis Set

Visit/ Assessment	Statistic	HP-3070 18.0 mg	HP-3070 9.0 mg	Placebo
Adhesive Residue				
0=None	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1=Mild	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2=Medium	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3=Heavy	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any Occurrence of Medium or Heavy	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Skin Irritation – Dermal Response Scale				
0=No evidence of irritation	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1=Minimal erythema	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2=Definite erythema, readily visible; minimal edema or minimal papular response	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3=Erythema and papules	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
4=Definite edema	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
5=Erythema, edema, and papules	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
6=Vesicular eruption	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
7=Strong reaction spreading beyond test (application) site	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: N = number of subjects with data at the given visit.
Note: A subject's maximum adhesive residue score and maximum skin irritation score per visit are shown.
Note: Percentages are calculated as (n/N)*100.
Note: Patch adhesion is determined from the following yes/no questions: "Is the patch fully attached to the skin?" and "If 'No', did the patch detach completely?"
Note: Skin irritation combined score is the sum of the numerical scores from the skin irritation – dermal response score and the skin irritation – other effects scores, where N=0, A=0, B=1, C=2, F=3, G=3 and H=3 for the other effects score. If no grade was assigned for the other effects observations (N) score the combined score will consist of the dermal response scale score only.
Note: Skin irritation concatenated score is determined by concatenating the dermal response score and other effects score (i.e., 0N, 1N, 2N, 2A, 2B, 3N, 3A, 3B, 3C, 3F, etc.).

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Table 14.3.6 Summary of Patch Adhesion, Adhesive Residue, and Skin Irritation
Safety Analysis Set

Visit/ Assessment	Statistic	HP-3070 18.0 mg	HP-3070 9.0 mg	Placebo
Skin Irritation – Other Effects				
A(0)=Slightly glazed appearance	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
B(1)=Marked glazing	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
C(2)=Glazing with peeling and cracking	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
F(3)=Glazing with Fissures	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
G(3)=Film of dried, serous exudate covering all or part of the patch site	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
H(3)=Small petechial erosions and/or scabs	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Skin Irritation - Combined Score (Concatenated Score)				
0=No evidence of irritation / No other effects (0N)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1=Minimal erythema, barely perceptible / No other effects (1N)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2=Definite erythema / No other effects (2N)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3=Erythema and papules / No other effects (3N)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<repeat for all combinations of dermal response scale and other effects>				

Note: N = number of subjects with data at the given visit.
Note: A subject's maximum adhesive residue score and maximum skin irritation score per visit are shown.
Note: Percentages are calculated as (n/N)*100.
Note: Patch adhesion is determined from the following yes/no questions: "Is the patch fully attached to the skin?" and "If 'No', did the patch detach completely?"
Note: Skin irritation combined score is the sum of the numerical scores from the skin irritation – dermal response score and the skin irritation – other effects scores, where N=0, A=0, B=1, C=2, F=3, G=3 and H=3 for the other effects score. If no grade was assigned for the other effects observations (N) score the combined score will consist of the dermal response scale score only.
Note: Skin irritation concatenated score is determined by concatenating the dermal response score and other effects score (i.e., 0N, 1N, 2N, 2A, 2B, 3N, 3A, 3B, 3C, 3F, etc.).

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Programming note: Repeat for all visits.

Table 14.3.7 Summary of Plasma Asenapine and Desmethyl-asenapine Concentrations (ng/mL)) by Treatment
PK Analysis Set

Plasma Asenapine (ng/mL)
Treatment: HP-3070 9 mg

Visit	Statistic	2 hours	14 Hours	22 Hours
Week 3/ Day 21	n	xx	xx	xx
	Mean	xxxx.xx	xxxx.xx	xxxx.xx
	SD	xxxx.xx	xxxx.xx	xxxx.xx
	%CV	xxxx.xx	xxxx.xx	xxxx.xx
	Median	xxxx.xx	xxxx.xx	xxxx.xx
	Min	xxxx.xx	xxxx.xx	xxxx.xx
	Max	xxxx.xx	xxxx.xx	xxxx.xx
	Geometric Mean	xxxx.xx	xxxx.xx	xxxx.xx
Week 6/ Day 42	n	xx	xx	xx
	Mean	xxxx.xx	xxxx.xx	xxxx.xx
	SD	xxxx.xx	xxxx.xx	xxxx.xx
	%CV	xxxx.xx	xxxx.xx	xxxx.xx
	Median	xxxx.xx	xxxx.xx	xxxx.xx
	Min	xxxx.xx	xxxx.xx	xxxx.xx
	Max	xxxx.xx	xxxx.xx	xxxx.xx
	Geometric Mean	xxxx.xx	xxxx.xx	xxxx.xx

Note: Concentrations that are BLQ are treated as zero for descriptive statistics.
Note: Summary statistics apply to Pharmacokinetic Population only

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Programming note: Repeat for HP-3070 18 mg. Blood samples will be collected for asenapine and desmethyl-asenapine concentration; on Day 21 and 42 of HP-3070 9 mg and 18 mg at 2, 14 and 22 hours after dosing.

2. LISTINGS

Listing 16.2.1.1 Randomization
ITT Analysis Set

Subject ID	Date of Randomization	Randomization Number	Treatment Group	Country
xxxx-xxxx	YYYY-MM-DD	xxx	18.0 mg	xxxxx
xxxx-xxxx	YYYY-MM-DD	xxx	9.0 mg	xxxxx
xxxx-xxxx	YYYY-MM-DD	xxx	Placebo	xxxxx

Note: ITT = Intent-to-treat.
Note: Randomization to treatment arms is stratified by country.
Note: The first four digits of the subject ID contains the site number.

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Listing 16.2.1.2 Disposition
All Subjects Screened Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Date of Birth	Sex	Race	Region/ Country	Ethnicity	Period	Disposition Event	Date (Study Day)	Reason
xxxx-xxxx	YYYY-MM-DD	Female	White	Russia	Hispanic or Latino	SB	Entered Screening/Run-In Period	YYYY-MM-DD (XX)	
						SB	Entered Informed Consent	YYYY-MM-DD (XX)	
						SB	Entered Run-In Patch Application	YYYY-MM-DD (XX)	
						SB	Screening/Run-In Failure	YYYY-MM-DD (XX)	Adverse Event: XXXXX
xxxx-xxxx	YYYY-MM-DD	Female	OTHER: XXXXXXX	North America/ United States	Hispanic or Latino	SB	Entered Screening/Run-In Period	YYYY-MM-DD (XX)	
						SB	Entered Informed Consent	YYYY-MM-DD (XX)	
						SB	Entered Run-In Patch Application	YYYY-MM-DD (XX)	
						DB	Randomized	YYYY-MM-DD (XX)	
						DB	Discontinued Study Due to Adverse Event	YYYY-MM-DD (XX)	

Note: SB = Single-Blind, DB = Double-Blind, FU = Follow-up, IVRS = Interactive Voice Activated Response System, IWRS = Interactive Web-based Response System.
Note: The study includes a run-in period of 3 to 14 days, during which placebo patches are administered, screening procedures are completed, and antipsychotic or other prohibited medications are washed out. Demographics and Screening/Run-In dispositions are based on data collected in the IVRS/IWRS.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period. During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication.

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Programming note: Repeat for HP-3070 9.0 mg, Placebo, and Subjects Not Randomized. Sort by subject and date. (Treatments are based on randomized treatment. Subjects Not Randomized are those in All Subjects Screened Analysis Set but not in ITT Analysis Set. These will be listed last.)
Programming note: In Race column, if "OTHER" is selected, concatenate the Specify data following a colon (:). In the Reason column, if "Adverse Event" is selected, concatenate the Adverse Event specification following a colon; if "Inclusion Criteria" is selected, concatenate the Inclusion Reason(s), if "Exclusion Criteria" is selected, concatenate the Exclusion Reason(s).

Listing 16.2.1.3 Demographics
ITT Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Date of Birth	Age (Years)	Sex	Race	Region/ Country	Ethnicity	Date of First Diagnosis of Schizophrenia	Start Date of Current Acute Episode	Antipsychotic Medication
xxxx-xxxx	YYYY-MM-DD	xx	Male	Asian	North America/ United States	Not Hispanic or Latino	YYYY-MM-DD	YYYY-MM-DD	Y
xxxx-xxxx	YYYY-MM-DD	xx	Female	White	Russia	Hispanic or Latino	YYYY-MM-DD	YYYY-MM-DD	N
xxxx-xxxx	YYYY-MM-DD	xx	Female	Other: XXXXXXX	Rest of the World/ Bulgaria	Hispanic or Latino	YYYY-MM-DD	YYYY-MM-DD	N

Note: ITT = Intent-to-treat.

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Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Programming note: In Race column, if multiple races are selected, concatenate all races selected with a comma (,) in between. If "Other" is selected, concatenate the Specify data following a colon (:)

Listing 16.2.1.4 Inclusion/Exclusion Criteria Not Met
ITT Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Category	Criteria not Met
xxxx-xxxx	Inclusion	xx
xxxx-xxxx	Exclusion	xx

Note: ITT = Intent-to-treat.

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Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Listing 16.2.1.5 Medical History
ITT Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	MH Number	SYSTEM ORGAN CLASS/ Preferred Term/ Verbatim Term	Start date (Study Day)	End date (Study Day)
xxxx-xxxx	xx	xxxxxxxxxxxx/ xxxxxxxxxxxxxx/ xxxxxxxxxx	YYYY-MM-DD (-xx)	YYYY-MM-DD (-xx)
	xx	xxxxxxxxxxxx/ xxxxxxxxxxxxxx/ xxxxxxxxxx	YYYY-MM-DD (-xx)	Ongoing

Note: ITT = Intent-to-treat.
Note: Medical conditions are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version xx.x.

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Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Programming note: SOC should be displayed in all caps. Preferred Term should include lower case.

Listing 16.2.1.6 Patch Application
ITT Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Period	Date/Time of Application (Study Day)	Site	Removed Prior to Scheduled Time/Reason	Detach Completely (Date/Time)	Date/Time of Removal (Study Day)	Date/Time of Irritation Assessment (Study Day)	Skin Irritation: Dermal Response Scale	Skin Irritation: Other Effects
xxxx-xxxx	SB	YYYY-MM-DD(xx)	Abdomen: Right	N	N	YYYY-MM-DD (-xx)	YYYY-MM-DD(-xx)	No evidence of irritation	
	DB	YYYY-MM-DD(xx)	Hip: Left	Y/Irritation	Y(YYYY-MM-DD)	YYYY-MM-DD (xx)	YYYY-MM-DD(xx)	Definite edema	Slightly glazed appearance

Note: ITT = Intent-to-treat, SB = Single-Blind, DB = Double-Blind, FU = Follow-up.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period. During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication.
Note: The study includes a run-in period of 3 to 14 days, during which placebo patches are administered, screening procedures are completed, and antipsychotic or other prohibited medications are washed out.

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Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Listing 16.2.1.7 Adhesive Residue Assessment
ITT Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Period	Date/Time of Assessment (Study Day)	Adhesive Residue Score
xxxx-xxxx	SB	YYYY-MM-DD(xx)	0 = None
	DB	YYYY-MM-DD(xx)	2 = Medium

Note: ITT = Intent-to-treat, SB = Single-Blind, DB = Double-Blind, FU = Follow-up.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period. During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication.
Note: The study includes a run-in period of 3 to 14 days, during which placebo patches are administered, screening procedures are completed, and antipsychotic or other prohibited medications are washed out. Demographics and Screening/Run-In dispositions are based on data collected in the IVRS/IWRS.

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Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Listing 16.2.1.8 Day Passes
ITT Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Period	Date of Day Pass (Study Day)	Drug Screen Performed/Date(Study Day)	Drug Screen Result	Alcohol Breathalyzer Performed/Date(Study Day)	Alcohol Breathalyzer Result	Pregnancy Test Performed/Date(Study Day)	Pregnancy Result
xxxx-xxxx	DB	YYYY-MM-DD(xx)	Y/YYYY-MM-DD(xx)	Negative	Y/YYYY-MM-DD(xx)	Negative	Y/YYYY-MM-DD(xx)	Negative

Note: ITT = Intent-to-treat, SB = Single-Blind, DB = Double-Blind, FU = Follow-up.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period.
During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication.

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Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Listing 16.2.1.9 Prior, Concomitant, and Post-Treatment Medications
ITT Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Med Number	Period	Preferred Name/ Verbatim Med Name	Start Date (Study Day)/ Stop Date (Study Day)	Indication (Medical History or Adverse Event Number)	To Treat Current Acute Exacerbation of Schiz	Dose (Unit)/ Frequency/ Route	Prior Med	Concomitant Med	Post-Treatment Med
xxxx-xxxx	xx	SB	xxxxxxxxxxxxx/ xxxxxxxxxxxxxxx/ xxxxxxxxxx	YYYY-MM-DD (xx)/ YYYY-MM-DD (xx)	Medical History (MH Number XX)	N	xx/ xxx/ xxxx	Y	Y	N
	xx	DB	xxxxxxxxxxxxx/ xxxxxxxxxxxxxxx/ xxxxxxxxxx	YYYY-MM-DD (xx)/ YYYY-MM-DD (xx)	Prophylaxis	N	xx/ xxx/ xxxx	N	Y	N

Note: ITT = Intent-to-treat, Med = Medication, Schiz = Schizophrenia, SB = Single-Blind, DB = Double-Blind, FU = Follow-up.
Note: Prior medications are medications which started and stopped prior to the first dose of double-blind study medication. Medications taken from 6 months prior to screening are included.
Note: Concomitant medications are medications which started prior to, on, or after the first dose of double-blind study medication and no later than 1 day following the date of last study medication patch removal, and ended on or after the date of first dose of study medication or were ongoing at the end of the study.
Note: Post-treatment medications are medications which started more than 1 day following the date of last double-blind study medication patch removal.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period. During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication.
Note: Medications are coded using World Health Organization Drug Dictionary (WHO DD) Version 19.
Note: Medication number is assigned separately for Lorazepam and for all other concomitant medications for each subject.

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Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Listing 16.2.1.10 Mini International Neuropsychiatric Interview (MINI) at Screening
ITT Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Date of Assessment (Period, Study Day)	Module	Item	Result (Scoring Points)
xxxx-xxxx	YYYY-MM-DD (xx, xx)	A: Major Depressive Episode	A1a: Ever depressed for two weeks	No
			A1b: Depressed every day for past two weeks	No
			A2a: Ever less able to enjoy things for two weeks	Yes
			A2b: Less able to enjoy things in the past 2 weeks	No
			A3a: Appetite change over the past two weeks	No
			A3a: Appetite change during most symptomatic episode	Yes
			A3b: Trouble sleeping every night over the past two weeks	No
			A3b: Trouble sleeping every night during most symptomatic episode	Yes
			A3c: Move slowly or restlessly over the last two weeks	No
			A3c: Move slowly or restlessly during most symptomatic episode	Yes
			A3d: Feel tired every day over the last two weeks	No
			A3d: Feel tired every day during most symptomatic episode	Yes
			A3e: Worthless every day over the last two weeks	No

		A3e: Worthless every day during most symptomatic episode	No
		A3f: Difficulty concentrating every day over past two weeks	No
		A3f: Difficulty concentrating every day during most symptomatic episode	No
		A3g: Feel suicidal over past two weeks	No
		A3g: Feel suicidal during most symptomatic episode	No
		A4: Symptoms cause problems over past two weeks	No
		A4: Symptoms cause problems during most symptomatic episode	Yes
		A5: Two month interval of no depression between bounts of depression	No
		A6: How many episodes of depression in lifetime	No
		Major Depressive Episode- Current	No
		Major Depressive Episode- Past	Yes
		Major Depressive Episode- Recurrent	No
		Major Depressive Disorder- Current	No
		Major Depressive Disorder- Past	Yes
		Major Depressive Disorder- Recurrent	No
	B: Suicidality	B1: Have any accident in past month	No (0)
		B1a: Plan or intend to hurt yourself in past month	No (0)
		B1b: Intend to die in past month	No (0)
		B2: Feel hopeless in past month	Yes (1)

	B3: Better off dead in past month	No (0)
	B4: Think about hurting or injuring yourself in the past month	Yes (4)
	B5: Think about suicide in past month	Yes (6)
	B5: Frequency of thoughts	Occasionally
	B5: Intensity of suicidal thoughts	Mild
	B6: Difficulty restraining yourself in past month	No (0)
	B7: Have suicide method in mind in past month	No (0)
…	…	

Note: ITT = Intent-to-treat, SB = Single-Blind, DB = Double-Blind, FU = Follow-up.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period.
During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication.

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Programming note: Repeat for each subject and MINI Module, for HP-3070 9.0 mg and Placebo.

Listing 16.2.2.1 Positive and Negative Syndrome Scale (PANSS)
ITT Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Visit	Date of Assessment (Period, Study Day)	Item	Result
xxxx-xxxx	Screening	YYYY-MM-DD (xx, -xx)	P1. Delusions	xx
			P2. Conceptual Disorganization	xx
			P3. Hallucinatory Behavior	xx
			P4. Excitement	xx
			P5. Grandiosity	xx
			P6. Suspiciousness/Persecution	xx
			P7. Hostility	xx
			N1. Blunted Affect	xx
			N2. Emotional Withdrawal	xx
			N3 Poor Rapport	xx
			…	…
			Positive Subscale Score	xx
			Negative Subscale Score	xx
			General Psychopathy Subscale Score	xx
			Total Score	xx
xxxx-xxxx	Week 1	YYYY-MM-DD (xx, xx)	P1. Delusions	xx
			P2. Conceptual Disorganization	xx

Note: ITT = Intent-to-treat, SB = Single-Blind, DB = Double-Blind, FU = Follow-up.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period.
During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication.

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Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Listing 16.2.2.2 Clinical Global Impression – Severity of Illness Scale (CGI-S)
ITT Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Visit	Date of Assessment (Period, Study Day)	Result
xxxx-xxxx	Screening	YYYY-MM-DD (xx, xx)	4 = Moderately ill
	Week 1	YYYY-MM-DD (xx, xx)	xxx
xxxx-xxxx	Screening	YYYY-MM-DD (xx, xx)	xxx

Note: ITT = Intent-to-treat, SB = Single-Blind, DB = Double-Blind, FU= Follow-up.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period.
During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication.

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Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Listing 16.2.2.3 Clinical Global Impression – Improvement Scale (CGI-I)
ITT Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Visit	Date of Assessment (Period, Study Day)	Result
xxxx-xxxx	Week 1	YYYY-MM-DD (xx, xx)	2 = Much Improved
	Week 2	YYYY-MM-DD (xx, xx)	xxx
xxxx-xxxx	Week 1	YYYY-MM-DD (xx, xx)	xxx

Note: ITT = Intent-to-treat, SB = Single-Blind, DB = Double-Blind, FU = Follow-up.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period.
During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication.

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Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Listing 16.2.2.4 Calgary Depression Scale for Schizophrenia (CDSS)
ITT Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Visit	Date of Assessment (Period, Study Day)	Item	Result
xxxx-xxxx	Screening	YYYY-MM-DD (xx, -xx)	1. Depression	0 = Absent
			2. Hopelessness	1 = Mild
			3. Self Depreciation	2 = Moderate
			4. Guilty Ideas of Reference	3 = Severe
			5. Pathological Guilt	X = xxxxxx
			6. Morning Depression	X = xxxxxx
			7. Early Wakening	X = xxxxxx
			8. Suicide	X = xxxxxx
			9. Observed Depression	X = xxxxxx
			Total Score	xx
xxxx-xxxx	Week 1	YYYY-MM-DD (xx, xx)	1. Depression	X = xxxxxx
			2. Hopelessness	X = xxxxxx

Note: ITT = Intent-to-treat, SB = Single-Blind, DB = Double-Blind, FU = Follow-up.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period.
During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication..

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Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Listing 16.2.2.5 Medical Satisfaction Questionnaire
ITT Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Visit	Date of Assessment (Period, Study Day)	Overall, how satisfied are you with your current antipsychotic medication(s)?
xxxx-xxxx	Screening	YYYY-MM-DD (xx, -xx)	1 = extremely dissatisfied
	Week 2	YYYY-MM-DD (xx, -xx)	4 = neither satisfied nor dissatisfied
xxxx-xxxx	Screening	YYYY-MM-DD (xx, -xx)	2 = very dissatisfied

Note: ITT = Intent-to-treat, SB = Single-Blind, DB = Double-Blind, FU = Follow-up.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period.
During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication..

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Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Listing 16.2.3.1.1 Adverse Events
Safety Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Period	AE Number	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	TEAE	SAE	AESI	Occur at Patch Application Site	Severity
xxxx-xxxx	SB	xx	xxxxxxxxxxx/ xxxxxxxxx/ xxxxxxxxxxxxx	YYYY-MM-DD (xx)/ YYYY-MM-DD (xx)	N	N	N	N	Mild
	DB	xx	xxxxxxxxxxx/ xxxxxxxxx/ xxxxxxxxxxxxx	YYYY-MM-DD (xx)/ YYYY-MM-DD (xx)	Y	Y	N	Y	Moderate

Note: SB = Single-Blind, DB = Double-Blind, FU = Follow-up, TEAE = Treatment-Emergent Adverse Event, SAE = Serious Adverse Event, AE = Adverse Event, AESI = Adverse Event of Special Interest.
Note: TEAEs are defined as all AEs which start (or increase in severity) on or after the date of first dose of double-blind study medication through the 30 day follow-up period.
Note: Potential Hy's Law events are to be entered as AESIs.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period. During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication.
Note: Adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version xx.x.

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Programming note: Repeat for HP-3070 9.0 mg, and Placebo.

Listing 16.2.3.1.1 Adverse Events
Safety Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Period	AE Number	System Organ Class/ Preferred Term/ Verbatim Term	Relationship to Study Drug	Action Taken with Study Drug	Other Action	Outcome	Caused Discontinuation from the Study
xxxx-xxxx	SB	xx	xxxxxxxxxx/ xxxxxxxxx/ xxxxxxxxxxxx	Unrelated	Not Applicable	None	Recovered/ Resolved	N
	DB	xx	xxxxxxxxxx/ xxxxxxxxx/ xxxxxxxxxxxx	Possible	Dose not changed	Concomitant Medications	Recovering/ resolving	N

Note: SB = Single-Blind, DB = Double-Blind, FU = Follow-up, TEAE = Treatment-Emergent Adverse Event, SAE = Serious Adverse Event, AE = Adverse Event, AESI = Adverse Event of Special Interest.
Note: TEAEs are defined as all AEs which start (or increase in severity) on or after the date of first dose of double-blind study medication through the 30 day follow-up period.
Note: Potential Hy's Law events are to be entered as AESIs.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period. During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication.
Note: Adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version xx.x.

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Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Listing 16.2.3.1.2 Serious Adverse Events
Safety Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Period	AE Number	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ Stop Date (Study Day)	TEAE	AESI	Occur at Patch Application Site	Criteria	Abate After Discont-inuation	Reappear After Drug Re-introduction
xxxx-xxxx	SB	xx	xxxxxxxxxx/ xxxxxxxxx/ xxxxxxxxxxxx	YYYY-MM-DD (xx)/ YYYY-MM-DD (xx)	N	N	N	Important Medical Event	NA	NA
	DB	xx	xxxxxxxxxx/ xxxxxxxxx/ xxxxxxxxxxxx	YYYY-MM-DD (xx)/ YYYY-MM-DD (xx)	Y	Y	Y	Life-threatening/ Hospital-ization	Y	N

Note: SB = Single-Blind, DB = Double-Blind, FU = Follow-up, TEAE = Treatment-Emergent Adverse Event, SAE = Serious Adverse Event, AE = Adverse Event, AESI = Adverse Event of Special Interest.
Note: TEAEs are defined as all AEs which start (or increase in severity) on or after the date of first dose of double-blind study medication through the 30 day follow-up period.
Note: Potential Hy's Law events are to be entered as AESIs.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period. During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication.
Note: Adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version xx.x.

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Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Listing 16.2.3.1.3 Adverse Events Leading to Discontinuation of Study Medication
Safety Analysis Set

This listing will be similar to 16.3.1.1.
Programming note: Remove column 'Caused Discontinuation'.

Listing 16.2.3.1.4 Adverse Events Leading to Death
Safety Analysis Set

This listing will be similar to 16.3.1.1.

Listing 16.2.3.1.5 Commonly Occurring Adverse Events
Safety Analysis Set

This listing will be similar to 16.3.1.1.
Programming note: Add footnote: "Note: Commonly Occurring TEAE is defined as any TEAE occurring in at least 5% of subjects in any treatment arm."

Listing 16.2.3.1.6 Adverse Events at Patch Application Site
Safety Analysis Set

This listing will be similar to 16.3.1.1.
Programming note: Remove column 'Occur at Patch Application Site'.

Listing 16.2.3.2.1 Clinical Laboratory Results - Hematology
Safety Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Age/Gender	Visit	Date (Period, Study Day)	Parameter	Result	Unit	Normal Range	CTCAE Grade
xxxx-xxxx	xx/xxxx	xxxxxx	YYYY-MM-DD (xx, xx)	xxxxxx	xx	xx	xx - xx	x
xxxx-xxxx	xx/xxxx	xxxxxx	YYYY-MM-DD (xx, xx)	xxxxxx	xx (H)	xx	xx - xx	x
xxxx-xxxx	xx/xxxx	xxxxxx	YYYY-MM-DD (xx, xx)	xxxxxx	xx (L)	xx	xx - xx	x

Note: CTCAE = Common Terminology Criteria for Adverse Events, SB = Single-Blind, DB = Double-Blind, FU = Follow-up, H = High (above upper limit of normal), L = Low (below lower limit of normal), M = Male, F = Female.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period. During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication.
Note: CTCAE Grade refers to the severity. As a general guideline: Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe or medically significant but not immediately life-threatening, and Grade 4 is life-threatening consequences.

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Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Listing 16.2.3.2.2 Clinical Laboratory Results – Blood Chemistry
Safety Analysis Set

This listing will be similar to 16.3.2.1.

Listing 16.2.3.2.3 Clinical Laboratory Results – Urinalysis
Safety Analysis Set

This listing will be similar to 16.3.2.1.

Programming note: This listing will include urine drug screen and pregnancy testing.

Listing 16.2.3.2.4 Subjects with Clinically Significant or NCI CTCAE Grade >= 3 Laboratory Results
Safety Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Age/Gender	Visit	Date (Period, Study Day)	Parameter (Low/High)	Result (Unit)	Normal Range	CTCAE Grade
xxxx-xxxx	xx/xxxx	xxxxxx	YYYY-MM-DD (xx, xx)	xxxxxx	xxx (xx) (L)	xxx - xxx	x
xxxx-xxxx	xx/xxxx	xxxxxx	YYYY-MM-DD (xx, xx)	**x**xxxxx	**xx**x **(xx) (H)**	**xx**x **- xxx**	x

Note: NCI = National Cancer Institute, CTCAE = Common Terminology Criteria for Adverse Events, SB = Single-Blind, DB = Double-Blind, FU = Follow-up, M = Male, F = Female.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period. During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication.
Note: CTCAE Grade refers to the severity. As a general guideline: Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe or medically significant but not immediately life-threatening, and Grade 4 is life-threatening consequences.

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Programming note: Repeat for HP-3070 9.0 mg and Placebo.
Programming note: If a subject has any result meeting criteria, present all results the subject has for that parameter.

Listing 16.2.3.3 12-Lead ECG
Safety Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Visit	Date of Assessment (Period, Study Day)	Parameter (Units)	Result	Markedly Abnormal
xxxx-xxxx	Screening	YYYY-MM-DD (xx, xx)	Overall Assessment by Investigator	Normal	
			Overall Assessment by Vendor	xxxx	
			Diagnosis 1	xxxx	
			Diagnosis 2	xxxx	
			HR (bpm)	xx	N
			PR Interval (msec)	xx	N
			QRS Interval (msec)	xx	N
			QT Interval (msec)	xx	N
			RR Interval (msec)	xx	N
			QTcF Interval (msec)	xx	N
			QTcB Interval (msec)	xx	N
xxxx-xxxx	Week 1	YYYY-MM-DD (xx, xx)	Comparison to Prior ECG	xxxx	
			Overall Assessment by Investigtor	Abnormal, Clinically Significant	
			Overall Assessment by Vendor	xxxx	
			Diagnosis 1	xxxx	
			Diagnosis 2	xxxx	
			HR (bpm)	xx	N

PR Interval (msec)	xx	N
QRS Interval (msec)	xx	N
QT Interval (msec)	xx	N
RR Interval (msec)	xx	N
QTcF Interval (msec)	xx	N
QTcB Interval (msec)	xx	N

Note: SB = Single-Blind, DB = Double-Blind, FU = Follow-up.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period. During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication.

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Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Listing 16.2.3.4 Vital Signs
Safety Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Visit	Date of Assessment (Period, Study Day)	Parameter/Position	Result	Unit	Markedly Abnormal
xxxx-xxxx	Screening	YYYY-MM-DD (xx, xx)	Oral Temperature	xx	xx	N
			Height	xx	xx	N
			Weight	xx	xx	N
			BMI	xx	Xx	N
			Systolic Blood Pressure/ Sitting	xx	xx	N
			Diastolic Blood Pressure/ Sitting	xx	xx	N
			Pulse/ Sitting	xx	xx	N
			Systolic Blood Pressure/ Supine	xx	xx	N
			Diastolic Blood Pressure/ Supine	xx	xx	N
			Pulse/ Supine	xx	xx	N
			Systolic Blood Pressure/ Standing	xx	xx	N
			Diastolic Blood Pressure/ Standing	xx	xx	N
			Pulse/ Standing	xx	xx	N
xxxx-xxxx	Week 1	YYYY-MM-DD (xx, xx)	Oral Temperature	xx	xx	N

Note: SB = Single-Blind, DB = Double-Blind, FU = Follow-up.
Note: Sitting indicates 5 minutes sitting, supine indicates 5 minutes supine, and standing indicates 1-3 minutes after standing.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period.
During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication.

Noven\HP-3070\XWA17541\Biostatistics\Production\Listings\xxxxx.sas ddmmmyyyy hh:mm
Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Listing 16.2.3.5 Simpson Angus Scale (SAS)
Safety Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Visit	Date of Assessment (Period, Study Day)	Item	Result
xxxx-xxxx	Screening	YYYY-MM-DD (xx, xx)	1. Gait	0 = Normal
			2. Arm Dropping	xx
			3. Shoulder Shaking	xx
			4. Elbow Rigidity	xx
			5. Fixation of Position	xx
			6. Leg Pendulousness	xx
			7. Head Dropping	xx
			8. Glabella Tap	xx
			9. Tremor	xx
			10. Salivation	xx
			Total Score	xx
xxxx-xxxx	Week 1	YYYY-MM-DD (xx, xx)	1. Gait	xx
			2. Arm Dropping	xx

Note: SB = Single-Blind, DB = Double-Blind, FU = Follow-up.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period.
During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication..

Noven\HP-3070\XWA17541\Biostatistics\Production\Listings\xxxxx.sas ddmmmyyyy hh:mm
Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Listing 16.2.3.6 Abnormal Involuntary Movement Scale (AIMS)
Safety Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Visit	Date of Assessment (Period, Study Day)	Item	Result
xxxx-xxxx	Screening	YYYY-MM-DD (xx, xx)	1. Muscles of Facial Expression	xx
			2. Lips and Perioral Area	xx
			3. Jaw	xx
			4. Tongue	xx
			5. Upper	xx
			6. Lower	xx
			7. Neck, Shoulders, Hips	xx
			8. Severity of Abnormal Movements	xx
			9. Incapacitation due to Abnormal Movements	xx
			10. Patient's Awareness of Abnormal Movements	xx
			Total Score	xx
xxxx-xxxx	Week 1	YYYY-MM-DD (xx, xx)	1. Muscles of Facial Expression	xx
			2. Lips and Perioral Area	xx

Note: SB = Single-Blind, DB = Double-Blind, FU = Follow-up.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period.
During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication.

Noven\HP-3070\XWA17541\Biostatistics\Production\Listings\xxxxx.sas ddmmmyyyy hh:mm
Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Listing 16.2.3.7 Barnes Akathisia Rating Scale (BARS)
Safety Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Visit	Date of Assessment (Period, Study Day)	Item	Result
xxxx-xxxx	Screening	YYYY-MM-DD (xx, xx)	Objective	xx
			Awareness of Restlessness	xx
			Distress Related to Restlessness	xx
			Global Clinical Assessment of Akathisia	xx
			Total Score	xx
xxxx-xxxx	Week 1	YYYY-MM-DD (xx, xx)	Objective	xx
			Awareness of Restlessness	xx

Note: SB = Single-Blind, DB = Double-Blind, FU = Follow-up.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period.
During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication.

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Programming note: Repeat for HP-3070 9.0 mg and Placebo.

Listing 16.2.3.8 Columbia-Suicide Severity Rating Scale (C-SSRS)
Safety Analysis Set

Treatment Group: HP-3070 18.0 mg

Subject ID	Visit	Date of Assessment (Period, Study Day)	Item	Result
xxxx-xxxx	Screening	YYYY-MM-DD (xx, xx)	1. Wish to be Dead	xx
			2. Non-Specific Active Suicidal Thoughts	xx
			3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act	xx
			4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan	xx
			5. Active Suicidal Ideation with Specific Plan and Intent	xx
			Most Severe Ideation	xx
			Frequency	xx
			Duration	xx
			Controllability	xx
			Deterrents	xx
			…	…
xxxx-xxxx	Week 1	YYYY-MM-DD (xx, xx)	1. Wish to be Dead	xx
			2. Non-Specific Active Suicidal Thoughts	xx

Note: SB = Single-Blind, DB = Double-Blind, FU = Follow-up.
Note: During the SB period, study day is calculated relative to the first dose of study medication during the run-in period.
During the DB and FU periods, study day is calculated relative to the first dose of double-blind study medication..

Noven\HP-3070\XWA17541\Biostatistics\Production\Listings\xxxxx.sas ddmmmyyyy hh:mm
Programming note: Repeat for HP-3070 9.0 mg and Placebo.
Programming note: The non-missing descriptive variable responses should go next to the corresponding categorical result.

Listing 16.2.3.9 Plasma Concentrations of Asenapine and Desmethyl-asenapine (ng/mL) by Treatment
PK Analysis Set

Subject ID	Treatment	Visit	Scheduled Time (hr)	Sample Collection Date/Time	Actual Time (hr)	Asenapine Concentration (ng/mL)	Desmethyl-asenapine Concentration (ng/mL)	Comment
xxxx-xxxx	**HP-3070 9.0 mg**	Week 3	2	DDMONYYYY/HH:MM	x	xx.xx	xx.xx	
			14	DDMONYYYY/HH:MM	x	xx.xx	xx.xx	
			22	DDMONYYYY/HH:MM	x	xx.xx	xx.xx	
xxxx-xxxx	**HP-3070 9.0 mg**	Week 6	2	DDMONYYYY/HH:MM	x	xx.xx	xx.xx	
			14	DDMONYYYY/HH:MM	x	xx.xx	xx.xx	
			22	DDMONYYYY/HH:MM	x	xx.xx	xx.xx	
xxxx-xxxx	**HP-3070 18.0 mg**	Week 3	2	DDMONYYYY/HH:MM	x	xx.xx	xx.xx	
			14	DDMONYYYY/HH:MM	x	xx.xx	xx.xx	
			22	DDMONYYYY/HH:MM	x	xx.xx	xx.xx	
xxxx-xxxx	**HP-3070 18.0 mg**	Week 6	2	DDMONYYYY/HH:MM	x	xx.xx	xx.xx	
			14	DDMONYYYY/HH:MM	x	xx.xx	xx.xx	
			22	DDMONYYYY/HH:MM	x	xx.xx	xx.xx	

Note: The lower limit of quantification is 0.0200 ng/mL.

Note to Programmer: Sort by Subject No. and Treatment. Blood samples will be collected for PK analysis of asenapine and desmethyl-asenapine; on Day 21 and 42 for both treatments (9 and 18 mg) at 2, 14 and 22 hours after dosing.