Title Page

Protocol Title: A Phase IV, Multi-center, Open-label, Single-arm 24-hour Ambulatory Blood Pressure Monitoring (ABPM) Study of 16 Weeks Treatment with Androderm® in Hypogonadal Men

Protocol Number: 3146-402-016

Compound Number: AGN-195263

Brief Protocol Title: Androderm® ABPM Study in Hypogonadal Men

Study Phase: IV

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Regulatory Agency Identifying Number(s): NDA 020489, IND 034028

Approval Date: 28 May 2020

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SAP Version History

SAP Version History Summary			
SAP Version	**Approval Date**	**Change**	**Rationale**
1		Not Applicable	Original version

1. Introduction

This Statistical Analysis Plan (SAP) provides a technical and detailed elaboration of the statistical analyses of the efficacy and/or safety data as outlined and specified in the final protocol of 3146-402-016 dated 08 Nov 2019. Specifications of tables, figures and data listings are contained in a separate document.

1.1. Objectives and Endpoints

Table 1-1

Objective Clinical Category	Statistical Category	Estimand[1]
Primary Objective: To determine whether Androderm has a meaningful effect on 24-hour average systolic blood pressure (SBP) as measured by ABPM in men who use testosterone replacement treatment.		
Efficacy category 1	Primary	• Variable: change from baseline in 24-hour average SBP obtained at Week 16 • Population: modified intent-to-treat (mITT) • IES: Hypothetical Strategy o Data after treatment discontinuation are treated as missing • PLS: the difference in the variable means between at baseline and at Week 16 o Descriptive analysis including two-sided 95% confidence interval
	Sensitivity (Missing in 24-hour average SBP at Week 16 under missing at random assumption)	o Multiple imputation (MI) for missing data
Secondary Objective: To determine whether Androderm has a meaningful effect on 24-hour blood pressure (BP) parameters as measured by ABPM in men who use testosterone replacement treatment		
Efficacy category 2	Secondary	• Variable: Change from baseline in 24-hour average diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse pressure and heart rate obtained at Week 16. • Population: mITT
Exploratory: To determine whether Androderm has a meaningful effect on BP parameters as measured by ABPM in men who use testosterone replacement treatment		
Efficacy category 3	Other	• Change from baseline in daytime average SBP, DBP, MAP, pulse pressure and heart rate obtained at Week 16

Objective Clinical Category	Statistical Category	Estimand[1]
		• Change from baseline in night-time average SBP, DBP, MAP, pulse pressure and heart rate obtained at Week 16 • Change from baseline over time (hourly average) by nominal clock time and time after dose: SBP, DBP, MAP, pulse pressure and heart rate • Status (yes/no) of participants with new anti-hypertensive medications • Status (yes/no) of participants with dose increases in anti-hypertensive medications • Outlier responder for participants meeting SBP ≥ 160 mm Hg for 24-hour average • Outlier responder for participants meeting SBP change from baseline ≥ 20 mm Hg for 24-hour average • Outlier responder for participants meeting DBP ≥ 100 mm Hg for 24-hour average • Outlier responder for participants meeting DBP change from baseline ≥ 15 mm Hg for 24-hour average • Status (yes/no) of participants with normalized testosterone concentrations at Week 16
Safety Objective: To demonstrate the safety of once daily Androderm for 16 weeks in hypogonadal men.		
Safety		• Variable: Presence of TEAEs • Population: Safety • Analysis: descriptive • Variable: change from baseline in clinical laboratory tests and vital sign • Population: Safety • Analysis: descriptive • Variable: potentially clinically significant in clinical laboratory tests and vital sign • Population: Safety • Analysis: descriptive

IES = Intercurrent event(s) strategy; PLS = Population-level summary.
[1] All estimand attributes explicitly identified for primary/secondary and select key estimands only.

1.2. Study Design

This is a multi-center, open-label, single-arm study in hypogonadal men to evaluate the effect of once daily Androderm on BP parameters as measured by 24-hour ABPM. It is projected that approximately 40 sites in the United States will enroll approximately 150 participants who will receive at least 1 dose for this study.

The study will consist of a screening period of approximately 3 weeks (21 days), followed by an intervention period of 16 weeks (minimum of 113 + 7 days), for a total study duration of approximately 19 weeks (133 days). All participants who meet the criteria for participation in the study will be administered Androderm at the starting dose of 4 mg/day. On Visit 2, study participants will have morning serum concentrations of testosterone measured. If participants have a serum concentration below 400 ng/dL, the dose of Androderm will be increased to 6 mg/day (one 4 mg/day system and one 2 mg/day system). If the serum concentration is above 930 ng/dL, the dose of Androderm will be decreased to 2 mg/day. All others will remain on 4 mg/day.

Approximately 300 participants will be screened to achieve approximately 150 enrolled participants who will receive at least 1 dose and 120 participants with interpretable 24-hour ABPM data at both baseline and the end of Week 16. Participants who prematurely discontinue from the study will not be replaced but will be followed to obtain the last 24-hour ABPM assessment.

Figure 1-1 Study Design

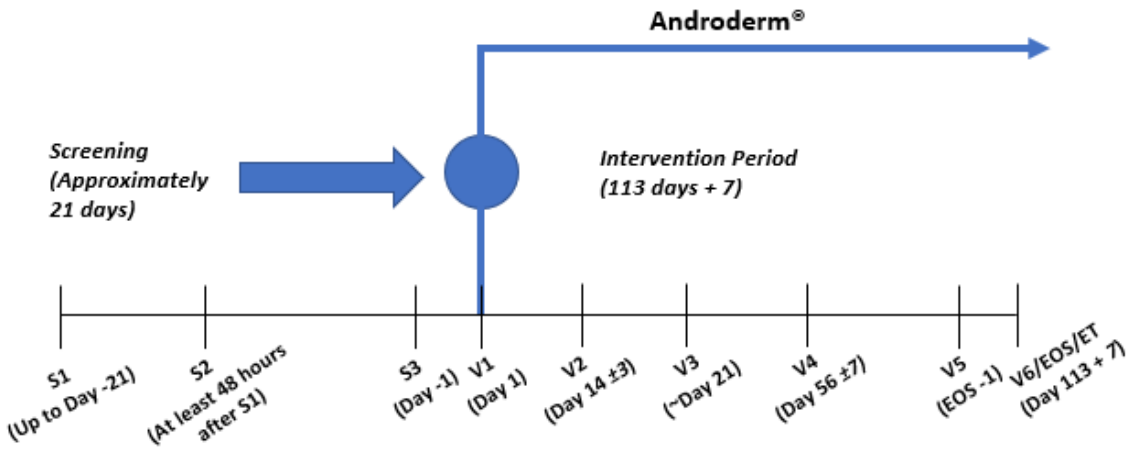

Table 1-2 Schedule of Visits and Procedures

Procedure	Screening Period			Intervention Period/Study Day						Notes
Visit Name	S1	S2	S3	V1	V2	V3/TC	V4	V5	V6/EOS/ET	V3 only if dose titration is needed, otherwise TC
Visit Windows	Up to Day -21	At least 48 hours after S1	Day -3 to -1	Day 1	Day 14 ± 3	~Day 21	Day 56 ± 3	EOS -1	Day 113 + 7	V3/TC after V2 morning testosterone results are available
Informed consent	X									
Inclusion and exclusion criteria	X	X	X	X						Recheck eligibility at V1 before dispensing study intervention
Demography	X									
Medical and surgical history (includes prior medications)	X									
Height and weight	X								X	Height at S1 only
Vital signs	X	X	X	X	X		X	X	X	Triplicate sitting BP and heart rate; temperature
Physical examination		X		X					X	
Fasting morning testosterone	X	X	X		X		X	X		Between 0700 and 1100 local time Obtain a fasting morning testosterone sample before ABPM device placement
Fasting laboratory assessments	X								X	Hematology (including PT and INR), chemistry (including liver chemistry and HbA1c), PSA, urinalysis

Procedure	Screening Period			Intervention Period/Study Day						Notes
Visit Name	S1	S2	S3	V1	V2	V3/TC	V4	V5	V6/EOS/ET	V3 only if dose titration is needed, otherwise TC
Visit Windows	Up to Day -21	At least 48 hours after S1	Day -3 to -1	Day 1	Day 14 ± 3	~Day 21	Day 56 ± 3	EOS -1	Day 113 + 7	V3/TC after V2 morning testosterone results are available
I-PSS		X							X	
Prostate digital rectal exam		X							X	Not required if normal digital rectal exam within 6 months of S1; at V6/EOS/ET only if clinically indicated
Apply ABPM			X					X		24-hour ABPM at ET if feasible
Remove ABPM				X					X	24 hours after applying ABPM device
Dispense/Begin study intervention				X		X				At V3 only if dose titration is needed
Return/Reconcile study intervention						X			X	At V3 only if dose titration is needed
AE review	←==========								→|	
SAE review	←==========								→|	
Concomitant medication review				←==========					→|	

2. Statistical Hypotheses

The null and alternative hypotheses for change from baseline in 24-hour average SBP obtained at baseline and Week 16 (Week 16 minus baseline) are as follows:

H_0: mE - mB $\geq$ 3.0 versus H_a: mE - mB < 3.0

Where mB and mE are mean 24-hour average SBP obtained at baseline and Week 16 respectively.

3. Sample Size Determination

Based on the FDA advice letter dated 24 May 2019, and the assumption that the mean difference in 24-hour SBP obtained at baseline and Week 16 is 0.0, with the upper bound of 3.0 mm Hg and the standard deviation of 10.0 mm Hg, 120 participants with available ABPM data at Week 16 will be required to provide 90% power to reject the null hypothesis at the 2 sided 5% significance level. Assuming a 25% dropout rate, 150 participants will be enrolled.

Approximately 300 participants will be screened, to achieve 150 enrolled who receive ≥ 1 administration of study intervention, for an estimated total of 120 evaluable participants.

4. Populations for Analysis

The analysis populations will consist of participants as defined below:

- The mITT population includes all participants with valid baseline ABPM session, who received ≥ 1 administration of study intervention, ≥ 1 post-treatment assessments of SBP, and at least 85% compliance to study intervention for the duration of the study.
- The safety population includes all treated participants who receive ≥ 1 administration of study intervention.

5. Statistical Analyses

5.1. General Considerations

The ABPM analyses will be based on the mITT population. Baseline is defined as the last nonmissing assessment before the first application of study intervention. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All CIs will be 2-sided 95% CIs, unless stated otherwise. No multiple comparison procedures will be applied.

5.2. Participant Disposition

Number of participants screened for the study will be provided.
The summary of study disposition in the Safety population will be provided as treated for the following:

- Number and percentage of participants treated
- Number and percentage of participants completed
- Number and percentage of participants discontinued
- Reasons for discontinuation from study
- In addition, a listing will be provided for participant disposition.

5.3. Primary Endpoint Analysis

5.3.1. Definition of Endpoint

The primary efficacy endpoint is change from baseline in 24-hour average SBP obtained at Week 16.

5.3.2. Primary Efficacy Analysis

Continuous descriptive statistics (n, mean, SD, median, min, max, Q1 and Q3) of 24-hour average SBP at baseline, Week 16, and change from baseline at Week 16 will be presented. Change from baseline at Week 16 will be tested using paired t-test, along with a 2-sided 95% CI.

If the upper bound of the two-sided 95% CI is less than 3.0, the alternative hypothesis of excluding an increase of 3 mm Hg in SBP will be inferred.

5.3.3. Sensitivity Analysis

Missing value in 24-hour average 24 hours SBP obtained at Week 16 will be imputed using multiple imputation (MI). In the MI analysis, the missing data will be assumed to follow a missing at random (MAR) pattern.

5.4. Secondary and Other Endpoints Analyses

Secondary and other efficacy endpoints are defined as follows.

Secondary efficacy endpoints:

- Change from baseline in 24-hour average DBP, MAP, pulse pressure, and heart rate obtained at Week 16

Other efficacy endpoints:

- Change from baseline in daytime average SBP, DBP, MAP, pulse pressure, and heart rate obtained at Week 16
- Change from baseline in night-time average SBP, DBP, MAP, pulse pressure, and heart rate obtained at Week 16
- Change from baseline over time (hourly average) by nominal clock time and time after dose: SBP, DBP, MAP, pulse pressure, and heart rate
- The status (yes or no) of participants with new anti-hypertensive medications
- The status (yes or no) of participants with dose increases in anti-hypertensive medications
- Outlier responder for participants meeting SBP ≥ 160 mm Hg for 24-hour average and for hourly average
- Outlier responder for participants meeting SBP change from baseline ≥ 20 mm Hg for 24-hour average and for hourly average
- Outlier responder for participants meeting DBP ≥ 100 mm Hg for 24-hour average and for hourly average
- Outlier responder for participants meeting DBP change from baseline ≥ 15 mm Hg for 24-hour average and for hourly average
- Status (yes/no) of participants with normalized testosterone concentrations (within range of 300 to 1030 ng/dL inclusive) at Week 16

Continuous secondary endpoints will be summarized by descriptive statistics (n, mean, SD, median, min, max, Q1 and Q3).

Categorical secondary and other endpoints will be summarized by number and percentage of participants in specified categories.

Plots of hourly average in SBP and DBP included deviation bars for baseline and Week 16.

Cumulative distribution curves of change from baseline in 24-hour average SBP and DBP at Week 16.

Forest plots of daytime, nighttime, and 24-hour change from baseline with 95% confidence interval displays for SBP and DBP.

5.5. Other Safety Analyses

5.5.1. Extent of Exposure

The exposure to study intervention, calculated as (*last study intervention date - first study intervention date + 1*), will be summarized using descriptive statistics for the Safety population.

Patient-years, defined as exposure to the study intervention in years, will be summarized for the Safety Population

5.5.2. Treatment Compliance

Dosing compliance for a specified period is defined as the number of transdermal systems applied by a patient during that period divided by the number of transdermal systems prescribed for the same period multiplied by 100. This information will be obtained from Study Intervention Record of the patient's electronic case report form.

Descriptive statistics for study intervention compliance will be presented for each period between 2 consecutive visits for the Safety Population.

5.5.3. Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or higher.

An AE will be considered a TEAE if the AE began or worsened (increased in severity or became serious) on or after the date (and time, if known) of the first dose of study intervention. However, an AE that occurs more than 30 days after the last dose of study intervention will not be counted as a TEAE.

An AE will be considered a TESAE if it is a TEAE that additionally meets any SAE criterion.

The number and percentage of participants with TEAEs during the study will be tabulated by system organ class and preferred term and by system organ class, preferred term, and severity.

The number and percentage of participants with treatment-related TEAEs during the study will be tabulated by system organ class and preferred term.

If more than 1 AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarizations by severity and by relationship to study intervention.

The incidence of common (≥ 2% of participants in any treatment group) TEAEs will be summarized by preferred term.

Summary tables will be provided for participants with TESAEs and participants with TEAEs leading to discontinuation if these occurred in 5 or more participants. Listings of all AEs, SAEs, and AEs leading to discontinuation by participant will be presented.

5.5.3.1. Adverse Events of Special Interest

Potential Hy's Law criteria within a 24-hour window is defined by a post baseline elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 x ULN, along with total bilirubin (TBL) ≥ 2 x ULN and a non-elevated alkaline phosphatase (ALP) < 2 x ULN, all based on blood draws collected within a 24-hour period. Potential Hy's Law criteria without time window is defined by maximum of post baseline elevation of ALT or AST ≥ 3 x ULN, along with maximum of post baseline elevation of TBL ≥ 2 x ULN. Patients who meet the potential Hy's Law criteria from the first dose of study drug to the end of study will be summarized. Supportive tabular displays will also be provided.

Prostate events will be summarized and provided in a listing.

5.5.4. Additional Safety Assessments

For clinical laboratory, vital sign, and ECG, the last nonmissing safety assessment before the first dose of study intervention will be used as the baseline for all analyses of that safety parameter.

5.5.4.1. Clinical Laboratory Parameters

Descriptive statistics for values and changes from the baseline in standard units at each assessment time point will be presented for the following laboratory parameters:

Laboratory Assessments	Parameters			
Hematology	Platelet count RBC count Hemoglobin Hematocrit PT INR	RBC indices: MCV MCH MCHC %Reticulocytes	WBC count with differential (absolute): Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry	BUN Creatinine Glucose, fasting HbA1c Prolactin	Potassium Sodium Calcium PSA	AST ALT Alkaline phosphatase Fasting morning testosterone	Total, direct and indirect bilirubin Total protein Cholesterol, chloride, albumin
Routine Urinalysis[a]	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			

[a] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Section 6.3.7.1. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated by study intervention group. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 postbaseline assessment for the double-blind treatment period. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value during the study. A supportive tabular display of PCS values will be provided, including the PID number, baseline and all postbaseline values.

In addition, a tabular display showing all AEs that occurred in participants who had PCS postbaseline clinical laboratory values will be provided.

5.5.4.2. Vital Signs

Descriptive statistics for vital signs and their changes from baseline at each assessment timepoint will be presented by study intervention group.

Vital sign values will be considered PCS if they meet both the observed value criterion and the change from baseline value criterion, if both criteria are available, or meet either the observed value criterion or the change from baseline value criterion that will be detailed in Section 6.3.7.2. The number and percentage of participants who have PCS postbaseline vital sign values will be tabulated by study treatment. The percentages will be calculated relative to the number of participants who have available baseline or non-PCS baseline (for parameters with only the observed value criterion) values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value during the study. A supportive listing of PCS values will be provided. In addition, a tabular display showing all AEs that occurred in participants who had PCS postbaseline vital sign values will be provided.

5.6. Other Analyses

5.6.1. Other variables and/or parameters.

5.6.2. Subgroup analyses

Participants without baseline medical history of hypertension, with baseline medical history of hypertension untreated and with baseline medical history of hypertension treated will be performed for following endpoints and graphs.

- Change from baseline in 24-hour average SBP and DSP obtained at Week 16
- Change from baseline hourly average by nominal clock time and time after dose: SBP and DBP
- Outlier responder for participants meeting SBP ≥ 160 mm Hg for 24-hour average and for hourly average

- Outlier responder for participants meeting SBP change from baseline ≥ 20 mm Hg for 24-hour average and for hourly average
- Outlier responder for participants meeting DBP ≥ 100 mm Hg for 24-hour average and for hourly average
- Outlier responder for participants meeting DBP change from baseline ≥ 15 mm Hg for 24-hour average and for hourly average
- Plots of hourly average in SBP and DBP included deviation bars for baseline and Week 16
- Cumulative distribution curves of change from baseline in 24-hour average SBP and DBP at Week 16
- Forest plots of daytime, nighttime, and 24-hour change from baseline with 95% confidence interval displays for SBP and DBP.

5.7. Interim Analyses

No interim analysis is planned.

6. Supporting Documentation

6.1. Appendix 1 List of Abbreviations

Abbreviation	Definition
ABPM	ambulatory blood pressure monitoring
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
DBP	diastolic blood pressure
DHEA	dehydroepiandrosterone
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	Independent Ethics Committee
INR	international normalized ratio
I-PSS	International Prostate Symptom Score
IRB	Internal Review Board
ISO	International Organization for Standardization
IUD	intrauterine device
IUS	intrauterine system

Abbreviation	Definition
MAR	missing at random
MAP	mean arterial pressure
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MI	multiple imputation
mITT	modified intent-to-treat
N/A	not applicable
NCI	National Cancer Institute
PCS	potentially clinically significant
PK	pharmacokinetic
PSA	prostate specific antigen
PT	prothrombin time
Q1	quartile 1
Q3	quartile 3
RBC	red blood cell
S1	Screening Visit 1
S2	Screening Visit 2
S3	Screening Visit 3
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
TC	teleconference
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
V1	Intervention Period Visit 1
V2	Intervention Period Visit 2
V3	Intervention Period Visit 3
V4	Intervention Period Visit 4
V5	Intervention Period Visit 5
V6	Intervention Period Visit 6
WBC	white blood cell

6.2. Appendix 2: Changes to Protocol-Planned Analyses

There are no changes from the protocol-planned analyses.

6.3. Appendix 3: Supporting Study Information

6.3.1. Demographics

Demographic parameters (eg, age, race, ethnicity, sex) will be summarized descriptively for the Safety Population.

6.3.2. Baseline and Disease Characteristics

Baseline characteristics (weight; height; and body mass index, calculated as weight [kg]/(height [m])2 and baseline medical history of without hypertension, with hypertension untreated and treated will be summarized descriptively for the Safety Population.

6.3.3. Protocol Deviations

Protocol deviations will be defined in Protocol Deviation Requirement Specification, including importance classification. The number and percentage of participants with important protocol deviations will be summarized for Safety Population.

6.3.4. Medical and Surgical History

Abnormalities in participants' medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities, version 22.1 or higher. The number and percentage of participants with abnormalities in medical and surgical histories in each system organ class and preferred term will be summarized for the Safety Population.

6.3.5. Prior/Concomitant/Follow-up medications (including dictionary)

The medication data will be coded using the World Health Organization (WHO) Drug Global B3 version March 2019 or higher.

Prior medication is defined as any medication taken before the first dose of study intervention. Concomitant medication is defined as any medication taken on or after the date of the first dose of study intervention.

The number and percentage of participants reporting prior or concomitant medications will be summarized for ATC class and code, and preferred drug name. If more than one medication is coded to the same preferred drug name for the same participant, the participant will be counted only once for that preferred drug name. Prior and concomitant medications will be summarized separately.

6.3.6. Adverse Events of Special Interest

1. Potential Hy's Law cases:

- ALT or AST ≥ 3 × ULN and
- Total Bilirubin ≥ 2 × ULN and
- Alkaline Phosphatase < 2 × ULN

Anytime from the time the participant signs the ICF for the trial, until the final follow-up visit, investigators will notify the sponsor immediately when all the above criteria have been met. A potential Hy's law case will be sent directly to the sponsor by emailing IR-clinical-SAE@allergan.com on an AE of Special Interest Form along with the SAE Report Form as soon as possible (within 24 hours of learning of the potential Hy's Law). The CRF for potential Hy's law cases will be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities will be made, and close monitoring will be initiated in conjunction with the medical monitor and in accordance with the FDA "Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation" July 2009.

2. Prostate events:

- Lower urinary tract symptoms of prostatic hyperplasia

Potential lower urinary tract symptoms of prostatic hyperplasia will be sent directly to the sponsor by emailing IR-clinical-SAE@allergan.com on an AE of Special Interest Form along with the SAE Report Form as soon as possible (within 24 hours of learning of the event). The CRF for lower urinary tract symptoms of prostatic hyperplasia will be completed within 7 calendar days.

6.3.7. Potentially Clinically Significant Criteria for Safety Endpoints

The potentially clinically significant criteria for clinical laboratory parameters and vital signs are provided in the following sections.

6.3.7.1. Potential Clinically Significant for Clinical Laboratory Parameters

Parameter	*SI Unit*	*Lower Limit*	*Higher Limit*
CHEMISTRY			
Albumin	g/L	< 0.9 × LLN	> 1.1 × ULN
Alanine aminotransferase (ALT)	U/L	—	≥ 3 × ULN
Alkaline phosphatase	U/L	—	≥ 3 × ULN

Parameter	*SI Unit*	*Lower Limit*	*Higher Limit*
Aspartate aminotransferase (AST)	U/L	—	≥ 3 × ULN
Bilirubin, total	µmol/L	—	> 1.5 × ULN
Calcium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Chloride	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Cholesterol, Total	mmol/L	—	> 1.3× ULN
Creatinine	µmol/L	—	> 1.3 × ULN
Glucose, fasting, serum	mmol/L	< 0.8 × LLN	> 1.2× ULN
Glucose, random, serum	mmol/L	< 0.8 × LLN	> 1.4 × ULN
Potassium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Protein, total	g/L	< 0.9 × LLN	> 1.1 × ULN
Sodium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Urea Nitrogen (BUN)	mmol/L	—	> 1.2 × ULN
HEMATOLOGY			
Basophils, absolute cell count	10^9/L	—	> 3 × ULN
Neutrophils, absolute cell count	10^9/L	< 0.8 × LLN	> 1.5 × ULN
Hematocrit	Ratio	< 0.9 × LLN	> 1.1 × ULN
Hemoglobin	g/L	< 0.9 × LLN	> 1.1 × ULN
Platelet count	10^9/L	< 0.5 × LLN	> 1.5 × ULN
Red blood cell count	10^{12}/L	< 0.9 × LLN	> 1.1 × ULN
White blood cell count	10^9/L	< 0.7 × LLN	> 1.5 × ULN
URINALYSIS			
pH	—	< 0.9 × LLN	> 1.1 × ULN
Specific gravity	—	—	> 1.1 × ULN

LLN = lower limit of normal value provided by the laboratory; SI = *Le Système International d'Unités* (International System of Units); ULN = upper limit of normal value provided by the laboratory.

6.3.7.2. Potentially Clinically Significant Criteria for Vital Signs

Parameter	Flag	Criteria	
		Observed Value	Change from Baseline
Systolic blood pressure, mm Hg	High	≥ 140	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Diastolic blood pressure, mm Hg	High	≥ 90	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Pulse rate, bpm	High	≥ 100	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Weight, kg	High	—	Increase of ≥ 5%
	Low	—	Decrease of ≥ 5%

SBP = Systolic blood pressure, DBP = Diastolic blood pressure, bpm = beats per minute.

6.4. Data handling convention

6.4.1. Analysis Window

Table 6-1 presents the visits assigned for analyses and the corresponding range of treatment days (window) during which an actual visit may occur.

Table 6-1 Visit Time Windows for Safety Analysis

Derived Visit	***Scheduled Test / Visit Day[a]***	***Window***
Day 1	Day 1	Days ≤ 1
Week 2	Day 14	Days [2, 17]
Week 3	Day 21	Days [18, 38]
Week 8	Day 56	Days [39, 79]
Week 16	Day 112	Days > 79
End of Treatment Period	Final or termination visit during the Treatment Period	

Test/Visit Day will be calculated as follows: test/visit date – date of the first dose of study drug + 1.

If a participant has 2 or more visits within the same window, the last visit with a nonmissing value will be used for analysis

6.4.2. Derived Efficacy and Health Outcome Data

6.4.2.1. Derivation of Efficacy Endpoints

BP parameters, including SBP, DBP, MAP, pulse pressure, and heart rate will be collected by 24-hour ABPM at Baseline and Week 16.

Term	Definition
Baseline ABPM	Any assessment recorded during the approximately 24-hour period starting on Screening Visit 3; after the ABPM device is applied, through Visit 1, when the ABPM device is removed
Week 16 (End of study intervention)	Any assessment recorded during the approximately 24-hour period starting on Visit 5, after the ABPM device is applied, through Visit 6/EOS/ET, when the ABPM device is removed
24-hour ABPM	Any assessment recorded at the specified analysis timepoint (baseline, Week 16) during the approximately 24-hour period after the ABPM device is applied through when the ABPM device is removed
Daytime ABPM	Any assessment recorded between 0900 and 2100 on either: • the day the ABPM device is applied • the day the ABPM device is removed
Night-time ABPM	Any assessment recorded between 0100 and 0600 on either: • the day the ABPM device is applied • the day the ABPM device is removed
Hours 0 through 23	For each Hour X, any assessment recorded between XX00 and XX59, on either: • the day the ABPM device is applied • the day the ABPM device is removed

Continuous BP endpoints are 24-hour, daytime or night-time average on nonmissing values in BP for baseline, Week 16 or change from baseline at Week 16.

6.4.3. Repeated or Unscheduled Assessments of Safety Parameters

Baseline is defined as the last assessment made before the first dose of study intervention. If end-of-study assessments are repeated or if unscheduled visits occur, the last nonmissing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

6.4.4. Missing Date of the Last Dose of Study treatment

When the date of the last dose of study intervention is missing, all efforts should be made to obtain the date from the Investigator. If it is still missing after all efforts have been made, the last available study medication date will be used in the calculation of treatment duration.

6.4.5. Missing Severity Assessment for Adverse Events

If severity is missing for an AE that started before the date of the first dose of study intervention, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of study intervention, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

6.4.6. Missing Causal Relationship to Study treatment for Adverse Events

If the causal relationship to the study intervention is missing for an AE that started on or after the date of the first dose of study intervention, a causality of yes will be assigned. The imputed values for causal relationship to double-blind treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

6.4.7. Missing Date Imputation

The following imputation rules only apply to cases in which the start date for AEs is incomplete (ie, partly missing).

Missing month and day

If the year of the incomplete start date is the same as the year of the first dose of study intervention, the month and day of the first dose of study intervention will be assigned to the missing fields

If the year of the incomplete start date is before the year of the first dose of study intervention, *December 31* will be assigned to the missing fields

If the year of the incomplete start date is after the year of the first dose of study intervention, *January 1* will be assigned to the missing fields

Missing month only

If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

If the month and year of the incomplete start date are the same as the month and year of the first dose of study intervention, the day of the first dose of study intervention will be assigned to the missing day

If either the year of the incomplete start date is before the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study intervention, the last day of the month will be assigned to the missing day

If either the year of the incomplete start date is after the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study intervention, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of study intervention, the date of the first dose of study intervention will be assigned to the missing start date

If the stop date is before the date of the first dose of study intervention, the stop date will be assigned to the missing start date

6.4.8. Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (ie, partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a participant, the start date will be imputed first.

6.4.8.1. Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day

If the year of the incomplete start date is the same as the year of the first dose of study intervention, the month and day of the first dose of study intervention will be assigned to the missing fields

If the year of the incomplete start date is before the year of the first dose of study intervention, December 31 will be assigned to the missing fields

If the year of the incomplete start date is after the year of the first dose of study intervention, January 1 will be assigned to the missing fields

Missing month only

If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

If the month and year of the incomplete start date are the same as the month and year of the first dose of study intervention, the day of the first dose of study intervention will be assigned to the missing day

If either the year of the incomplete start date is before the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study intervention, the last day of the month will be assigned to the missing day.

If either the year of the incomplete start date is after the year of the date of the first dose of study intervention or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study intervention, the first day of the month will be assigned to the missing day

6.4.8.2. Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last dose of study treatment is missing, replace it with the last visit date in the imputations described below. If the imputed stop date is before the start date (imputed or nonimputed start date), the imputed stop date will be equal to the start date.

Missing month and day

If the year of the incomplete stop date is the same as the year of the last dose of study treatment, the month and day of the last dose of study treatment will be assigned to the missing fields

If the year of the incomplete stop date is before the year of the last dose of study treatment, December 31 will be assigned to the missing fields

If the year of the incomplete stop date is after the year of the last dose of study treatment, January 1 will be assigned to the missing fields

Missing month only

If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

If the month and year of the incomplete stop date are the same as the month and year of the last dose of study treatment, the day of the last dose of study treatment will be assigned to the missing day

If either the year of the incomplete stop date is before the year of the date of the last dose of study treatment or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of study treatment, the last day of the month will be assigned to the missing day

If either the year of the incomplete stop date is after the year of the date of the last dose of study treatment or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of study treatment, the first day of the month will be assigned to the missing day

6.4.9. Character Values of Clinical Laboratory Parameters

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, a coded value must be appropriately determined for use in the statistical analyses. The actual values, however, as reported in the database will be presented in the data listings.

7. References

None.