Statistical Analysis Plan

Sponsor Name:	Jazz Pharmaceuticals
Protocol Number:	14-005
Protocol Title:	A Long-Term Safety and Maintenance of Efficacy Study of JZP-110 [(*R*)-2-amino-3-phenylpropylcarbamate hydrochloride] in the Treatment of Excessive Sleepiness in Subjects with Narcolepsy or Obstructive Sleep Apnea
Protocol Version and Date:	Original protocol, 18 December 2014 Amendment 1, 18 February 2015 Amendment 2, 11 September 2015 Amendment 3, 2 February 2016 Amendment 4, 17 November 2016
SAP Version:	1.0
SAP Version Date:	31 March, 2017

Statistical Analysis Plan

Version: ____1.0_____ Version Date: _____31 March 2017_____

I confirm that I have reviewed this document and agree with the content.

APPROVALS	
Jazz Pharmaceuticals	
Approved by: [redacted]	**Date**
Approved by: [redacted]	**Date**

TABLE OF CONTENTS

1. ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CGIc	Clinical Global Impression of Change
CGIs	Clinical Global Impression of Severity
CI	Confidence Interval
C-SSRS	Columbia-Suicide Severity Rating Scale
CRF	Case Report Form
CSR	Clinical Study Report
ECG	Electrocardiogram
ESS	Epworth Sleepiness Scale
ET	Early Termination
FDA	Food and Drug Administration
FOSQ-10	Functional Outcomes of Sleep Questionnaire Short Version
ICH	International Conference on Harmonization
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
IXRS	Interactive Voice/Web Randomization System
LOCF	Last Observation Carried Forward
LOE	Lack of Efficacy
LS	Least Square
MAR	Missing at Random
Max	Maximum
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation

Abbreviation	Description
Min	Minimum
mITT	Modified Intent-to-Treat
MNAR	Missing Not at Random
MWT	Maintenance of Wakefulness Test
OL	Open Label
OSA	Obstructive Sleep Apnea
OTC	Over-the-Counter
PAP	Positive airway pressure
PGIc	Patient Global Impression of Change
PP	Per Protocol
PT	Preferred Term
QTcF	QT Corrected with Fridericia's Formula
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	Single Imputation
SF-36V2	36-Item Short Form Health Survey Version 2
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TLF	Table, Listing and Figure
VAS	Visual Analogue Scale
WHO	World Health Organization
WPAI:SHP	Work Productivity Activity Impairment Questionnaire: Specific Health Problem

2. PURPOSE

This Statistical Analysis Plan (SAP) is created based on Protocol 14-005 Amendment 4 (17 November 2016) and it describes in detail the statistical methodology and the statistical analyses to be conducted for the above mentioned protocol.

Results obtained from the analyses outlined in this document will become the basis of the final clinical study report (CSR) for this protocol. The purpose of this plan is to provide specific instructions as to how each analysis will be conducted. Any deviations from these guidelines must be substantiated by sound statistical reasoning and documented in the final CSR.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE(S)

The primary objective of this study is to evaluate the safety and tolerability of JZP-110 administered once daily for up to 52 weeks in doses of 75, 150, and 300 mg.

The primary objective of the Randomized Withdrawal Period in the Maintenance Phase of this study is to evaluate the maintenance of efficacy of JZP-110 compared to placebo in the treatment of excessive sleepiness in adult subjects with narcolepsy or obstructive sleep apnea (OSA) after at least 26 weeks of daily administration of JZP-110.

3.2. SECONDARY OBJECTIVE(S)

The key secondary objective of this study is to evaluate the maintenance of efficacy of open-label (OL) JZP-110 administered once daily for up to 52 weeks in doses of 75, 150, and 300 mg in the treatment of excessive sleepiness in adult subjects with narcolepsy or OSA.

Another secondary objective is to evaluate the safety and tolerability of JZP-110 compared to placebo during the randomized withdrawal period in the Maintenance Phase.

3.3. STUDY DESIGN

The Schedule of Events is presented in Table 1 and Table 2 for subjects who have completed Study 14-002 or 14-003 (Group A), or Study 14-004, 15-004, 15-005, ADX-N05 201 or ADX-N05 202 (Group B), respectively. The Study Schema for both Groups is presented in Figure 1 and Figure 2.

This is a Phase 3 study to assess the long-term safety and maintenance of efficacy of JZP-110 under open-label and double-blind, placebo-controlled conditions, in subjects who have completed Study 14-002, 14-003, 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202. The study will consist of a 2-week Titration Phase for all subjects, a 38-week Maintenance Phase for subjects who completed Study 14-002 or 14-003 or a 50-week Maintenance Phase for subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201 or ADX-N05 202, and a 2-week Safety Follow-up Period.

During the 2-week Titration Phase, subjects will begin with a once-daily dose of 75 mg JZP-110 and will be able to titrate up one dose level (to 150 mg/day or a maximum dose of 300 mg/day) once every 3 days following a telephone consultation with investigative site staff. Subjects will also be able to titrate down to 75 or 150 mg at any time following a telephone consultation with investigative site staff to achieve a maximal dose that is tolerable. After the 2-week Titration Phase, subjects will enter the Maintenance Phase at the stable dose that was reached at the end of the Titration

Phase. After entering the Maintenance Phase, only three dose adjustments (to doses of 75 mg, 150 mg or 300 mg daily) will be allowed during the first 12 weeks of the Maintenance Phase. If the dose cannot be successfully adjusted within these parameters, the subject will be discontinued from the study.

Subjects who completed Study 14-002 or 14-003 (Group A) will return to the clinic for assessments at the end of the 2-week Titration Phase and at approximately 14, 27, 29, and 40 weeks after the start of treatment with JZP-110 in this study. Subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 (Group B) will return to the clinic for assessments at the end of the 2-week Titration Phase and at approximately 14, 26, 28, 39, and 52 weeks after the start of treatment with JZP-110 in this study. The Randomized Withdrawal Period of the Maintenance Phase of the study will be conducted from weeks 27-29 in Group A and from weeks 26-28 in Group B. At the beginning of the Randomized Withdrawal Period, subjects will be randomly assigned in a 1:1 ratio to continue to receive JZP-110 at the dose that they are currently receiving or to receive placebo for 2 weeks. At the end of the 2-week Randomized Withdrawal Period, subjects will receive the same dose that they had been receiving at the beginning of the Randomized Withdrawal Period for the remainder of the study (a fixed titration of 3 days will be included for subjects on the 150 and 300 mg doses).

When approximately 300 subjects are randomized into the randomized withdrawal period, no more subjects will be randomized into the period. All subjects who have not entered the randomized withdrawal period at that time will receive open-label JZP-110 treatment for the remainder of the study. All subjects who have entered the randomized withdrawal period will complete all scheduled assessments for the period.

Subjects who completed Study 14-002 or 14-003 (Group A) and who are not randomized into the randomized withdrawal period will return to the clinic for assessments at the end of the 2-week Titration Phase and at approximately 14, 27, and 40 weeks after the start of treatment with JZP-110 in this study. Subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05-202 (Group B) and who are not randomized into the randomized withdrawal period will return to the clinic for assessments at the end of the 2-week Titration Phase and at approximately 14, 26, 39, and 52 weeks after the start of treatment with JZP-110 in this study.

All subjects will be contacted monthly by phone, and the investigator will determine whether subjects need to be seen in the clinic at any other time(s) during the study to ensure their safety.

Safety will be assessed throughout the study and will include the Columbia-Suicide Severity Rating Scale (C-SSRS) administered at each clinic visit.

Open-Label maintenance of efficacy will be assessed by the Epworth Sleepiness Scale (ESS), Patient Global Impression of Change (PGIc), Clinical Global Impression of Change (CGIc), and several quality of life and economic measures, such as the Functional Outcomes of Sleep Questionnaire Short Version (FOSQ-10), 36-Item Short Form Health Survey version 2 (SF-36v2), EuroQoL EQ-5D-5L, and the Work Productivity Activity Impairment (WPAI:SHP) Questionnaire. Double-blind, placebo-controlled maintenance of

efficacy in the Randomized Withdrawal Period will be assessed by changes on the ESS and FOSQ-10, and ratings on the PGIc and CGIc from the beginning to the end of the 2-week Randomized Withdrawal Period (from Week 27 to 29 or from Week 26 to 28 in Groups A and B, respectively) in approximately 300 subjects.

At the 14 and 40 week visits for subjects in Group A and at the 26 and 52 week visits for subjects in Group B, subjects will be asked about their healthcare resource utilization over the past 3 months in terms of physician visits.

All subjects will return to the site 2 weeks after the final clinic visit of the Maintenance Phase for safety follow-up assessments. Unless there are any outstanding safety issues that require follow-up, subjects will be discharged from the study at that visit.

Figure 1 Study Schema for Subjects Randomized into the Randomized Withdrawal Period

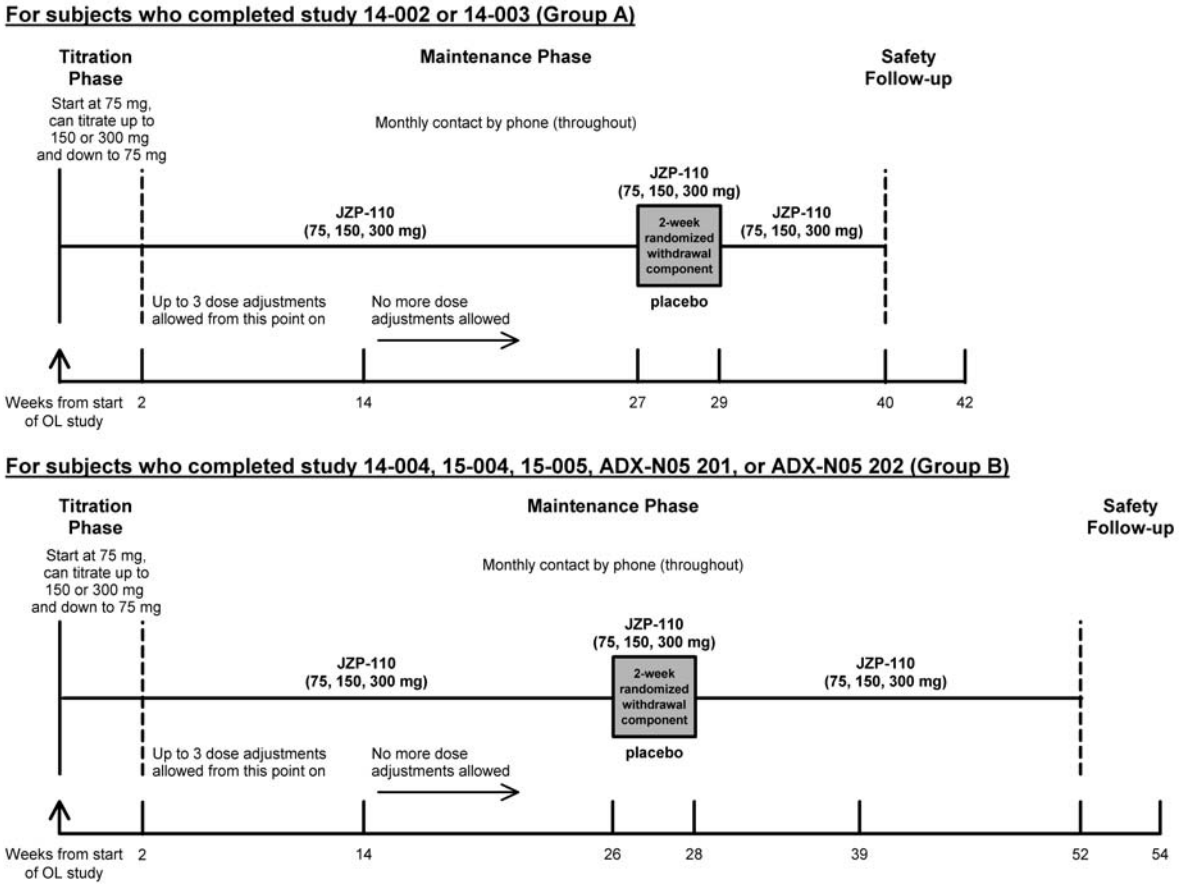

Figure 2 Study Schema for Subjects not Randomized into the Randomized Withdrawal Period

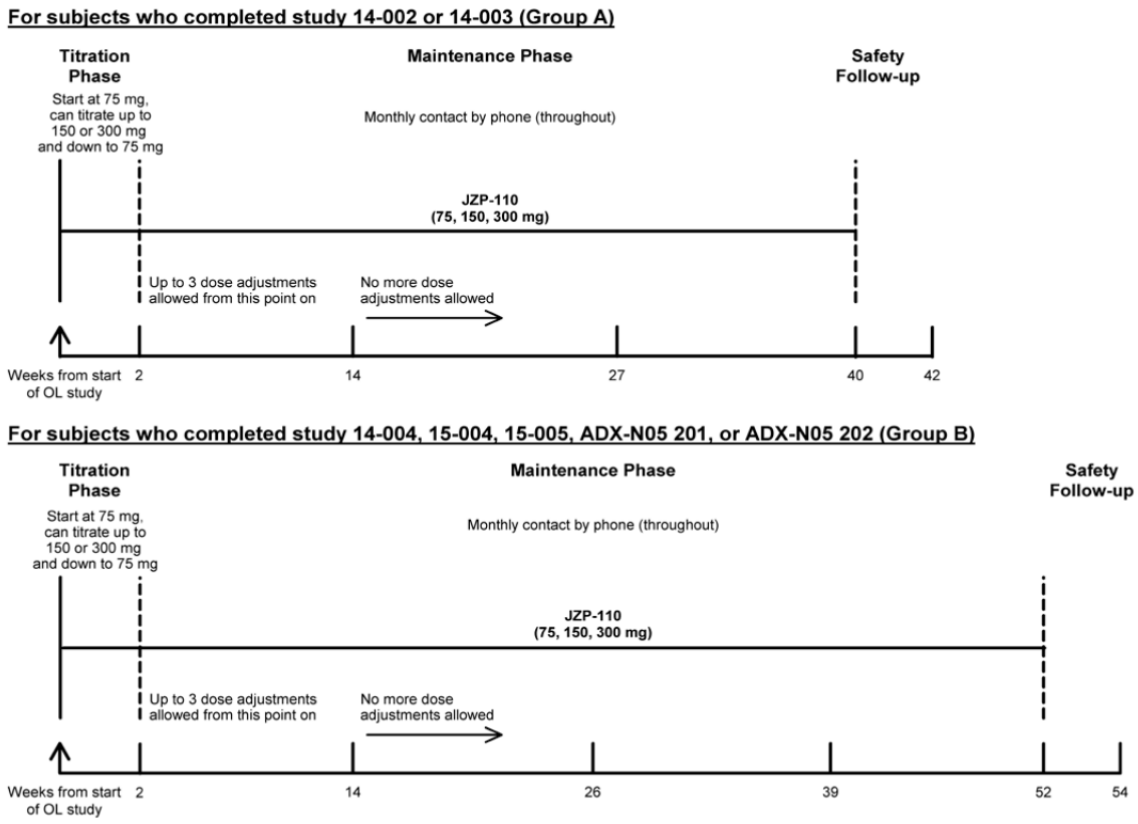

Table 1 Schedule of Events – Group A
Subjects Who Participated in Study 14-002 or 14-003

Phase	Scree-ning/Baseline	Titration					Maintenance											Early Term[a]	Follow-up
												Randomized Withdrawal Period							
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	***12.1****	***12.2****	**13**	**14**	**15**		**16**
Time from Study Start Day/End of Week	D -1	D 3 ±1	D 6 ±1	D 9 ±1	D 12 ±1	D 15 ±2 Wk 2	D 43 ±7 Wk 6	D 71 ±7 Wk 10	D 99 ±7 Wk 14	D 127 ±7 Wk 18	D 155 ±7 Wk 22	D 190 ±7 Wk 27	D 197 ±3 Wk 28	D 204 ±7 Wk 29	D 218 ±7 Wk 31	D 246 ±7 Wk 35	D 281 ±7 Wk 40		D 295 ±7 Wk 42
Clinic Visit	X					X			X			X		*X*			X	X	X
Phone Contact		X	X	X	X		X	X		X	X		X		X	X			
Informed Consent	X																		
Inclusion/ Exclusion	X																		
Physical Examination																	X	X	
Weight						X			X			X		X			X	X	X
Vital Signs						X			X			X		X			X	X	X
ECG						X			X			X		X			X	X	X
Fasting, hematology, serum chemistry; urinalysis									X			X					X	X	
Light breakfast									X			X					X	X	
Urine drug screen						X			X			X		X			X	X	

Statistical Analysis Plan

Phase	**Scree-ning/Baseline**	**Titration**					**Maintenance**											**Early Term[a]**	**Follow-up**
												Randomized Withdrawal Period							
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	***12.1****	***12.2****	**13**	**14**	**15**		**16**
Time from Study Start Day/End of Week	D -1	D 3 ±1	D 6 ±1	D 9 ±1	D 12 ±1	D 15 ±2 Wk 2	D 43 ±7 Wk 6	D 71 ±7 Wk 10	D 99 ±7 Wk 14	D 127 ±7 Wk 18	D 155 ±7 Wk 22	D 190 ±7 Wk 27	D 197 ±3 Wk 28	D 204 ±7 Wk 29	D 218 ±7 Wk 31	D 246 ±7 Wk 35	D 281 ±7 Wk 40		D 295 ±7 Wk 42
Urine pregnancy test																	X	X	
C-SSRS						X			X			X		X			X	X	X
Enroll via IVRS/IWRS	X																		
Randomize via IVRS/IWRS												X							
Dispense Study Drug	X					X			X			X		X					
Provide instructions for titration		X	X	X	X	X													
Collect Study Drug/assess compliance						X			X			X		X			X	X	
Concomitant Meds		X	X	X	X	X	X	X	X	X	X	X	*X*	X	X	X	X	X	X
Review and remind to record primary OSA therapy use	X	X	X	X	X	X	X	X	X	X	X	X	*X*	X	X	X	X		
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	*X*	X	X	X	X	X	X
ESS						X			X			X		X			X		

Statistical Analysis Plan

Phase	Scree-ning/Baseline	Titration					Maintenance											Early Term[a]	Follow-up
												Randomized Withdrawal Period							
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	***12.1****	***12.2****	**13**	**14**	**15**		**16**
Time from Study Start Day/End of Week	D -1	D 3 ±1	D 6 ±1	D 9 ±1	D 12 ±1	D 15 ±2 Wk 2	D 43 ±7 Wk 6	D 71 ±7 Wk 10	D 99 ±7 Wk 14	D 127 ±7 Wk 18	D 155 ±7 Wk 22	D 190 ±7 Wk 27	D 197 ±3 Wk 28	D 204 ±7 Wk 29	D 218 ±7 Wk 31	D 246 ±7 Wk 35	D 281 ±7 Wk 40		D 295 ±7 Wk 42
CGIc – Compared to Baseline[b]						X			X			X					X		
PGIc – Since Started Treatment[b]						X			X			X					X		
CGIc – Compared to Beginning of RW Period[c]														X					
PGIc – Since Last Visit[c]														X					
FOSQ-10									X			X		X			X		
SF-36v2									X			X					X		
EQ-5D-5L									X			X					X		
WPAI:SHP									X			X					X		
Resource Utilization									X								X		
Schedule next visit or phone contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

D=day; Wk=week

Shaded columns indicate clinic visits.

*When approximately 300 subjects are randomized into the randomized withdrawal period, no more subjects will be randomized into the period. All subjects who have not entered the randomized withdrawal period at that time will receive open-label JZP-110 treatment at Visit 12 and will not complete Visits 12.1 and 12.2.

a. If a subject withdraws or is withdrawn from the study after completing the Week 2 Visit (Visit 6) and no more than 3 days have passed since the subject's last dose of study drug was taken, the Maintenance Phase Final Clinic Visit (Visit 15) procedures should be conducted. If more than 3 days have passed since the subject's last dose of study drug was taken, only the final safety assessments listed in the Early Termination column should be conducted (ESS, CGIc, PGIc, FOSQ-10, SF-36v2, EQ-5D-5L, WPAI:SHP, and Resource Utilization assessments are not required).

   If a subject withdraws or is withdrawn prior to completing the Week 2 Visit (Visit 6), only the final safety assessments listed in the Early Termination column should be conducted (ESS, CGIc, PGIc, FOSQ-10, SF-36v2, EQ-5D-5L, WPAI:SHP, and Resource Utilization assessments are not required).

b. CGIc change from baseline version and PGIc change from start of treatment version should be used.
c. CGIc change from the beginning of the randomized withdrawal (RW) period version and PGIc change from the last visit version should be used.

Table 2 Schedule of Events – Group B
Subjects Who Participated in Study 14-004, 15-004, 15-005, ADX-N05 201 or ADX-N05 202

Phase	**Scre e-ning**	**Base -line**	**Titration**					**Maintenance**													**Early Term** [a]	**Follo w-up**
													Randomized Withdrawal Period									
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	***13. 1****	***13. 2****	**14**	**15**	**16**	**17**	**18**	**19**		**20**
Time from Study Start Day/End of Week	D -30 to -2	D -1	D 3 ±1	D 6 ±1	D 9 ±1	D 12 ±1	D 15 ±2 Wk 2	D 43 ±7 Wk 6	D 71 ±7 Wk 10	D 99 ±7 Wk 14	D 127 ±7 Wk 18	D 155 ±7 Wk 22	D 183 ±7 Wk 26	*D 190 ±3 Wk 27*	*D 197 ±7 Wk 28*	D 211 ±7 Wk 30	D 239 ±7 Wk 34	D 274 ±7 Wk 39	D 302 ±7 Wk 43	D 330 ±7 Wk 47	D 365 ±7 Wk 52		D 379 ±7 Wk 54
Clinic Visit	X	X					X			X			X		X			X			X	X	X
Phone Contact			X	X	X	X		X	X		X	X		*X*		X	X		X	X			
Informed Consent	X																						
Inclusion /Exclusion	X	X																					
Demo-graphics	X																						
Medical History	X	X																					
Physical Exam-inations	X																				X	X	
Instruct how to dis-continue excluded	X																						

Statistical Analysis Plan

Phase	**Scre e-ning**	**Base -line**	**Titration**					**Maintenance**														**Early Term** [a]	**Follo w-up**
													Randomized Withdrawal Period										
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	***13. 1****	***13. 2****	**14**	**15**	**16**	**17**	**18**	**19**		**20**
Time from Study Start Day/End of Week	D -30 to -2	D -1	D 3 ±1	D 6 ±1	D 9 ±1	D 12 ±1	D 15 ±2 Wk 2	D 43 ±7 Wk 6	D 71 ±7 Wk 10	D 99 ±7 Wk 14	D 127 ±7 Wk 18	D 155 ±7 Wk 22	D 183 ±7 Wk 26	*D 190 ±3 Wk 27*	*D 197 ±7 Wk 28*	D 211 ±7 Wk 30	D 239 ±7 Wk 34	D 274 ±7 Wk 39	D 302 ±7 Wk 43	D 330 ±7 Wk 47	D 365 ±7 Wk 52		D 379 ±7 Wk 54
medication																							
Weight	X	X					X			X			X		X			X			X	X	X
Height	X																						
Vital Signs	X	X					X			X			X		X			X			X	X	X
ECG	X	X					X			X			X		X			X			X	X	X
Fasting hemat-ology, serum chemistry; urinalysis	X	X[b]								X			X					X			X	X	
Light breakfast	X	X[b]								X			X					X			X	X	
Urine drug screen	X	X					X			X			X		X			X			X	X	
Serum pregnancy test	X																						
Urine pregnanc		X																			X	X	

Statistical Analysis Plan

Phase	**Scre e-ning**	**Base -line**	**Titration**					**Maintenance**														**Early Term** [a]	**Follo w-up**
													Randomized Withdrawal Period										
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	***13. 1****	***13. 2****	**14**	**15**	**16**	**17**	**18**	**19**		**20**
Time from Study Start Day/End of Week	D -30 to -2	D -1	D 3 ±1	D 6 ±1	D 9 ±1	D 12 ±1	D 15 ±2 Wk 2	D 43 ±7 Wk 6	D 71 ±7 Wk 10	D 99 ±7 Wk 14	D 127 ±7 Wk 18	D 155 ±7 Wk 22	D 183 ±7 Wk 26	*D 190 ±3 Wk 27*	*D 197 ±7 Wk 28*	D 211 ±7 Wk 30	D 239 ±7 Wk 34	D 274 ±7 Wk 39	D 302 ±7 Wk 43	D 330 ±7 Wk 47	D 365 ±7 Wk 52		D 379 ±7 Wk 54
y test																							
C-SSRS	X	X					X			X			X		X			X			X	X	X
Dispense Study Drug		X					X			X			X		X			X					
Enroll via IVRS/ IWRS		X																					
Randomize via IVRS/ IWRS													X										
Provide instructions for titration		X	X	X	X	X	X																
Collect Study Drug							X			X			X		X			X			X	X	
Concom-itant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Statistical Analysis Plan

Phase	**Scre e-ning**	**Base -line**	**Titration**					**Maintenance**														**Early Term** [a]	**Follo w-up**
													Randomized Withdrawal Period										
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	***13. 1****	***13. 2****	**14**	**15**	**16**	**17**	**18**	**19**		**20**
Time from Study Start Day/End of Week	D -30 to -2	D -1	D 3 ±1	D 6 ±1	D 9 ±1	D 12 ±1	D 15 ±2 Wk 2	D 43 ±7 Wk 6	D 71 ±7 Wk 10	D 99 ±7 Wk 14	D 127 ±7 Wk 18	D 155 ±7 Wk 22	D 183 ±7 Wk 26	*D 190 ±3 Wk 27*	*D 197 ±7 Wk 28*	D 211 ±7 Wk 30	D 239 ±7 Wk 34	D 274 ±7 Wk 39	D 302 ±7 Wk 43	D 330 ±7 Wk 47	D 365 ±7 Wk 52		D 379 ±7 Wk 54
ESS		X					X			X			X		X			X			X		
CGIs		X																					
CGIc - *compared to baseline*[d]							X			X			X					X			X		
PGIc - *Since Started Treatment*[d]							X			X			X					X			X		
CGIc - Compared to Beginning of RW Period[e]															X								
PGIc - Since Last Visit[e]															X								
FOSQ-10		X								X			X		X			X			X		
SF-36v2		X								X			X					X			X		
EQ-5D-5L		X								X			X					X			X		

Statistical Analysis Plan

Phase	**Scre e-ning**	**Base -line**	**Titration**					**Maintenance**														**Early Term** [a]	**Follo w-up**
													Randomized Withdrawal Period										
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	***13. 1****	***13. 2****	**14**	**15**	**16**	**17**	**18**	**19**		**20**
Time from Study Start Day/End of Week	D -30 to -2	D -1	D 3 ±1	D 6 ±1	D 9 ±1	D 12 ±1	D 15 ±2 Wk 2	D 43 ±7 Wk 6	D 71 ±7 Wk 10	D 99 ±7 Wk 14	D 127 ±7 Wk 18	D 155 ±7 Wk 22	D 183 ±7 Wk 26	*D 190 ±3 Wk 27*	*D 197 ±7 Wk 28*	D 211 ±7 Wk 30	D 239 ±7 Wk 34	D 274 ±7 Wk 39	D 302 ±7 Wk 43	D 330 ±7 Wk 47	D 365 ±7 Wk 52		D 379 ±7 Wk 54
WPAI:SHP		X								X			X					X			X		
Resource Utilization													X								X		
Review and remind to record primary OSA therapy use[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Schedule next visit or phone contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

D=day; Wk=week

Shaded columns indicate clinic visits.

*When approximately 300 subjects are randomized into the randomized withdrawal period, no more subjects will be randomized into the period. All subjects who have not entered the randomized withdrawal period at that time will receive open-label JZP-110 treatment at Visit 13 and will not complete Visits 13.1 and 13.2

a. If a subject withdraws or is withdrawn from the study after completing the Week 2 Visit (Visit 7) and no more than 3 days have passed since the subject's last dose of study drug was taken, the Maintenance Phase Final Clinic Visit procedures should be conducted (Visit 19). If more than 3 days have passed since the subject's last dose of study drug was taken, only the final safety assessments listed in the Early Termination column should be conducted (ESS, CGIc, PGIc, FOSQ, SF-36 v2, ED-5D-5L, WPAI:SHP and Resource Utilization assessments are not required).

   If a subject withdraws or is withdrawn prior to completing the Week 2 Visit (Visit 7), only the final safety assessments listed in the Early Termination column should be conducted (ESS, CGIc, PGIc, FOSQ, SF-36 v2, ED-5D-5L, WPAI:SHP and Resource Utilization assessments are not required).

b. If the Baseline (Day -1) visit occurs more than 28 days after the Screening visit, obtain fasting blood samples for serum chemistry and hematology and a urine sample for urinalysis. Provide a light breakfast for subjects who have their blood drawn.
c. Review and reminders regarding primary OSA therapy use only apply to subjects with OSA from the 14-004 and 15-004 studies.
d. CGIc change from baseline version and PGIc change from start of treatment version should be used.
e. CGIc change from the beginning of the randomized withdrawal (RW) period version and PGIc change from the last visit version should be used.

3.4. DETERMINATION OF SAMPLE SIZE

The sample size of this study is based on ICH Guidance on the Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions (E1) and on guidance from FDA. Approximately 600 subjects are planned for enrollment with the intention of completing at least 50 subjects with narcolepsy and at least 50 subjects with OSA with an exposure to JZP-110 of 52 weeks and at least 100 subjects with narcolepsy and at least 200 subjects with OSA with an exposure to JZP-110 of 26 weeks. A sample size of 300 subjects in the Randomized Withdrawal Period in the Maintenance Phase with approximately 150 subjects per treatment group will provide at least 95% power to detect a difference of 3 points in the ESS score from the beginning to the end of the 2-week Randomized Withdrawal Period. This calculation assumes a common standard deviation of 7 points for the ESS change during the Randomized Withdrawal Period and a two-sided significance level of 0.05 using a t-test.

3.5. RANDOMIZATION AND STRATIFICATION

At the beginning of the Randomized Withdrawal Period of the Maintenance Phase (the Week 27 visit for Group A or the Week 26 visit for Group B), subjects will be randomly assigned in a 1:1 ratio to continue to receive JZP-110 at the dose that they are currently receiving or to receive placebo for 2 weeks in a double-blind manner. The investigator will access an Interactive Voice Response System (IVRS) or an Interactive Web Response System (IWRS) to randomize subjects. The randomization will be stratified on the basis of subjects' diagnosis of narcolepsy or OSA. When approximately 300 subjects have been randomized into the randomized withdrawal period, the clinical sites will be notified and the IVRS/IWRS will not permit additional randomization. After approximately 300 subjects have been randomized into the randomized withdrawal period, use of the IVRS or IWRS will continue for the purpose of enrolling subjects, assigning subject identification numbers and tracking open-label study drug.

A statistician selected by Jazz Pharmaceuticals will prepare and retain the master randomization code for the Randomized Withdrawal Period of this study. This statistician will not be involved in the analysis of this study. The randomization codes will be generated and retained according to Jazz Pharmaceuticals standard operating procedure on the generation, distribution, and access to randomization information for clinical studies. Unless there is an emergency that requires the release of the subject's assigned treatment, the code will not be broken or released until all study data are collected and accepted for analysis.

3.6. ADMINISTRATION OF STUDY MEDICATION

Subjects will receive open-label JZP-110 75, 150, or 300 mg once daily throughout the study except during the 2-week Randomized Withdrawal Period of the Maintenance Phase, when subjects will either receive JZP-110 at their current dose or placebo in a double-blind manner.

Study drug will be dispensed at clinic visits at Baseline, at the end of the Titration Phase, and approximately every 3 months thereafter (except during the 2-week Randomized Withdrawal Period during which study drug will be dispensed for a 2 week interval), as indicated in the Schedule of Events in Table 1 and Table 2 and, if applicable, at alternative intervals specified by State or local regulations. Study drug will be dispensed by qualified study site personnel.

4. ENDPOINTS

4.1. PLACEBO-CONTROLLED RANDOMIZED WITHDRAWAL PERIOD

4.1.1. Efficacy Endpoints

- Primary efficacy endpoint:
    - ESS: Change in ESS score from the beginning to the end of the Randomized Withdrawal Period
- Second efficacy endpoints:
    - PGIc: Percentage of subjects reported as worse (minimally, much, or very much) on the PGIc at the end of the Randomized Withdrawal Period
    - CGIc: Percentage of subjects reported as worse (minimally, much, or very much) on the CGIc at the end of the Randomized Withdrawal Period

4.1.2. Functional Outcomes and Quality of Life Endpoints

- FOSQ-10: Change in total score and 5 subscale score from the beginning to the end of the Randomized Withdrawal Period

4.1.3. Use of primary OSA therapy

Use of primary OSA therapy for the randomized subjects from study 14-003, 14-004, and 15-004 in the Randomized Withdrawal Period of the Maintenance Phase will be summarized as follows:

- For Group A and B
    - Percentage of nights that subjects use their primary OSA therapy in the Randomized Withdrawal Period
    - Change in the percentage of nights that the primary OSA therapy is used from the visit before Randomized Withdrawal Period to the Randomized Withdrawal Period

4.2. OPEN-LABEL (OL) PHASES

4.2.1. Efficacy Endpoints

- For Group A:
    - ESS: Change from the baseline in the previous study over time

- ESS: Change from the last assessment in the previous study over time

- For Group B:
  - ESS: Change from the study baseline over time

- For Group A and B:
  - CGIc: Percentage of subjects reported as improved (minimally, much, or very much) at each time point
  - PGIc: Percentage of subjects reported as improved (minimally, much, or very much) at each time point

4.2.2. Functional Outcomes and Quality of Life Endpoints

For all functional outcomes (FOSQ-10 total score and 5 subscales) and quality of life endpoints (SF-36v2 8 subscale scores, Physical and Mental Health Component summary scores, EQ-5D-5L Index, and EQ VAS), the following changes will be summarized:

- For Group A:
  - Change from the baseline in the previous study over time
  - Change from the last assessment in the previous study over time

- For Group B:
  - Change from the study baseline over time

EuroQoL (EQ-5D-5L) will be summarized as follows:

- EQ-5D Dimensions
  - Number and percentage of subjects in each of the 5 levels of severity (e.g., no problem, slight problem, moderate problem, severe problem, unable) for each of the 5 dimensions (e.g., mobility, self-care) over time
  - Number and percentage of subjects reporting any problems (levels 2-5) for each of the 5 dimensions (e.g., mobility, self-care) over time
- EQ-5D-5L Index
- EQ VAS

4.2.3. Use of Primary OSA Therapy

Use of primary OSA therapy for the subjects from the study 14-003, 14-004, and 15-004 will be summarized as follows:

- For Group A
    - Change in the percentage of nights that the primary OSA therapy is used from the Screening period in the previous study to each time point
    - Change in the percentage of nights that the primary OSA therapy is used from the last period in the previous study to each time point
- For Group B
    - Change in the percentage of nights that the primary OSA therapy is used from the Screening period (e.g., all available data prior to the first dose date of study drug in this study) to each time point
- For Group A and B
    - Percentage of nights that subjects use their primary OSA therapy will be summarized by visit and treatment group

4.2.4. Economic Assessments Endpoints

Data from the economic assessments will be summarized over time.

- Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP):
    - Percent work time missed due to problem
    - Percent impairment while working due to problem
    - Percent overall work impairment due to problem
    - Percent activity impairment due to problem
- Resource Utilization Questionnaire:
    - Number of visits in past 3 months
    - Mean/median healthcare costs over the one-year period based on standard unit costs and any hospitalizations reported as SAEs.

The following changes will be summarized for the WPAI:SHP:

- For Group A:
    - Change from the baseline in the previous study over time
    - Change from the last assessment in the previous study over time
- For Group B:
    - Change from the study baseline over time

4.3. PHARMACOKINETIC ENDPOINTS

Not applicable

4.4. PHARMACODYNAMIC ENDPOINTS

Not applicable

4.5. SAFETY ENDPOINTS

To evaluate the safety and tolerability evaluations as determined by the occurrence of and/or changes in:

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- Vital signs
- 12-lead electrocardiograms (ECGs)
- Columbia-Suicide Severity Rating Scale (C-SSRS)

5. STATISTICAL HYPOTHESES FOR TRIAL OBJECTIVES

5.1. MAINTENANCE OF EFFICACY ENDPOINTS FROM THE PLACEBO-CONTROLLED RANDOMIZED WITHDRAWAL PERIOD

The primary hypothesis, corresponding to the primary efficacy variable (ESS), is the following:

- JZP-110 is superior to placebo as measured by the change in the ESS score from the beginning to the end of the 2-week Randomized Withdrawal Period

  The statistical null hypothesis is that for the ESS score, the mean change from the beginning to the end of the 2-week Randomized Withdrawal Period for the JZP-110 group is the same as the mean change from the beginning to the end of the 2-week Randomized Withdrawal Period for the placebo group.

In addition to the primary hypothesis, the secondary hypotheses are:

- JZP-110 is superior to placebo as measured by the Patient Global Impression of Change (PGIc) at the end of the Randomized Withdrawal Period (Week 29 for subjects in Group A and Week 28 for subjects in Group B)

  The statistical null hypothesis is that for the PGIc, the percentage of subjects reported as worse (minimally, much, or very much) at the end of the 2 week Randomized Withdrawal Period compared to the beginning of the Randomized Withdrawal Period for the JZP-110 group is the same as the percentage of subjects reported as worse (minimally, much, or very much) at the end of the 2-week Randomized Withdrawal Period for the placebo group.

- JZP-110 is superior to placebo as measured by the Clinical Global Impression of Change (CGIc) at the end of the Randomized Withdrawal Period (Week 29 for subjects in Group A and Week 28 for subjects in Group B)

  The statistical null hypothesis is that for the CGIc, the percentage of subjects reported as worse (minimally, much, or very much) at the end of the 2 week Randomized Withdrawal Period compared to the beginning of the Randomized Withdrawal Period for the JZP-110 group is the same as the percentage of subjects reported as worse (minimally, much, or very much) at the end of the 2-week Randomized Withdrawal Period for the placebo group.

5.2. MAINTENANCE OF EFFICACY ENDPOINTS FROM THE OPEN-LABEL (OL) PHASES

To evaluate the maintenance of efficacy of OL JZP-110 administered once daily for up to 52 weeks, no formal statistical testing will be performed; only summary statistics will be provided.

6. ANALYSIS POPULATIONS

6.1. SAFETY POPULATION

The Safety Population will include all subjects who received at least one dose of study medication in this study. This population will be analyzed for the safety evaluation and the open-label maintenance of efficacy of JZP-110 and will be presented in the tables and listings. All open-label analyses will be performed on the Safety Population.

6.2. MODIFIED INTENT-TO-TREAT POPULATION

The Modified Intent-to-Treat (mITT) Population for the evaluation of Double-Blind, Placebo-Controlled maintenance of efficacy in the Randomized Withdrawal Period will include subjects who were randomized in the 2-week Randomized Withdrawal Period, who received at least one dose of study medication in the 2-week Randomized Withdrawal Period, and who have evaluable efficacy data at Week 29 (Group A) or Week 28 (Group B). If a subject in the mITT Population does not have an assessment for a particular efficacy endpoint, that subject will be excluded in the analysis of that endpoint.

6.3. PER-PROTOCOL POPULATION

The Per-Protocol Population will include mITT subjects who completed the 2-week Randomized Withdrawal Period according to protocol specifications without a major protocol violation. Based on the protocol deviation management plan, a major violation will be identified by an exclusion from Per-Protocol population flag in the study protocol deviation report. The reasons for exclusion will also be detailed in the in the study protocol deviation report.

The categories of major protocol deviation will be defined in the protocol deviation management plan, and the plan will be approved before unblinding the study.

The Per-Protocol population will be used in a secondary analysis of the primary and secondary efficacy endpoints.

7. EFFICACY ASSESSMENTS

7.1. EPWORTH SLEEPINESS SCALE (ESS)

The ESS provides a measure of a person's general level of daytime sleepiness, or their mean sleep propensity in daily life. It is a self-administered questionnaire with 8 questions asking the subject how likely they would be to doze off or fall asleep in different situations. Responses range from 0 = would never doze to 3 = high chance of dozing (see Protocol Appendix 5). It provides a measure of a person's general level of daytime sleepiness, or their mean sleep propensity in daily life. The ESS is a validated measure with high specificity and sensitivity for assessing subjective sleepiness.

Subjects who are randomized in the randomized withdrawal period will be asked to complete the ESS with regard to the level of sleepiness they experienced over approximately the past 7 days at the following times:

- For Group A, at Weeks 2, 14, 27, 29, 40, and at Early Termination visits that occur after Week 2.
- For Group B, at Baseline, Weeks 2, 14, 26, 28, 39, 52 and at Early Termination visits that occur after Week 2.

Subjects who are not randomized into the randomized withdrawal period will be asked to complete the ESS with regard to the level of sleepiness they experienced over approximately the past 7 days at the following times:

- For Group A: at Weeks 2, 14, 27, 40, and at Early Termination visits that occur after Week 2.
- For Group B: at Baseline, Weeks 2, 14, 26, 39, 52, and Early Termination visits that occur after Week 2.

7.2. CLINICIAN GLOBAL IMPRESSION OF SEVERITY (CGI_S)

The CGIs is a 7-point Likert-type rating scale and a widely used assessment in clinical psychopharmacology trials to assess the severity of illness (see Protocol Appendix 12). The responses of this investigator-completed scale range from 1 = normal, no signs of illness to 7 = among the most extremely ill patients. For Group B subjects, the Investigator will rate his/her impression of the severity of the subject's current condition at baseline relative to his/her experience with this patient population at Baseline. For Group A subjects, this rating will be captured at baseline in the previous study.

7.3. CLINICIAN GLOBAL IMPRESSION OF CHANGE (CGI_C)

The CGIc is a 7-point Likert-type rating scale and a widely used assessment to assess efficacy in clinical drug trials. For the open-label efficacy assessments, investigators will rate their impression of any change of the subject's condition from baseline (before the start of treatment in this study for subjects in Group B or before the start of treatment in the previous study for subjects in Group A) on a 7-point scale ranging from 1 = very much improved to 7 = very much worse. Subjects in Group A will be assessed at Weeks 2, 14, 27, and 40; subjects in Group B will be assessed at Weeks 2, 14, 26, 39, and 52. All subjects will be assessed at early termination visits that occur after Week 2 (see Protocol Appendix 13). For the double-blind, placebo-controlled assessment of the maintenance of efficacy, investigators will rate their impression of any change in the subject's condition from the beginning of the Randomized Withdrawal Period on a 7 point scale ranging from 1 = very much improved to 7 = very much worse at Week 29 (for subjects in Group A) or at Week 28 (for subjects in Group B). For additional information, see Appendix 14 of the Protocol.

7.4. PATIENT GLOBAL IMPRESSION OF CHANGE (PGI_C)

The PGIc is a 7-point Likert-type rating scale and a widely used assessment to assess efficacy in clinical drug trials. For the open-label efficacy assessments, subjects will rate the change in their current overall condition since they started treatment (in this study for subjects in Group B or in the previous study for subjects in Group A) on a 7-point scale ranging from 1 = very much improved to 7 = very much worse. Group A subjects will provide ratings at Weeks 2, 14, 27, and 40; Group B subjects will provide ratings at Weeks 2, 14, 26, 39, and 52. All subjects will provide ratings at early termination visits that occur after Week 2 (see Protocol Appendix 15). For the double-blind, placebo-controlled assessment of the maintenance of efficacy, subjects will rate the change in their current overall condition since their last visit on a 7-point scale ranging from 1 = very much improved to 7 = very much worse at Week 29 (for subjects in Group A) or at Week 28 (for subjects in Group B). For additional information, see Appendix 16 of the Protocol.

7.5. FUNCTIONAL OUTCOMES OF SLEEP QUESTIONNAIRE SHORT VERSION (FOSQ-10)

The FOSQ is a 30-item disease specific quality of life questionnaire to determine functional status in adults. Measures are designed to assess the impact of disorders of excessive sleepiness on multiple activities of everyday living and the extent to which these abilities are improved by effective treatment. The FOSQ-10 is a short version of the original 30-item FOSQ that has been shown to perform similarly to the longer version. The FOSQ-10 has been shown to exhibit high internal consistency, effect sizes,

and pre- and post-treatment differences that are highly correlated with the longer version.

Subjects who are randomized into the randomized withdrawal period will be asked to complete the FOSQ-10 at the following times (see Protocol Appendix 6):

- For Group A, at Weeks 14, 27, 29, 40, and at Early Termination visits that occur after Week 2.
- For Group B, at Baseline, Weeks 14, 26, 28, 39, 52, and at Early Termination visits that occur after Week 2.

Subjects who are not randomized into the randomized withdrawal period will be asked to complete the FOSQ-10 at the following times (see Protocol Appendix 6):

- For Group A: at Weeks 14, 27, 40, and at Early Termination visits that occur after Week 2.
- For Group B: at Baseline, Weeks 14, 26, 39, 52, and Early Termination visits that occur after Week 2.

7.6. 36-ITEM SHORT FORM HEALTH SURVEY VERSION 2 (SF-36V2)

The SF-36v2 is a multi-purpose, short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index (see Protocol Appendix 7). Group A subjects will complete the SF-36v2 at Weeks 14, 27, and 40; Group B subjects will complete the questionnaire at baseline and Weeks 14, 26, 39, and 52. All subjects will complete the questionnaire at early termination visits that occur after Week 2.

7.7. EUROQOL (EQ-5D-5L)

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome that includes a descriptive system consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and an EQ visual analogue scale (VAS). It is applicable to a wide range of health conditions and treatments and provides a simple descriptive profile and a single index value for health status. The EQ-5D-5L includes five levels of severity (1=no problem, 2=slight problem, 3=moderate problem, 4=severe problem, 5=unable) for each of the 5 dimensions of the descriptive system and was developed to improve the instrument's reliability and sensitivity and to reduce ceiling effects. Group A subjects will complete the EQ-5D-5L at Weeks 14, 27, and 40; Group B subjects will complete the questionnaire at baseline and Weeks 14, 26, 39, and 52. All subjects will complete the questionnaire at early termination visits that occur after Week 2 (see Protocol Appendix 8).

7.8. PRIMARY OSA THERAPY USE

Subjects who reported using a primary OSA therapy during Study 14-003, 14-004, or 15-004 will continue to have information regarding whether they used their device each night and the duration of nightly use extracted from the data download from their device or memory card at each clinic visit from screening through the final visit of the Maintenance Phase (Week 40 for 14-003 or Week 52 for 14-004 and 15-004). If a subject's device usage cannot be extracted from his/her device, the subject should be instructed to record whether he/she used his/her primary OSA therapy and the estimated duration of use (more than half of the night, less than half of the night, or don't know) on a daily basis from screening through the final visit of the Maintenance Phase (Week 40 for 14-003 or Week 52 for 14-004 and 15-004). Subjects who reported not using a primary OSA therapy during Study 14-003, 14-004, or 15-004 will be asked to confirm that they have continued to not use a primary OSA therapy. The study staff will review the information that each subject provides regarding their primary OSA therapy use at each study visit and will discuss it with the subject at each phone contact.

Subjects will be encouraged to stay on their current primary OSA therapy at the same level of use throughout the study.

7.9. WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: SPECIFIC HEALTH PROBLEM V2.0 (WPAI:SHP)

The WPAI questionnaire is a 6-item self-administered questionnaire that measures work time missed and work and activity impairment because of a specified health problem during the past 7 days. The WPAI:SHP will be used with "narcolepsy" or "OSA" as the specified health problem. The validity of the WPAI has been established in a number of diseases and it is available in multiple languages (Reilly 1993). Group A subjects will complete the WPAI:SHP at Weeks 14, 27, and 40 for ; Group B subjects will complete the questionnaire at baseline and Weeks 14, 26, 39, and 52. All subjects will complete the questionnaire at early termination visits that occur after Week 14 (Protocol Appendix 10).

7.10. RESOURCE UTILIZATION QUESTIONNAIRE

Patient-reported resource utilization will be assessed at the Week 14 and Week 40 visits in Group A, at the Week 26 and Week 52 visits in Group B, and for all subjects at early termination visits that occur after Week 14. Information about the number of physician visits will be collected via questionnaire (Protocol Appendix 17). Standard unit costs will be applied to these resources (as well as to any hospitalizations reported as SAEs) in order to calculate the mean/median healthcare costs over the one-year period.

8. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

8.1. GENERAL METHODS

Unless otherwise specified, for numeric data, descriptive statistics will include the number of subjects with data to be summarized (n), mean, Standard Deviation (SD), median, minimum (min) and maximum (max). The same number of decimal places as in the raw data will be presented when reporting min and max, 1 more decimal place than in the raw data will be presented when reporting mean and median, and 2 more decimal places than in the raw data will be presented when reporting SD. If the raw data have 3 decimals or more, 3 decimals will be presented for the mean, median, min and max, and SD.

All categorical/qualitative data will be presented using absolute and relative frequency counts and percentages. All percentages will be presented with one decimal point. Percentages equal to 100 will be presented as 100%; percentages will not be presented for zero frequencies but the categories whose counts are zero will be displayed for the sake of completeness.

P-value > 0.9999 will be present as '>0.9999' and p-value < 0.0001 will be presented as '< 0.0001'.

All subject data will be summarized separately by open-label study phases and Randomized Withdrawal Period. All data will be summarized in the following manner, unless specified otherwise.

- In the open label phases, the analyses will be summarized overall and by modal dose level (e.g., JZP-110 75 mg, 150 mg, or 300 mg).

- In the Randomized Withdrawal Period, the analyses will be summarized by treatment group (Placebo or Combined JZP-110), and the analyses will be also summarized by dose level (e.g., JZP-110 75 mg, 150 mg, or 300 mg).

For Group A, additional summary tables will be provided by the treatment received in the previous studies.

Graphical presentations will be provided based on subject's modal dose to evaluate efficacy, functional outcomes and quality of life measures, and economic data over time in this study.

Data collected in this study will be presented in by-subject listings.

All analyses and outputs will be generated using SAS® version 9.3 (or higher).

8.2. KEY DEFINITIONS

8.2.1. Baseline

8.2.1.1. Placebo-Controlled Randomized Withdrawal Period

- For subjects who were randomized in the randomized withdrawal period, non-missing measurements taken at the beginning of the double-blind Randomized Withdrawal Period (Week 27 for Group A and Week 26 for Group B) will be used as the 'efficacy baseline' of the Randomized Withdrawal period.

8.2.1.2. Open-label (OL) Phases

- For Group A:
  - The baseline measurement for subjects is defined as the last non-missing value up to week 12 from the previous study, 14-002 or 14-003.
  - The baseline in the previous study will be also used as a reference for summary analysis (parent study baseline).
- For Group B:
  - The baseline measurement for subjects is defined as the last non-missing value from the baseline visit measured prior to the first dose of study drug in this study. If a subject has repeated measurements from the baseline visit, then the last non-missing value will be used. If there is no value from the scheduled baseline visit, the last non-missing value from other screening or unscheduled visits measured prior to the first dose of the study drug will be used.

8.2.2. Study Day

Study day will be assigned as follows:

- The first dose of study drug in this study is designated as day 1.
- For visit days after day 1, study day = visit date - day 1 date + 1.
- For visit days prior to day 1, study day = visit date - day 1 date. Thus, study days for screening visits are negative numbers. There is no "day 0".
- A subject's treatment end date is defined by the subject's last dose date in the study.
- A subject's study end date is defined by the date of the subject's last assessment, including the safety follow up in the study.

8.2.3. Modal Dose

The modal dose is defined as the dose level that the subject received most frequently in the study. If there is a tie between the two dose levels, the lower dose will be used.

8.2.4. JZP-110 Exposure

JZP-110 exposure is defined as the number of days that a dose of JZP-110 is taken, regardless of the JZP-110 dose level.

8.2.5. Study Phases and Periods

The following study phases and period are defined for analyses:

- For subjects who are randomized into the randomized withdrawal period:
  - The open label phases (Titration and Maintenance Phases) are from the first day that study drug is taken (Day 1) in this study up to end of Week 27 (Group A) or Week 26 (Group B), or to the ET date for the subjects who discontinue without reaching the end of Week 27 (Group A) or Week 26 (Group B) and after the end of Week 29 (Group A) or Week 28 (Group B) up to the end of date in the study, or to the ET date for the subjects who discontinue without completing the study.
- For subjects who are not randomized into the randomized withdrawal period:
  - The open label phases are from the first day that study drug is taken (Day 1) in this study up to the end of date in the study, or to the ET date for the subjects who discontinue without completing the study.
- The Randomized Withdrawal Period is from the end of Week 27 (Group A) or Week 26 (Group B) to the end of Week 29 (Group A) or Week 28 (Group B), or to the ET date for the subjects who discontinue without reaching the end of Randomized Withdrawal Period.

8.3. VISIT WINDOWS

The unscheduled or early termination (ET) visit will be mapped to a scheduled visit for analysis using the date of collection/assessment as a basis for determining study day and then study day will then be mapped to the intended visit. The table below contains the analysis visit windows.

Once analysis visit windows are assigned, all visits, including scheduled visits, unscheduled visits, and ET visits will be eligible for being flagged as the “analyzed record” within the analysis visit window, a subject’s individual analysis visit window

could potentially contain more than one visit. In the event of multiple visits falling within an analysis visit window or in case of a tie, the following rules will be used in sequence to determine the "analyzed record" for the analysis visit window:

- If there is a scheduled visit/week for the analysis visit window, the scheduled visit/week data will be used.
- If there is no scheduled visit/week for the analysis visit window, the data closest to the scheduled day will be used.
- If there is no scheduled visit/week for the analysis visit window and there is a tie between the data in the number of days before and after the scheduled day, the later visit will be used.

The unscheduled or early termination (ET) visit will be mapped to a scheduled visit before the imputation methods are used for handling dropouts and missing data for the efficacy endpoints.

The data not flagged as an "analyzed record" will be listed in subject listings.

Group A Visit Windows:

Study Day Window	Scheduled Study Day	Scheduled Visit/Week
Day (-1)	Day -1	Visit 1/Screening/Baseline
Day 1 – 4	Day 3	Visit 2/Day 3
Day 5 – 7	Day 6	Visit 3/Day 6
Day 8 – 10	Day 9	Visit 4/Day 9
Day 11 – 13	Day 12	Visit 5/Day 12
Day 14 – 29	Day 15	Visit 6/Week 2
Day 30 – 57	Day 43	Visit 7/Week 6
Day 58 – 85	Day 71	Visit 8/Week 10
Day 86 – 113	Day 99	Visit 9/Week 14
Day 114 – 141	Day 127	Visit 10/Week 18
Day 142 – 173	Day 155	Visit 11/Week 22
Non-randomized subjects: Day 174 – 193 Randomized subjects: Day 174 – day of randomization date	Day 190	Visit 12/Week 27
Randomized subjects: Day 1 - 10 after the randomization date	Day 197	Visit 12.1/Week 28
Randomized subjects: Day 11 - 20 after the day of randomization date	Day 204	Visit 12.2/Week 29
Non-randomized subjects: Day 194 to 232 Randomized subjects: (Day after Visit 12.2/Week 29 or Day > 20 after the day of randomization date if missing week 29) - 232	Non-randomized subjects: Day of Visit 12/Week 27 + 2 weeks Randomized subjects: Day 218	Visit 13/Week 31
Day 233 -264	Day 246	Visit 14/Week 35
Day 265 -288	Day 281	Visit 15/Week 40
Day >=289	Day 295	Visit 16/Week 42

Group B Visit Windows:

Study Day Window	Scheduled Study Day	Scheduled Visit/Week
Day (-30) - (-2)	Day -2	Visit 1/Screening
Day (-1)	Day -1	Visit 2/Baseline
Day 1 – 4	Day 3	Visit 3/Day 3
Day 5 – 7	Day 6	Visit 4/Day 6
Day 8 – 10	Day 9	Visit 5/Day 9
Day 11 – 13	Day 12	Visit 6/Day 12
Day 14 - 29	Day 15	Visit 7/Week 2
Day 30 – 57	Day 43	Visit 8/Week 6
Day 58 – 85	Day 71	Visit 9/Week 10
Day 86 – 113	Day 99	Visit 10/Week 14
Day 114 – 141	Day 127	Visit 11/Week 18
Day 142 - 169	Day 155	Visit 12/Week 22
Non-randomized subjects: Day 170 – 186 Randomized subjects: Day 170 – day of randomization date	Day 183	Visit 13/Week 26
Randomized subjects: Day 1 – 10 after the randomization date	Day 190	Visit 13.1/Week 27
Randomized subjects: Day 11 – 20 after the randomization date	Day 197	Visit 13.2/Week 28
Non-randomized subjects: Day 187 to 225 Randomized subjects: Day > 20 after the randomization date	Non-randomized subjects: Date of Visit 13/Week 26 Randomized subjects: Day 211	Visit 14/Week 30
Day 226 – 257	Day 239	Visit 15/Week 34
Day 258 – 288	Day 274	Visit 16/Week 39
Day 289 – 316	Day 302	Visit 17/Week 43
Day 317 – 348	Day 330	Visit 18/Week 47
Day 349 – 372	Day 365	Visit 19/Week 52
Day >= 373	Day 379	Visit 20/Week 54

8.4. MISSING DATA

8.4.1. Placebo-Controlled Randomized Withdrawal Period

ESS:
For the primary analysis, missing data will be imputed using a single imputation approach (SI) the last observation carried forward (LOCF, i.e. the last-observation during the Randomized Withdrawal Period). Another single imputation approach (SI) - mean imputation will be used to assess the potential impact of missing data as a sensitivity analysis as described in section 10.1.1.3.1. Additional sensitivity analyses will be conducted to investigate the robustness of the primary analysis method; the details are described in section 10.1.1.3.2.

The algorithm for calculating of the total ESS score is described in Section 10.1.

PGIc:
For the primary analysis, missing data will be imputed using a single imputation approach (SI) – the last observation carried forward (LOCF, i.e. the last-observation during the Randomized Withdrawal Period). Two SI approaches (worst case and varies by early termination reason) will be used to impute the missing data to assess the potential impact of missing data as sensitivity analyses.

CGIc:
For the primary analysis, missing data will be imputed using a single imputation approach (SI) – the last observation carried forward (LOCF, i.e. the last-observation during the Randomized Withdrawal Period).

Missing items on the functional outcomes and quality of life measures will be handled as described in Section 10.4.

8.4.2. Open-label (OL) Phases

Missing data for the efficacy parameters ESS, CGIc, PGIc will be imputed using an LOCF approach.

8.5. LEVEL OF SIGNIFICANCE AND MULTIPLICITY ADJUSTMENT

For comparisons between JZP-110 and placebo at the end of the Randomized Withdrawal Period, subjects who were randomized to continue on JZP-110 in the Randomized Withdrawal Period will be treated as a single group regardless of their diagnosis (narcolepsy or OSA) or dose of JZP-110 that they received. Thus, there will be no multiplicity issues with respect to multiple doses in the hypothesis testing. A significance level of 0.05 will be used. A fixed sequential testing strategy will be employed to address the multiplicity issues in testing primary and secondary endpoints.

To address the multiplicity issues in the analyses of the primary and secondary efficacy endpoints, a fixed hierarchical testing sequence will be used. Testing will begin with the comparison of combined JZP-110 versus placebo for the primary efficacy endpoint ESS. The p-value of the primary analysis of the ESS endpoint must be less than 0.05 before testing can proceed to the comparison of combined JZP-110 versus placebo for the secondary efficacy endpoints PGIc and CGIc (in that order). Testing will stop when the significance level exceeds 0.05 ($p \geq 0.05$). This gate-keeping approach will control the family-wise error rate at 0.05.

8.6. POOLING OF CENTERS AND REGION

Due to the large number of centers and the fact that many centers have a small number of subjects, analyses will not be performed by center and will not include an adjustment for center. Data from all investigational centers will be pooled for the primary analyses.

Data will also be summarized by region (North America and Europe) for specified analyses.

8.7. SUBGROUPS AND SUBGROUP ANALYSIS

Exploratory analyses of the key efficacy and safety endpoints will be conducted in the following subgroups of subjects:

- Subjects with narcolepsy (from study 14-002, 15-005, ADX-N05 201, or ADX-N05 202)
- Subjects with OSA (from study 14-003, 14-004, or 15-004)
- Subjects with narcolepsy who report the presence or absence of cataplexy at randomization in a previous study (Group A subjects) or at baseline in this study (Group B subjects)
- Subjects with compliant or non-compliant use of a primary OSA therapy at randomization in a previous study (14-003 and 14-004) or at baseline in this study (15-004)
- Region (North America and Europe)

The following endpoints will be included in the subgroup analyses:

- ESS: Change from the beginning to the end of the Randomized Withdrawal Period
- ESS: Change from the study baseline (Group B)
- ESS: Change from the last assessment in the previous study (Group A)
- ESS: Change from the baseline in the previous study (Group A)

- FOSQ-10: Change in total score and 5 subscale scores from the beginning to the end of the Randomized Withdrawal Period
- FOSQ-10: Change in total score and 5 subscale scores from the study baseline (Group B)
- FOSQ-10: Change in total score and 5 subscale scores from the last assessment in the previous study (Group A)
- FOSQ-10: Change in total score and 5 subscale scores from the Baseline in the previous study (Group A)
- PGIc: Percentage of subjects reported as improved in the OL Phases at each time point (Group A and B)
- CGIc: Percentage of subjects reported as improved in the OL Phases at each time point (Group A and B)
- PGIc: Percentage of subjects reported as worse at the end of Randomized Withdrawal Period
- CGIc: Percentage of subjects reported as worse at the end of Randomized Withdrawal Period
- TEAEs
- EQ-5D-5L:
    - Number and percentage of subjects in each of the 5 levels (e.g., no problem, slight problem, moderate problem, severe problem, unable) for each dimension at study Baseline and each post-baseline time point (Group B)
    - Number and percentage of subjects in each of the 5 levels (e.g., no problem, slight problem, moderate problem, severe problem, unable) for each dimension at last assessment and baseline in the previous study and each post-baseline time point (Group A)
    - Number and percentage of subjects reporting any problems (levels 2-5) for each dimension at study Baseline and each post-baseline time point (Group B)
    - Number and percentage of subjects reporting any problems (levels 2-5) for each dimension at last assessment and baseline in the previous study and each post-baseline time point (Group A)
    - EQ VAS score at each time point and change from study Baseline to each post-baseline time point (Group B)

- EQ VAS score at each time point and change from baseline in the previous study (Group A)
- EQ VAS score at each time point and change from the last assessment in the previous study (Group A)

9. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

9.1. SUBJECT DISPOSITION AND WITHDRAWALS

The number of all enrolled subjects and the number and percentage of subjects in the each analysis population will be presented. For Group A, data will also be summarized by previous study treatment. In addition, the number of subjects who completed/prematurely discontinued and the reason for discontinuation will also be presented by study phases and period. Disposition information will be summarized for the Safety and mITT population and for the subgroups of subjects by region.

The summary of disposition over time will show the number of subjects terminating the study in each week

For the Group A subjects, disposition information will be also summarized by treatment group from the previous study.

For screen failure subjects in Group B, reasons for screen failure will be summarized separately.

9.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized for the safety, mITT, Per-Protocol populations, and subgroups of subjects by region.

Demographic information will be collected for subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 (Group B). Demographic information for subjects who completed Study 14-002 or 14-003 (Group A) will be obtained from those study databases.

For Group A subjects, demographic and baseline characteristics will be also summarized by treatment group from the previous study.

Demographic and baseline characteristics include age, gender, race, ethnicity, region, country, height, weight and Body Mass index (BMI).

- Height (in cm) = height (in inches) * 2.54
- Weight (in kg) = weight (in lbs) * 0.4536

For screen failure subjects in Group B, demographic data will be summarized separately.

In addition, the following variables will be summarized:

- Baseline disease severity: total ESS score and clinical global impression of severity (CGIs)

- Randomization stratification factors from previous studies: narcolepsy and OSA, presence of cataplexy, and primary OSA therapy use (compliant, non-compliant) for Group A
- Efficacy endpoints at the beginning of Randomized Withdrawal Period: total ESS score, CGIc, and PGIc

9.3. MEDICAL/SURGICAL HISTORY

A complete medical/surgical history from the time of participation in Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 (Group B) will be collected for each subject during the Screening visit. Any updates to the medical/surgical history for Group B subjects will be assessed at Day -1. The medical history for subjects who completed Study 14-002 or 14-003 will be re-entered from those study records.

Medical/surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.0.

Medical/surgical history data will be summarized by system organ class (SOC) and preferred term (PT) for the Safety Population.

9.4. MEDICATION/PROCEDURE

Medications will be coded using WHO DRUG dictionary, Version: March, 2015.

Procedures will be coded using MedDRA, Version 18.0

9.4.1. Prior and Concomitant Medication/Procedure

During the Screening Phase, prior (30 days or more) and concomitant medication use and any medications used for the treatment of narcolepsy or OSA (including devices used for OSA) since diagnosis will be recorded on the case report form (CRF) for subjects who participated in Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202 (Group B). Concomitant medications for subjects who participated in 14-002 or 14-003 (Group A) will be captured on the CRF pages in those respective studies.

9.4.2. Prior Medication

Prior medication will be defined as any medication (except for investigational product in one of the prior studies) with a start date prior to the first dose of study drug in this study. The stop date of the medication may be before or after the first dose of study drug, or the medication may be ongoing. If a start date is completely missing, then the medication will be considered a prior medication.

Prior medications will be summarized by anatomical therapeutic chemical (ATC) level 3 term and preferred term based on the Safety Population.

9.4.3. Concomitant Medication and Procedure

Concomitant medication will be defined as any medication with a stop date on or after the first dose of study drug or any medication that is ongoing. The start date of the medication may be before or after the first dose of study drug in this study. A medication with complete missing use dates or partial missing use dates without evidence that the medication stopped prior to the first dose of study drug will be considered a concomitant medication. Concomitant procedures will be defined as procedures with a procedure date on or after first dose of study drug. A procedure with a completely or partially missing use date without evidence that the procedure was conducted prior to the first dose of study drug will be considered a concomitant procedure.

Concomitant medications will be summarized by ATC level 3 term and preferred term based on safety population. Procedures will be summarized by MedDRA SOC and PT. The summaries will be based on the Safety Population.

9.5. PROTOCOL DEVIATIONS

Before database lock, the cumulative protocol deviation report will be generated by the [redacted] clinical team and reviewed by the Jazz Medical Monitor and Lead Statistician per the protocol deviation management plan. Source data will include both deviations reported directly from the sites and deviations identified from CRF data through programmatic edit checks. A flag of exclusion from Per-Protocol population due to major violation(s) will be identified and the reasons for exclusion from Per-Protocol population will be documented based on discussion by the Jazz Medical Monitor, Lead Statistician, and Clinical Operations Lead. The flag of exclusion from Per-Protocol population and the reason for exclusion from Per-Protocol population will be included in the cumulative protocol deviation report and the final protocol deviation report. After database lock, the final protocol deviations report will be filed in the TMF and will be used as source data for the clinical study database.

Major protocol deviations will be summarized for study phases and period based on the Safety Population. Major protocol deviations will also be summarized by randomized treatment group for the Randomized Withdrawal Period based on the mITT Population.

10. EFFICACY

Observed data at each time point and change from baseline to each post-baseline time point during each phases and period will be summarized as described below. For categorical data, frequency counts and percentages will be presented in a similar manner.

10.1. ESS SCORE: PRIMARY EFFICACY ENDPOINT AND ANALYSES

The ESS total score is the sum of eight item scores. If three or more item scores are missing at a specific time point the ESS total score will be set to missing.

If one or two ESS items are missing at a specific time point, the mean of the remaining seven or six non-missing ESS items at that time point will be used to impute the missing ESS items. The ESS total score will be calculated as the sum of the observed and the imputed item scores.

The ESS score can range from 0 to 24 points, with higher scores indicating a greater chance of dozing. Thus, a decrease in ESS score represents an improvement in excessive sleepiness.

10.1.1. Placebo-Controlled Randomized Withdrawal Period

10.1.1.1. Primary Analysis

For the primary analysis of the ESS score, an analysis of covariance (ANCOVA) model will be used. The response variable will be the change from the beginning to the end of Randomized Withdrawal Period The model will include the following fixed effects:

- Treatment group (with 2 levels: Combined JZP-110 and Placebo)
- Randomization stratification factor (narcolepsy vs. OSA)
- 'Efficacy Baseline', defined as the ESS total score at the beginning of the Randomized Withdrawal Period

SAS procedure PROC GLM will be used to carry out this analysis. Estimates of the least squares (LS) mean treatment difference versus placebo and their 95% confidence interval will be presented. The LOCF approach will be used for subjects who discontinued early in the Randomized Withdrawal Period.

The analysis will be based on the mITT Populations.

10.1.1.2. Secondary Analysis

For primary efficacy endpoints, the analysis will be performed using the same statistical model as the primary analysis based the PP population, instead of the mITT population.

10.1.1.3. Sensitivity Analysis

This section describes analyses to explore the potential impact of missing data. Importantly, the analyses described in Section 10.1.1.1 are anticipated to be the most appropriate methods; the methods described in this section will be used to qualitatively evaluate the robustness of the primary analysis method. Sensitivity analyses will be based on the mITT population.

10.1.1.3.1. Sensitivity Analyses using Single Imputation (SI) Approach

The ANCOVA model described in Section 10.1.1.1 will be used to evaluate the change in in the ESS score from the beginning to the end of the Randomized Withdrawal Period using the SI approach described below.

The mean imputation approach assumes missing completely at random, meaning that the probability of observed data being missing does not depend on observed data or on unobserved data. For each subject, missing data at the beginning to the end of Randomized Withdrawal Period will be replaced with the corresponding treatment group mean.

10.1.1.3.2. Sensitivity Analyses using Multiple Imputation (MI) Approach

Pattern Mixture Model using dropout pattern imputation is planned to explore the possibility of non-ignorable missing data for the placebo-controlled maintenance of efficacy of the ESS score analysis.

For missing data due to dropouts, pattern mixture imputation will be considered based on dropout patterns below.

Scenario 1:

MNAR (missing not at random):

- dropout due to lack of efficacy (LOE) in JZP-110 treatment group

MAR (missing at random):

- dropout due to other reason (not LOE) in JZP-110 treatment group
- dropout due to any reason in the placebo group

Scenario 2:

MNAR (missing not at random):

- dropout due to adverse event (AE) in JZP-110 treatment group

MAR (missing at random):

- dropout due to other reason (not AE) in JZP-110 treatment group
- dropout due to any reason in the placebo group

Scenario 3:

MNAR (missing not at random):

- dropout due to AE or LOE in JZP-110 treatment group

MAR (missing at random):

- dropout due to other reasons (not AE or LOE) in the treatment group
- dropout due to any reason in the placebo group

A tipping point approach will be used to test the robustness of the primary analysis method; imputed values for subjects in the JZP-110 treatment group that fall into a MNAR pattern will be adjusted under the different scenarios above (Carpenter and Kenward 2013, pp. 237–239; van Buuren 2012, pp. 88–89) using the delta adjustment imputation method.

If the missing data in the combined JZP-110 treatment group falls into a MNAR pattern, the analysis will assume the treatment differences over the missing visit (e.g., Week 29 (Group A) or Week 28 (Group B)) progressively decrease from 0%, 10%, 20%, .., and up to 100% (i.e., equivalent to placebo). Otherwise, the regression method for monotone missing data on the basis of the predicted future pattern for the same treatment group will be applied.

The tipping point analysis will be performed for the primary endpoint of ESS if the primary analysis results are statistically significant (p-value < 0.05). The procedure will be implemented using the steps delineated below:

Step 1: For JZP-110 treatment group that fall into an MNAR pattern, delta = k (0%, 10%, 20%, …,100%) * LS mean treatment difference obtained from the primary ANCOVA analysis will be subtracted from the imputed values. The delta adjustment will be performed for the three dropout pattern scenarios separately: dropout due to LOE in

the JZP-110 treatment groups, dropout due to AE in the JZP-110 treatment group, and dropout due to LOE or AE in the JZP-110 treatment group.

Step 2: For other missingness, the regression method for monotone missing data on the basis of the predicted future pattern for the same treatment group will be applied.

Step 3: One hundred (100) imputed datasets will be generated for each MI analysis. Each imputed dataset will be analyzed separately using the ANCOVA model specified in Section 10.1.1.1. The final estimate of treatment difference will be the average of the estimates based on the 100 individual imputed datasets. The pooling of the individual estimates and inferences based on the combined estimate will be handled by SAS procedure MIANALYZE.

Step 1 will be repeated iteratively while increasing the penalty (e.g., 10%, 20%, …, 100%) for the JZP-110 treatment group that falls into an MNAR pattern until the tipping point value (i.e., where p-value > 0.05) is identified.

10.1.2. Open-label (OL) Phases

For the OL maintenance of efficacy analyses, ESS scores will be summarized by time point as following:

- For Group A:
    - Change in ESS score from the baseline in the previous study
    - Change in ESS score from the last assessment in the previous study

For the Group A, the ESS analysis will also be summarized by the treatment in the previous study.

- For Group B:
    - Change in ESS score from the study baseline

The analysis will be based on the Safety Population.

10.1.3. Subgroup Analyses

The approach described in the primary analysis in Section 10.1.1.1 will also be used for the subgroup analyses. The analysis will be performed for the Randomized Withdrawal Period (based on the mITT Population) and the OL Phases (based on the Safety Population) separately. The primary analysis in Section 10.1.1.1 will be used for the subgroup analyses, however the randomization stratification factor (with 2 levels, narcolepsy vs. OSA) will be removed from the model for analysis the subgroup of subjects with narcolepsy or OSA at randomization. Similar analyses will be conducted for

the subgroups listed in Section 8.7. No formal statistical testing will be performed for the open-label analyses; only summary statistics will be provided.

10.2. CGI_C: CLINICAL GLOBAL IMPRESSION OF CHANGE

10.2.1. Placebo-Controlled Randomized Withdrawal Period

10.2.1.1. Primary Analysis

The percentage of subjects reported as worse on the CGIc at the end of Randomized Withdrawal Period will be calculated and summarized by treatment group. Comparison between combined JZP-110 doses and placebo will be performed using a chi-square test. 95% confidence intervals for the difference in percentages will be calculated. Missing data at the end of Randomized Withdrawal Period will be imputed using LOCF. The analysis will be based on the mITT population.

10.2.2. Open-label (OL) Phases

The percentage of subjects reported as improved on the CGIc at each time point will be summarized and presented graphically. LOCF will be used to impute data for subjects with missing post-baseline assessments. The summaries will be based on the Safety Population.

10.2.3. Subgroup Analyses

The approach described in the primary analysis in Section 10.2.1.1 will also be used for the subgroup analyses. The analysis will be performed for the Randomized Withdrawal Period (based on the mITT Population) and the OL Phases (based on the Safety Population) separately. No formal statistical testing will be performed for the open-label analyses; only summary statistics will be provided.

10.3. PGI_C: PATIENT GLOBAL IMPRESSION OF CHANGE

10.3.1. Placebo-Controlled Randomized Withdrawal Period

10.3.1.1. Primary Analysis

The percentage of subjects reported as worse on the PGIc at the end of Randomized Withdrawal Period will be calculated and summarized by treatment group. Comparison between combined JZP-110 doses and placebo will be performed using a chi-square test. 95% confidence intervals for the difference in percentages will be calculated. Missing

data at the end of Randomized Withdrawal Period will be imputed using LOCF. The analysis will be based on the mITT population.

10.3.1.2. Secondary Analysis

The analysis of the secondary endpoint will be performed using the same statistical method as the primary analysis based on the PP population instead of the mITT population

10.3.1.3. Sensitivity Analyses

Missing data at the end of the Randomized Withdrawal Period will be imputed using the following single imputation approaches:

Approach 1 – SI Varies by Early Termination Reason

Subjects with missing data the end of the Randomized Withdrawal Period due to lack of efficacy or adverse events will be considered worsened (minimally, much, or very much) at the end of Randomized Withdrawal Period. Subjects with missing data at the end of the RW Period for other reasons will be imputed using LOCF.

Approach 2 – SI by the Worst-Case

All subjects with missing data the end of the Randomized Withdrawal Period will be considered worsened (minimally, much, or very much).

The chi-square test will be used to test the treatment difference between combined JZP-110 and placebo. 95% confidence intervals for the difference in percentages between the treatment groups will be calculated. These analyses will be based on the mITT population.

10.3.2. Open-label (OL) Phases

The percentage of subjects reported as improved on the PGIc at each time point will be summarized and presented graphically. LOCF will be used to impute data for subjects with missing post-baseline assessments in the Open label Phases. The summaries will be based on the Safety Population.

10.3.3. Subgroup Analysis

The approach described in the primary analysis in Section 10.3.1 will also be used for the subgroup analyses. The analysis will be performed for the Randomized Withdrawal Period (based on the mITT Population) and the OL Phases (based on the Safety

Population) separately. No formal statistical testing will be performed for the open-label analyses; only summary statistics will be provided.

10.4. FUNCTIONAL OUTCOMES AND QUALITY OF LIFE ENDPOINTS

Outcome measures associated with the FOSQ-10, SF-36v2, EQ-5D-5L, and compliance with primary OSA therapy (OSA only) will be summarized by study phases and period. These results will also be displayed graphically over time. Changes (as described in Section 4.2) in these measures from the baseline and from the last assessment in the previous study will be examined.

10.4.1. FOSQ-10: Change in the Total Score

The FOSQ-10 total score is the mean of non-missing 5 subscales (General Productivity, Activity Level, Vigilance, Social Outcomes, Intimacy and Sexual Relationship) multiplied by 5.

10.4.1.1. Placebo-Controlled Randomized Withdrawal Period

Change in the FOSQ-10 total score from the beginning to the end of the Randomized Withdrawal Period will be analyzed using a similar ANCOVA model as the primary analysis of primary efficacy endpoint (Section 10.1.1.1).

Changes in the FOSQ-10 total score and the 5 subscale scores from the beginning to the end of the Randomized Withdrawal Period will be summarized.

The analysis will be based on the mITT Population.

10.4.1.2. Open-label (OL) Phases

FOSQ-10 scores will be summarized by time point as following:

For Group A:

- Change in FOSQ-10 total score and the 5 subscale scores from the baseline in the previous study
- Change in FOSQ-10 total score and the 5 subscale scores from the last assessment in the previous study

For Group B:

- Change in FOSQ-10 total score and the 5 subscale scores from baseline in this study.

Analyses will be based on the Safety Population.

10.4.1.3. Subgroup Analysis

The approach described in the primary analysis in Section 10.4.1 will also be used for the subgroup analyses. The analysis will be performed for the Randomized Withdrawal Period (based on the mITT Population) and the OL Phases (based on the Safety Population) separately. No formal statistical testing will be performed for the open-label analyses; only summary statistics will be provided.

10.4.2. SF-36v2: Change from Baseline by Domains

The SF-36v2 is composed of 8 domains/scales: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). From the eight domains, a physical component summary (PCS) (aggregate of the PF, RP, BP and GH scales) and mental component summary (MCS) (aggregate of the VT, SF, RE and MH scales) are derived.

10.4.2.1. Open-label (OL) Phases

SF-36 items and scales are scored so that a higher score indicates a better health state. Scoring the SF-36 involves several steps. First, 10 items are reverse-coded and an algorithm for an algebraic summation of item scores is applied to produce domain-specific raw scales that accounts for missing item responses. Domain-specific raw scales are then transformed to a 0 to a 100 range, after which a norm-based (T-score) transformation is applied so that each scale ranges from 0 to 100, with a mean of 50 and a standard deviation of 10 in the 1998 general U.S. population (Ware et al 2000). A norm-based transformation is applied so that domain-specific scales can be meaningfully compared between each other.

The mental and physical component summary scores (MCS/PCS) are computed by aggregating domain scores using factor score coefficients from the 1998 general U.S. population (Ware et al 2000). The aggregated summary scores are standardized to have a mean of 50 with a standard deviation of 10 in the general 1998 U.S. population (Ware et al 2000).

When calculating the raw domain scores, if at least half the item scores for a domain are non-missing, the missing item scores will be replaced with the average of the non-missing scores for the domain. Otherwise the raw domain score and corresponding norm-based domain scores will be set to missing.

Domain scores and component summary scores will be calculated using the Quality Metric (QM) Certified Scoring software and provided by Optum, Inc.

SF-36v2 analysis in domain scores (norm-based), the physical component summary (PCS) score, and mental component summary (MCS) score will be summarized by time point as following:

For Group A:

- Change from the baseline in the previous study
- Change from the last assessment in the previous study

For Group B:

- Change from the study baseline

The analysis above will be based on the Safety Population.

10.4.3. EQ-5D-5L: EQ-5D Dimensions

10.4.3.1. Open-label (OL) Phases

EQ-5D-5L has 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has 5 levels of response (e.g., 1=no problem, 2=slight problem, 3=moderate problem, 4=severe problem, 5=unable).

If multiple levels of response are checked for a single dimension, then the level of response will be treated as a "missing value" for the dimension.

The following categories will be summarized for EQ-5D-5L by time point :

- Number and percentage of subjects in each of the 5 levels of severity (e.g., no problem, slight problem, moderate problem, severe problem, unable) for each of the 5 dimension (e.g., mobility, self-care)
- Number and percentage of subjects reporting any problems (levels 2-5) for each dimension

Similar analyses will be conducted for the subgroups listed in Section 8.7.

The analyses above will be based on the Safety Population.

10.4.4. EQ VAS: Change in the VAS Score

10.4.4.1. Open-label (OL) Phases

The EQ VAS score ranges from 0 to 100, with a higher score indicating a better health condition.

For Group A:

- EQ VAS score and change from the baseline in the previous study
- EQ VAS score change from the last assessment in the previous study

For Group B:

- EQ VAS score change from this study baseline

Similar analyses will be conducted for the subgroups listed in Section 8.7.

The analysis above will be based on the Safety Population.

10.4.5. EQ-5D-5L index: Change in Index Value

10.4.5.1. Open-label (OL) Phases

Health states in the EQ-5D-5L can be converted into a single index value, where index values are presented in the country specific value sets to facilitate the calculation of quality-adjusted life years (QALYs). EQ-5D-5L value sets can be used to obtain the EQ-5D-5L index values based on the crosswalk for the respective countries: Denmark, France, Germany, Japan, the Netherlands, Spain, Thailand, UK, US, Zimbabwe. References: http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets.html; van Hout B, Janssen MF, et al. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health 2012 Jul-Aug; 15(5):708-15.

For Group A:

- Change in the EQ-5D-5L index value from the baseline in the previous study
- Change in the EQ-5D-5L index value from the last assessment in the previous study

For Group B:

- Change from the study baseline.

Similar analyses will be conducted for the subgroups listed in Section 8.7.

The analysis above will be based on the Safety Population.

10.4.6. Use of Primary OSA Therapy

Subjects who reported using a primary OSA therapy during Study 14-003, 14-004, or 15-004 will continue to record information regarding whether they used their device each night and the duration of nightly use. These data will be extracted from the data download from their device or memory card from screening through the final visit of the Maintenance Phase (Week 40 for 14-003 or Week 52 for 14-004 and 15-004). Subjects who do not have electronically retrievable data from their OSA therapy device will record their usage of their OSA therapy device using a daily diary.

Compliance with primary OSA therapy for the subjects from the study 14-003, 14-004, and 15-004 will be summarized by visit.

If daily data for primary OSA therapy use are missing, the missing daily data will be imputed using the LOCF method between each visit. LOCF will be applied up to the early termination date or the last date prior to the next visit, whichever is earlier. Otherwise these data will not be imputed.

10.4.6.1. Placebo-Controlled Randomized Withdrawal Period

Compliance with primary OSA therapy for the randomized subjects in the Randomized Withdrawal Period will be summarized as follows:

- Percentage of nights that subjects use their primary OSA therapy in the Randomized Withdrawal Period
- Change in the percentage of nights that the primary OSA therapy is used from the visit before Randomized Withdrawal Period to the Randomized Withdrawal Period

The change in the percentage of nights that the primary OSA therapy is used from the visit before the Randomized Withdrawal Period to the Randomized Withdrawal Period will be analyzed using a Wilcoxon-Mann-Whitney test to compare the treatment difference between combined JZP-110 with placebo.

For subjects who have electronically retrievable data,

- Average number of hours that a subject used the OSA device per night at each visit will be calculated as:
    - Total number of hours that a subject used the OSA device between visits/ total number of nights that the subject used the OSA device between visits. The nights that the subject did not use an OSA device will not be included in the calculation.

For subjects who do not have electronically retrievable data:

- Percentage of nights that subjects used an OSA device more than half of the night
- Percentage of nights that subjects used an OSA device less than half of the night
- Percentage of nights that subjects used an OSA device with unknown duration

10.4.6.2. Open-label (OL) Phases

Compliance with primary OSA therapy in the Open-label Period will be summarized as follows:

- For Group A and B
    - Percentage of nights that subjects use the primary OSA therapy in the Open label Phases
- For Group A
    - Change in the percentage of nights that the primary OSA therapy is used in the screening period in the previous study to each time point
    - Change in the percentage of nights that the primary OSA therapy is used in the last period in the previous study to each time point
- For Group B
    - Change in the percentage of nights that the primary OSA therapy is used from the Screening Period (e.g., all available data prior to the first dose date of study drug in this study) to each time point

In addition, the following exploratory summary analyses will be conducted:

- For subjects who have electronically retrievable data :
    - Average number of hours that a subject used OSA device per night in each period, will be calculated as: Total number of hours that a subject used the OSA device in a period/ total number of nights that the subject used OSA device in that period. The nights that the subject did not use an OSA device will not be included in the calculation.
- For subjects who do not have electronically retrievable data :

- Percentage of nights that subjects used an OSA device more than half of the night
- Percentage of nights that subjects used an OSA device less than half of the night
- Percentage of nights that subjects used an OSA device with unknown duration

The analyses above will be based on the Safety Population.

10.5. ECONOMIC ASSESSMENTS

10.5.1. WPAI:SHP

10.5.1.1. Open-label (OL) Phases

The outcome measures associated with the WPAI:SHP will be summarized overall and by modal dose and time point as described in Section 8. Results will also be displayed graphically. No missing data imputation will be performed.

The WPAI questionnaire is a 6-item self-administered questionnaire that measures work time missed and work and activity impairment due to a specified health problem during the past 7 days. The WPAI:SHP will be used with "narcolepsy" or "OSA" as the specified health problem. Subjects will complete the WPAI:SHP at Weeks 14, 27, and 40 for subjects in Group A; at baseline and Weeks 14, 26, 39, and 52 for subjects in Group B; and at early termination visits that occur after Week 14 (see Protocol Appendix 10).

Questions:

1 = currently employed

2a = hours missed from work due to problem

2b = hours missed from work other reasons

3 = hours actually worked

4 = degree problem affected productivity while working

5 = degree problem affected regular activities

Endpoints and Scoring:

The following four endpoints will be developed for the evaluation of work productivity and activity impairment. Multiply scores by 100 to express in percentages.

- Percentage of work time missed due to problem: Score = Q2a/(Q2a+Q2b+Q3)
- Percentage impairment while working due to problem: Score = Q4/10
- Percentage of overall work impairment due to problem:

Score = (Q2a+Q2b)/(Q2a+Q2b+Q3) + {(1-(Q2a+Q2b)/(Q2a+Q2b+Q3)) x Q4/10

- Percent of activity impairment due to problem: Score = Q5/10

Where applicable, the changes in the WPAI:SHP measures from the previous study baseline and from the last assessment of the previous study will be examined for the following categories:

- Percentage of work time missed due to problem
- Percentage of impairment while working due to problem
- Percentage of overall work impairment due to problem
- Percentage of activity impairment due to problem

The analyses above will be performed based on the Safety Population.

10.5.2. Resource Utilization Questionnaire

10.5.2.1. Open-label (OL) Phases

The outcome measures associated with the Resource Utilization Questionnaire will be summarized overall and by stable dose and time point as described in Section 8. Results will also be displayed graphically. No missing data imputation will be performed.

A patient-reported Resource Utilization Questionnaire will be administered at the Week 14 and Week 40 visits in Group A, at the Week 26 and Week 52 Visits in Group B, and at early Termination visits that occur after Week 14. Information about the number of physician visits will be collected via questionnaire (see Protocol Appendix 15). Standard unit costs will be applied to these resources (as well as to any hospitalizations reported as SAEs) in order to calculate the mean/median healthcare costs over the one-year period.

Questions:

In the past 3 months, how many times did you visit the following types of physicians for your own care (not related to this study):

- Primary care physician
- Sleep specialist
- Psychiatrist (for problems other than sleep)
- Ear nose and throat specialist
- Other type of specialist (please specify)

The statistical summary will include the number of visits for each type of visit in past 3 months. Mean/median healthcare costs over the one-year period will be summarized.

For Group A, resource utilization data will also be summarized by treatment in the previous study.

The analysis above will be performed based on the Safety Population.

10.6. SUMMARY OF PLACEBO-CONTROLLED EFFICACY ANALYSIS METHODS

Endpoint	Group A Time Point	Group B Time point	Analysis/ Population	Method	Missing Data Imputation
Primary					
Change from beginning to end of RW Period in ESS	Week 29	Week 28	Primary/ mITT	ANCOVA	SI: LOCF
			Secondary/ PP	ANCOVA	
			Sensitivity/ mITT	ANCOVA	SI: Mean Imputation MI: Pattern-mixture model using a dropout pattern imputation.
			Subgroup/ mITT	ANCOVA	SI: LOCF
Secondary					
Worsening in PGIc, at end of RW Period	Week 29	Week 28	Primary/ mITT	Chi-square	SI: LOCF
			Secondary/ PP	Chi-square	
			Sensitivity/ mITT	Chi-square	SI: Varies by early termination reason; SI: Worst-case
			Subgroup/ mITT	Chi-square	SI: LOCF
Worsening in CGIc, at end of RW Period	Week 29	Week 28	Primary/ mITT	Chi-square	SI: LOCF
			Subgroup/ mITT	Chi-square	SI: LOCF
Functional outcomes and quality of life					
Change from beginning to end of RW Period in FOSQ-10	Week 29	Week 28	Primary / mITT	ANCOVA	
			Subgroup/	ANCOVA	

Statistical Analysis Plan

Endpoint	Group A Time Point	Group B Time point	Analysis/ Population	Method	Missing Data Imputation
			mITT		
Change in the percentage of nights that the primary OSA therapy is used from the Maintenance Phase before RW Period to the RW Period	Week 29	Week 28	Primary / mITT	Wilcoxon rank sum	

11. SAFETY

Safety analyses will be based on the Safety Population. No inferential statistics will be performed; only summary statistics will be provided unless otherwise noted. Missing safety data will not be imputed.

11.1. EXTENT OF EXPOSURE

Exposure to study drug (in days) will be summarized for the Open label Phases and the Randomized Withdrawal Period. Exposure to study drug (in days) is calculated as last dose date of study drug – first dose date of study drug + 1.

Extent of exposure to study drug (in days) will also be summarized by JZP-110 dose level (placebo will be considered as dose of 0). Extent of exposure to study drug for a specific dose level will be calculated as total number of days during the study that the subject was exposed to the specific dose level of the study drug. In additional, overall exposure to JZP-110 (in days) is calculated as last dose date of study drug – first dose date of study drug + 1 regardless of the JZP-110 dose level.

Study drug exposure will also be summarized based on the treatment received in the previous study for Group A.

11.1. TREATMENT COMPLIANCE

Study drug compliance (%) during a specific period and overall is calculated as: 100 x (total number of capsules dispensed – total number of capsules returned)/ total number of tablets expected to be taken during the specific period (once daily).

Compliance will be summarized for the Open label Phases and the Randomized Withdrawal Period. In addition, the number and percentage of subjects in the following compliance categories (< 80%, 80-100%, >100%, and >120%) will be summarized similarly.

Overall Compliance will also be summarized across study phases and period, regardless of dose level.

11.2. ADVERSE EVENTS

Adverse events will be coded using MedDRA 18.0 to classify events under primary system organ class (SOC) and preferred term (PT).

A TEAE is defined as an AE that began after the first dose of study drug or worsened after the first dose of study drug.

AE and TEAE will be summarized by study phases and period (e.g., Open label Phases, Randomized Withdrawal Period)

An overview of all AEs, the incidence of TEAEs, and the incidence of serious TEAEs will be summarized across the study phases or period, respectively.

TEAEs will be summarized by SOC and PT, the sorting will be based on alphabetical order for the SOC and frequency count (descending order) for the PT. In addition, incidence of all TEAEs and serious TEAEs will be summarized by PT, the sorting is based on the frequency count (descending order).

For the Open label Phases, the TEAEs will be summarized by Overall, JZP-110 dose level (75 mg, 150 mg, and 300 mg).

In the Randomized Withdrawal Period, TEAEs will be presented by randomized treatment (placebo, combined JZP-110) and by JZP-110 dose level (75 mg, 150 mg, and 300 mg).

In the Open label Phases and the Randomized Withdrawal Period, TEAEs will be summarized by JZP-110 dose level (placebo is considered as JZP-110 dose of 0) at the time of onset during JZP-110 exposure in the study. In addition, this analysis will also be summarized by previous treatment group (Placebo in Group A) versus other subject (Combined JZP-110 in Group A and all subjects in Group B).

An overview of adverse events will include the number and percentage of subjects who had at least one TEAE, Serious TEAE, TEAE related/suspected to be related to study drug, TEAE related/suspected to be related to study procedure, study drug withdrawn due to TEAE, TEAE of maximum severity, and TEAE with fatal outcome.

Multiple occurrences of an AE are counted only once per subject per system organ class (SOC) and preferred term (PT) in the summary tables.

The following TEAEs will be summarized:

- Incidence of all TEAEs
- Incidence of all TEAEs by maximum severity (severe, moderate and mild) specified by investigators
- Incidence of TEAEs related/suspected to be related to study drug as specified by investigators
- Incidence of TEAEs related/suspected to be related to study procedure as specified by investigators
- Incidence of serious TEAEs
- Incidence of serious TEAEs related/suspected to be related to study drug specified by investigators
- Incidence of TEAEs leading to study drug dose reduction
- Incidence of TEAEs leading to study drug dose increase
- Incidence of TEAEs leading to study drug interruption
- Incidence of TEAEs leading to study drug withdrawn and subject withdrawn from study
- Incidence of TEAEs in which the outcome is fatal

Incidence of TEAEs occurring in ≥ 5% and ≥ 10% of subjects in any treatment group will be tabulated in a similar manner.

All data collected in the AE case report form (CRF) will be listed in by-subject listings.

11.2.1. Subgroup Analyses

The following analyses will be also repeated for the subgroups listed in Section 8.7.

- Overview of AEs
- Incidence of all TEAEs
- Incidence of TEAEs related/suspected to be related to study drug as specified by investigators
- Incidence of TEAEs leading to study drug withdrawn and withdrawn from study
- Incidence of Serious TEAEs
- Incidence of TEAEs in which the outcome is fatal

The above analysis will be summarized by the study period and across the study periods, respectively.

11.3. LABORATORY EVALUATIONS

If a continuous laboratory value is reported as below or above the limits of quantification, the qualifiers should be dropped and the numeric value will be used in the analysis (e.g., "< 3" should be "3" and "> 200" should be "200").

For Group A:

Observed data at each time point and the change from the last assessment from the previous study will be summarized by treatment in the previous studies.

For Group B:

Observed values at each time point and the change from baseline at each post-baseline time point in hematology, serum chemistry and quantitative urinalysis test results will be summarized.

For hematology and serum chemistry, including calculated creatinine clearance, normal ranges for each parameter will be used to categorize the test result as low (value lower than the lower limit), normal (value within the normal range), or high (value higher than the upper limit). For urinalysis, test results will be categorized as normal and abnormal. Frequency counts and percentages will be presented for these categorical data.

Additional information on clinical significance will also be included in the listing of lab values.

11.4. VITAL SIGNS

Vital signs will be summarized by observed value and change from baseline by visit.

For Group A:

The last assessment/baseline in the previous study will be used as a reference.

For Group B:

The baseline assessment in this study will be used as a reference.

For Group A and B:

The assessment at the beginning of Randomized Withdrawal Period will be used as reference for the analysis in the Randomized Withdrawal Period.

The number and percentage of subjects change from the reference in blood pressure and heart rate at the each time point will be summarized:

- % of subjects with an increase in HR of ≥15 and ≥30
- % of subjects with a decrease in HR of ≥15 and ≥30
- % of subjects with an increase in SBP of ≥10, ≥20, and ≥30
- % of subjects with a decrease in SBP of ≥10, ≥20, and ≥30
- % of subjects with an increase in DBP of ≥10, ≥20, and ≥30
- % of subjects with a decrease in DBP of ≥10, ≥20, and ≥30

Reference ranges for each vital sign parameter will be used to categorize the results as low (lower than the lower limit), within the reference range, or high (higher than the upper limit). In addition, shifts in categories from the reference at the each time point will be summarized.

Reference ranges:

Parameter	Lower Limit of Reference Range	Upper Limit of Reference Range
Systolic Blood Pressure (mmHg)	90	155
Diastolic Blood Pressure (mmHg)	60	95
Heart Rate (beats/min)	Female: 55, Male 50	Female: 95, Male 90
Respiration Rate (breaths/min)	12	30

An additional listing will be provided of those subjects who have clinically significant vital sign values.

11.5. ECG

Observed data and change in each ECG parameters [HR, RR, PR, QRS, QT and QT corrected with Fridercia's formula (QTcF)]from baseline to each time point and from the beginning of the Randomized Withdrawal Period to the end of the Randomized Withdrawal Period will be summarized.

For Group A:

The last assessment/baseline in the previous study will be used as a reference.

For Group B:

The baseline assessment in this study will be used as a reference.

For Group A and B:

The assessment at the beginning of the Randomized Withdrawal Period will be used as reference for the analysis in the Randomized Withdrawal Period.

The number and percentage of patients with QT and QTcF values falling into the following categories will be summarized within each study phases and period

- Change from reference of 30 – 60 msec in QT and QTcF.
- Change from reference of >60 msec in QT and QTcF
- Post- reference value > 480 msec and reference value <= 480 msec in QT and QTcF
- Post- reference value > 500 msec and reference value <= 500 msec in QT and QTcF

The subjects with other clinically significant ECG findings will also be listed.

Additional information on clinical significance will also be included in the listing of ECG measurements.

11.6. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Suicidal Ideation, Suicidal Behavior, and Self-Injurious Behavior without Suicidal Intent at each time point will be classified by C-SSRS outcomes and composite score.

11.6.1. C-SSRS Outcomes/Composite Endpoints

The following C-SSRS outcomes/composite endpoints have binary responses (yes/no).

- Suicidal Ideation (1 – 5)
    1. Wish to be dead
    2. Non-specific active suicidal thoughts
    3. Active suicidal ideation with any methods (not plan) without intent to act
    4. Active suicidal ideation with some intent to act, without specific plan
    5. Active suicidal ideation with specific plan and intent
- Suicidal Behavior (6 – 10)
    6. Preparatory acts or behavior
    7. Aborted attempt
    8. Interrupted attempt
    9. Non-fatal suicide attempt
    10. Completed suicide
- Suicidal Ideation or Behavior (1-10)
- Self-injurious behavior without suicidal intent

Composite endpoints based on the above categories are defined below:

- Suicidal Ideation: A "yes" answer during treatment to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS.
- Suicidal Behavior: A "yes" answer during treatment to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS.
- Suicidal ideation or behavior: A "yes" answer during treatment to any one of the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

Composite scores based on the above categories are defined below:

Suicidal Ideation score (0 to 5) is based on answers (Yes) to five suicidal ideation questions (Categories 1-5) on the C-SSRS.

0 = no suicidal ideation
1 = wish to be dead
2 = Non-specific active suicidal thoughts
3 = Activity suicidal ideation with any methods (not plan) without intent to act
4 = Activity suicidal ideation with some intent to act, without specific plan
5 = Activity suicidal ideation with specific plan and intent

Suicidal Behavior score (6 to 10) is based on answers (Yes) to the five suicidal behavior questions (Categories 6-10) on the C-SSRS.

0 = no suicidal behavior
6 = Preparatory acts or behavior
7 = Aborted attempt
8 = Interrupted attempt

9 = Non-fatal suicide attempt
10 = Completed suicide

Suicidal ideation or behavior score(0 to 10) is based on answers (Yes) to the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

If there is no "yes" answer to any of the ten suicidal or behavior questions, the composite scores will be set to 0.

11.6.2. C-SSRS Analyses

The number and percentage of subjects having a response of 'Yes' to the above outcomes/composite endpoints during each phases and period will be summarized by category.

In addition, to evaluate potential treatment emergent in C-SSRS, the following variables will be summarized:

- For Group A
    - Shift to the most serious outcome in the C-SSRS outcomes (No suicidal ideation or behavior, Suicidal Ideation, and Suicidal Behavior) from the last assessment in the previous study to each subsequent visit, from the baseline in the previous study to each subsequent visit, and from the beginning to the end of the Randomized Withdrawal Period
    - Shift to the maximum score in each of the C-SSRS composite score (Suicidal Ideation score, Suicidal Behavior score, Suicidal ideation or behavior score) from the last assessment in the previous study to each subsequent visit, from the baseline in the previous study to each subsequent visit, and from the beginning to the end of the Randomized Withdrawal Period
- For Group B
    - Shift to the most serious outcome in C-SSRS outcomes (No suicidal ideation or behavior, Suicidal Ideation, and Suicidal Behavior) from the study baseline to each subsequent visit, and from the beginning to the end of the Randomized Withdrawal Period
    - Shift to the maximum score in each of the C-SSRS composite scores (Suicidal Ideation score, Suicidal Behavior score, Suicidal Ideation or Behavior score) from the study baseline to each subsequent visit, and from the beginning to the end of the Randomized Withdrawal Period

A listing of subjects with suicidal Ideation, suicidal behavior, or self-injurious behavior without suicidal intent based on the C-SSRS will be provided.

12. INTERIM ANALYSES

Interim analyses are planned when the study has approximately 50 subjects with narcolepsy and 50 subjects with OSA with an exposure to JZP-110 of 52 weeks and 100 subjects with narcolepsy and 200 subjects with OSA with an exposure to JZP-110 of 26 weeks.

13. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

Changes from analysis planned in protocol include the following:

Item	Section	Category	Protocol	SAP
1	9.10	Functional outcomes and quality of Life endpoints	The outcome measures associated with the FOSQ-10, SF-36v2, EQ-5D-5L, and compliance with primary OSA therapy (OSA only) will be summarized by final dose and time point and displayed graphically	The outcome measures associated with the FOSQ-10, SF-36v2, EQ-5D-5L, and compliance with primary OSA therapy (OSA only) will be summarized by modal dose and time point and displayed graphically

14. REFERENCE

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