TITLE PAGE

Protocol Title: A Multicenter Phase 2, 12-week Double-blind, Placebo-controlled, Randomized, Parallel-group, Study of JZP150 for the Treatment of Posttraumatic Stress Disorder

Study Number: JZP150-201

Protocol Number: JZP150-201-02

Amendment Number: 02

Compound: JZP150

Brief Title: A Study of JZP150 in Adults with Posttraumatic Stress Disorder

Study Phase: Phase 2

Sponsor Name: Jazz Pharmaceuticals, Inc.

Legal Registered Address: 3170 Porter Drive, Palo Alto, CA, USA 94304

Regulatory Agency Identifier Number(s): IND: [redacted]

Sponsor Signatory:

{Please see appended electronic signature page}

[redacted] **MD**
Senior Director, Clinical Development

Date

Investigator Signatory:

[Name]
[Title]

Date

Medical monitor name and contact information can be found in the Investigator Trial Site Binder (or equivalent).

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	
Amendment 1	14 October 2021
Original Protocol	30 July 2021

Amendment 2

Overall Rationale for the Amendment:

This amendment is being implemented primarily to broaden the eligible participant population consistent with literature, and thereby allowing the study population to be more generalizable to the PTSD patient population. The sponsor has also taken the opportunity to include clarity and guidance for study procedures and assessments. There are no major changes to overall study design, primary or key secondary efficacy endpoints, dosing, or the participant population.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 4.1 Overall Design, and 4.2 Scientific Rationale for Study Design / PTSD diagnosis and severity of condition	PCL score requirement was lowered from ≥ 35 to ≥ 33.	A cut-score of ≥ 35 was originally implemented to be conservative end of a baseline score. However, the literature has demonstrated that scores between 31 and 33 on the PCL-5 are optimally efficient for diagnosing PTSD (Bovin, 2016). Thus, the minimum PCL-5 score has been reduced to ≥ 33 for consistency with the literature, recommendations of cut-scores by the National Center for PTSD, and to have a range of scores that is generalizable to the patient population.

Section # and Name	Description of Change	Brief Rationale
Synopsis and 3 Objectives and Estimands/Assessments	Revisions to the timing of the analyses of some secondary endpoints: • PCL-5 and PGI-S / CGI-S were separated into 2 endpoints. • PGI-S and CGI-S: Change from Baseline to Week 12 removed.	• This endpoint was separated into 2 as the change in patient and clinician-reported symptoms of PGI-S and CGI-S from Baseline to Week 12 is already captured as a key secondary endpoint.
	• The secondary endpoint for PTSD symptoms clusters were revised as: – 'Re-experiencing' has been changed to 'Intrusive symptoms,' – 'Avoidance' has been changed to 'Avoidance symptoms,' – 'Arousal' has been changed to 'Arousal/reactivity symptoms,' – 'Mood' has been changed to 'Negative alterations in mood and cognition.' • PTSD symptom clusters: Change from Baseline to Week 4 was added.	• PTSD symptom clusters were revised to reflect what is in DSM-5, and to include assessment of change from Baseline to Week 4.

Section # and Name	Description of Change	Brief Rationale
	• Mood and anxiety (PHQ-9): Change from Baseline to Week 1 added and Week 8 removed.	• PHQ-9 is assessed at Baseline and Weeks 1, 4, and 12.
1.3 Schedule of Activities	Minor procedural clarifications, consistent with the protocol body, were included.	To provide better guidance with the SoA.
	Dispensation and training on the digital tool and medication adherence application will be performed at Visit 2 post randomization (not Visit 1).	To ensure eligibility prior to additional training and equipment dispensation.
2.2 Background and 2.3 Benefit/Risk Assessment	Correction to the anticipated human exposure compared to the NOAELs from the 13-week studies in rats and dogs.	Alignment with the recently updated JZP150 Investigator's Brochure.
5.1 Inclusion Criteria	PCL score requirement was lowered from ≥ 35 to ≥ 33.	As noted above, the minimum PCL-5 score has been reduced to ≥ 33 for consistency with the literature, recommendations of cut-scores by the National Center for PTSD, and to have a range of scores that is generalizable to the patient population.
	Maximum BMI increased from 35 to 40 kg/m^2.	The increase in BMI should broaden the eligible participant population, as literature indicates an association between PTSD and higher BMI (Suliman, 2016). Eligibility criteria already in the

Section # and Name	Description of Change	Brief Rationale
		protocol will minimize risk associated with obesity.
5.2 Exclusion Criteria	#24. Examples of prescription drugs was removed.	The examples given led to confusion; participants receiving barbiturates, benzodiazepines should be excluded for safety reasons.
6.8 Concomitant Therapy	Added a sentence, "For details on prohibited and cautionary medications please refer to the Prohibited and Cautionary Medication document that has been provided."	Additional guidance.
7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal	"End of Study Visit" revised to "Early Discontinuation Visit, Efficacy Follow-up Visit (if applicable), and Safety Follow-up Visit."	Consistency with the SoA/Study Visits.
8.2.5 Brief Inventory of Psychosocial Functioning	Correction from 6- to 7-point scale.	Correction of a typographical error.
8.3.2 Vital Signs	Added guidance regarding repeating blood pressure measurements.	For clarification.
8.4.6 Adverse Events of Special Interest	Clarification regarding the intention for monitoring and reporting of AEOSIs.	Alignment with Protocol Clarification Letter, dated 17 November, 2021.
8.5 Pharmacokinetics	Revisions for internal consistency with text and intended procedures.	Clarification/consistency with the Laboratory Manual.
9.3 Analysis Sets	Revisions to the definitions of the FAS, mFAS (previously mITT), PK Analysis Sets and addition of a PD Analysis Set. Revision to analyses to be performed using the Enrolled Analysis Set.	Alignment with the recently-drafted Statistical Analysis Plan.

Section # and Name	Description of Change	Brief Rationale
9.4.2 Primary Estimand	Inclusion of "baseline-by-week" and "stratum-by-week" interactions in the MMRM to be used for efficacy analyses.	Alignment with the recently-drafted Statistical Analysis Plan to allow for a more appropriate model fit by accounting for different coefficients of baseline/stratum at each postbaseline visit and thus avoid potential convergence issue due to insufficient model specification.
Appendix 3 Clinical Laboratory Tests	Added specifics regarding fasting prior to visits.	Clarification regarding when participants needed to fast prior to study visits, aligned with the Protocol Clarification Letter, dated 15 August 2022.
Appendix 4 Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, and Follow-up, and Reporting	Deletion of reference to CTCAE, v5.0 for AE 'Assessment of Intensity.' Addition of note that the intensity scale to be used is based on the CTCAE, v5 or higher.	To alleviate confusion that CTCAE, v5.0 needed to be consulted for assessment of AE intensity.
	Minor revision to ensure review of Section 8.4.6 prior to reporting an AEOSI.	Clarification of reporting, in alignment with the revisions in Section 8.4.6.
Appendix 7 Liver Safety: Suggested Actions and Follow-up Assessments	Clarifications with respect to reporting liver abnormalities that may meet liver stopping or serious adverse event criteria. Clarification on reporting signs/symptoms, evaluations, and medications to facilitate a full understanding of reported liver abnormalities.	Clarification regarding how liver abnormalities and follow-up assessments should be reported to the sponsor.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Multicenter Phase 2, 12-week Double-blind, Placebo-controlled, Randomized, Parallel-group, Study of JZP150 for the Treatment of Posttraumatic Stress Disorder

Brief Title: A Study of JZP150 in Adults with Posttraumatic Stress Disorder

Rationale:

This is a 12-week, double-blind, placebo-controlled, randomized, parallel-group study of the safety and efficacy of JZP150 in the treatment of adult participants with posttraumatic stress disorder (PTSD). JZP150 (previously known as PF-04457845) is an orally available, highly selective and irreversible inhibitor of fatty acid amide hydrolase (FAAH).

The purpose of this phase 2 study is to provide an evaluation of the efficacy and safety of JZP150 in participants with PTSD, while evaluating a broad range of JZP150 doses to support pharmacokinetic (PK)/pharmacodynamics (PD) exposure-response analysis. Results from this study will be used to inform the study design, patient population, and dose selection for future studies in PTSD.

Multiple preclinical and clinical studies have demonstrated the association between the endocannabinoid system and the underlying pathophysiology of PTSD, which JZP150 directly targets (ie, augmentation of anandamide [AEA] levels).

A double-blind, placebo-controlled experimental study examined the effect of JZP150 on experimentally induced fear conditioning and extinction, and stress response among healthy volunteers. Study participants on 4 mg JZP150 once daily (QD) compared to placebo had improved recall of fear extinction 24 hours later and did not have the typical reduction in AEA in response to acute stress. Furthermore, those participants who were randomized to JZP150 had decreased stress-induced reactivity to emotional pictures demonstrating an attenuation of negative affect.

Results from previous studies in animals and humans suggest that FAAH inhibition with JZP150 may positively influence many of the core symptoms experienced by patients with PTSD.

Objectives and Estimands/Assessments:

Table 1: Objectives and Estimands/Assessments

Objectives	Estimands/Assessments
Primary	
To evaluate the efficacy of JZP150 administered once daily for up to 12 weeks at doses of 0.3 mg and 4 mg compared to placebo in the treatment of adults with PTSD, as measured by the change in Clinician Administered PTSD Scale (CAPS-5) total symptom severity score.	The primary estimand is defined as follows: • **Treatment:** 0.3 mg and 4 mg of JZP150, and placebo. • **Population:** Participants with PTSD (as defined in the eligibility criteria).

Objectives	Estimands/Assessments
	• **Variable (endpoint):** CAPS-5 total symptom severity score change from Baseline to Week 12. • **Intercurrent events (ICEs):** the "treatment policy strategy" will address all ICEs. • **Population-level summary:** The mean change from Baseline to Week 12 in CAPS-5 for each treatment group and the difference in means between each randomized treatment group compared to placebo.
Key Secondary	
To evaluate the efficacy of JZP150 administered once daily for 12 weeks at doses of 0.3 mg and 4 mg compared to placebo on overall clinician and patient global impression of severity.	The two key secondary estimands are defined as follows: Key Secondary Estimand 1: • **Treatment:** 0.3 mg and 4 mg of JZP150, and placebo. • **Population:** Participants with PTSD (as defined in the eligibility criteria). • **Variable (endpoint):** Change in Clinical Global Impression of Severity (CGI-S) from Baseline to Week 12. • **Intercurrent events (ICEs):** the "treatment policy strategy" will address all ICEs. • **Population-level summary:** The mean change from Baseline to Week 12 in CGI-S for each treatment group and the difference in means between each randomized treatment group compared to placebo. Key Secondary Estimand 2: • **Treatment:** 0.3 mg and 4 mg of JZP150, and placebo • **Population:** Participants with PTSD (as defined in the eligibility criteria). • **Variable (endpoint):** Change in Patient Global Impression of Severity (PGI-S) from Baseline to Week 12.

Objectives	Estimands/Assessments
	• **Intercurrent events (ICEs):** the "treatment policy strategy" will address all ICEs. • **Population-level summary:** The mean change from Baseline to Week 12 in PGI-S for each treatment group and the difference in means between each randomized treatment group compared to placebo.
Secondary	
To evaluate the efficacy of JZP150 administered once daily for 12 weeks at doses of 0.3 mg and 4 mg compared to Placebo on functional outcomes and patient reported symptoms in adults with PTSD	All other secondary and exploratory estimands are defined using the same estimand attributes (treatment, population, ICEs, and population-level summary, difference in means or proportions between each randomized treatment and placebo, as appropriate) as described above. The variables (endpoints) for the estimands are: • Responder analysis defined in 3 separate ways: o Percent of participants with ≥ 30% improvement on the CAPS-5 total symptom severity score from Baseline to Week 12 o Percent of participants who are very much or much improved on the CGI-C at Weeks 4 and 12 o Percent of participants with ≥ 1 unit of improvement on the PGI-S from Baseline to Week 12 • CAPS-5 total symptom severity score change from Baseline to Week 4. • Change in functional outcomes measured by the Brief Inventory of Psychosocial Functioning (B-IPF) and Sheehan Disability Scale (SDS) from Baseline to Week 12. • Change in patient-reported symptoms of PTSD as assessed by the PTSD Checklist (PCL-5) from Baseline to Week 1, 4, 8, and 12. • Change in patient- and clinician-reported symptoms of PTSD as assessed by the PGI-S,

Objectives	Estimands/Assessments
	and CGI-S from Baseline to Weeks 1, 4, and 8. • Change in self-reported sleep problems as measured by the Insomnia Severity Index (ISI) and Pittsburgh Sleep Quality Index-PTSD Addendum (PSQI-A) from Baseline to Week 12. • Change in PTSD symptom clusters (intrusive symptoms, avoidance symptoms, arousal/reactivity symptoms, negative alterations in mood and cognition) as assessed by the change in the sub-scales of the CAPS-5 from Baseline to Week 4 and Week 12. • Change in mood and anxiety from Baseline to Weeks 1, 4, and 12 as assessed by the Patient Health Questionnaire (PHQ-9) and change from Baseline to Weeks 4, 8, 12 on the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A). • Change in quality of life from Baseline to Week 12 as measured by the Recovering Quality of Life (ReQoL).
To evaluate the safety and tolerability of JZP150 administered once daily for up to 12 weeks at doses of 0.3 mg and 4 mg in adults with PTSD.	The safety of JZP150 will be evaluated by the following assessments: • Adverse events (AEs) • Vitals signs • Physical examinations [redacted] • 12-lead ECG • Clinical laboratory tests (chemistry, hematology, urinalysis [redacted] • C-SSRS • Withdrawal scale (marijuana withdrawal checklist)
To characterize the PK and PD of JZP150 in adults with PTSD using population PK modeling and simulation methodology.	Plasma concentration of AEA, JZP150 and its metabolites

Objectives	Estimands/Assessments
[redacted]	
[redacted]	[redacted]

Brief Summary:

This is a 12-week, double-blind, placebo-controlled, randomized, parallel-group, multicenter study of the safety and efficacy of JZP150 in the treatment of adult participants with PTSD. Participants who meet DSM-5 criteria for PTSD as confirmed by the Mini International Neuropsychiatric Interview (MINI), with a total PCL-5 score ≥ 33 at Screening and Baseline will be eligible for enrollment.

Approximately 270 participants will be randomized (2:1:2) to receive placebo, 0.3 mg JZP150, or 4 mg JZP150 to ensure that a minimum of 188 participants have 12 weeks of treatment data. Participants will be stratified by the presence or absence of concomitant use of selective serotonin reuptake inhibitor (SSRIs)/ serotonin norepinephrine reuptake inhibitor (SNRIs).

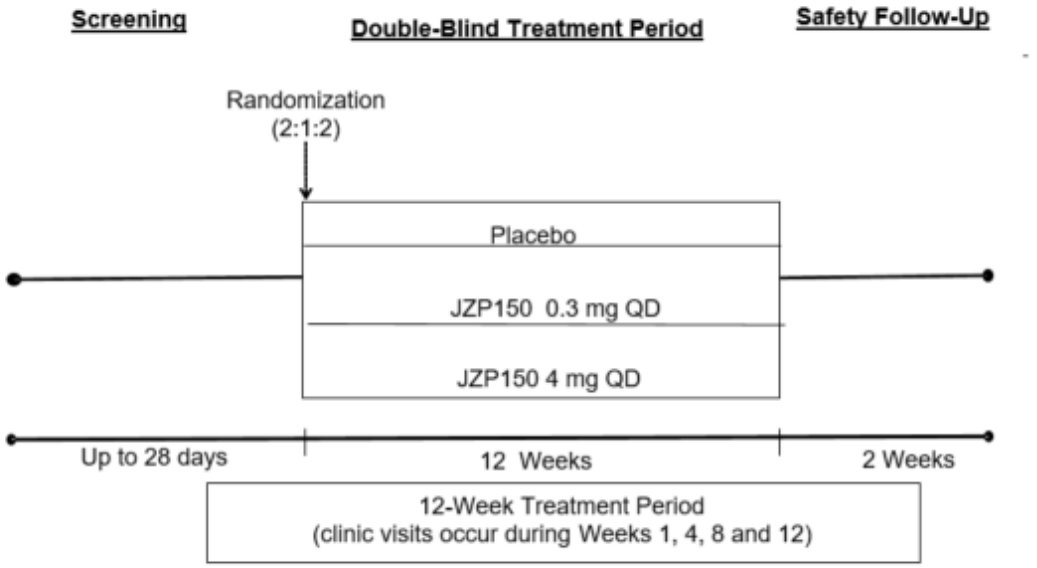
Overall Design:

Table 2: Overall Study Design

Overall Design	
Study Phase	2
Clinical Indication	PTSD
Study Type	Interventional
Type of Design	Randomized, parallel-group, multicenter. Participants will be stratified by the presence or absence of concomitant use of SSRIs/ SNRIs.
Type of Control	Placebo control
Study Blinding	Double-blind
Population	Participants who meet DSM-5 criteria for PTSD as confirmed by the MINI, with a total PCL-5 score ≥ 33 at Screening and Baseline to be eligible for enrollment.
Number of Participants	To account for a 30% dropout, approximately 270 participants will be randomized (2:1:2) to receive placebo, 0.3 mg JZP150, or 4 mg JZP150

Overall Design	
	to ensure that a minimum of 188 participants have 12 weeks of treatment data (Section 9).
Duration of Participation	Each subject will participate in the study from the time they sign the informed consent form (ICF) through the end of the study procedures/contact. The study comprises 3 phases: up to 28 days screening period followed by a 12-week double-blind treatment period and a 2-week safety follow-up. Each participant will be enrolled for approximately 18 weeks.
Number of Treatment Arms	3
Treatment Groups	Placebo, JZP150 (0.3 mg), JZP150 (4 mg)
Data Monitoring Committee	An independent data safety monitoring committee is not planned. An internal safety data review committee will review the accumulating safety data in a blinded manner.

1.2. Schema



QD = once daily.

1.3. Schedule of Activities (SoA)

Table 3: Schedule of Assessments

Procedure	Screening (up to 28 days)	Intervention Period (Weeks)								E/D[a]	Efficacy Follow-up[b] (Only conducted for participants that discontinue study intervention)	Safety Follow-up (14 days after last dose)	Notes
		Baseline/ Randomization -1[c]	1	2	4	6	8	10	12				
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	
Visit Window (days)			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**-5/+2**			**+5**	
Clinic Visits (end of week)	X	X	X		X		X		X	X	X	X	Week 8 clinic visit should be scheduled for the afternoon/evening; participants should dose at home in the morning on the day of the Week 8 clinic visit
Digital/Phone				X		X		X					
Informed consent	X												
Inclusion and exclusion criteria	X	X											
Demography	X												
Full physical examination including height, weight [redacted]	X	X			X		X		X	X			Height is collected at Screening only

Procedure	Screening (up to 28 days)	Intervention Period (Weeks)								E/D[a]	Efficacy Follow-up[b] (Only conducted for participants that discontinue study intervention)	Safety Follow-up (14 days after last dose)	Notes
		Baseline/ Randomization -1[c]	1	2	4	6	8	10	12				
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	
Visit Window (days)			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**-5/+2**			**+5**	
Medical history (includes substance use and legal claims/disability related to PTSD)	X												Substances: illicit drugs, alcohol, nicotine, caffeine, and cannabis
Past and current medical conditions	X												
Serum OR urine pregnancy test (WOCBP only)	X (S&U)	X(U)							X (U)	X (U)		X (U)	S = Serum U = Urine Urine pregnancy is conducted at the site via dipstick. A serum pregnancy test is also done at the central laboratory at Screening.
Laboratory assessments[d] (chemistry, hematology, urinalysi [redacted]	X	X	X		X		X		X	X		X	TSH is done at Screening only; HbA1c is done at Screening and Week 12. See Table 6 for details.
Triplicate 12-lead ECG	X	X	X		X		X		X	X			

Procedure	Screening (up to 28 days)	Intervention Period (Weeks)								E/D[a]	Efficacy Follow-up[b] (Only conducted for participants that discontinue study intervention)	Safety Follow-up (14 days after last dose)	Notes
		Baseline/ Randomization -1[c]	1	2	4	6	8	10	12				
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	
Visit Window (days)			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**-5/+2**			**+5**	
Urine drug screen	X	X	X		X		X		X	X			Conducted by the central laboratory at Screening and at the site via dipstick at visits subsequent to Screening.
Breath alcohol test	X	X	X		X		X		X	X			
Vital signs	X	X	X		X		X		X	X		X	Vitals can be repeated once at Screening and Baseline. See Section 8.3.2 for details.
Randomization		X											Stratified based on presence/absence of concomitant use of SSRI/SNRI
CAPS-5		X			X				X	X	X		
MINI	X												
Medication washout	X												Washout of prohibited medications if needed. Please refer to the Prohibited and Cautionary Medication Document for additional information.

Procedure	Screening (up to 28 days)	Intervention Period (Weeks)								E/D[a]	Efficacy Follow-up[b] (Only conducted for participants that discontinue study intervention)	Safety Follow-up (14 days after last dose)	Notes
		Baseline/ Randomization -1[c]	1	2	4	6	8	10	12				
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	
Visit Window (days)			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**-5/+2**			**+5**	
C-SSRS Baseline/Screening version	X												
C-SSRS Since last visit version		X	X	X	X	X	X	X	X	X	X	X	
CGI-S		X	X		X		X		X	X	X	X	
CGI-C					X				X	X	X	X	
PGI-S		X	X		X		X		X	X	X	X	
PCL-5	X	X	X		X		X		X	X	X	X	
LEC	X												
B-IPF		X							X	X			
ReQoL-10		X							X				
SDS		X			X				X	X			
PSQI-A		X	X		X		X		X	X		X	
ISI		X	X		X		X		X	X		X	
PHQ-9	X	X	X		X				X	X		X	
SIGH-A		X			X		X		X				

Procedure	Screening (up to 28 days)	Intervention Period (Weeks)								E/D[a]	Efficacy Follow-up[b] (Only conducted for participants that discontinue study intervention)	Safety Follow-up (14 days after last dose)	Notes
		Baseline/ Randomization -1[c]	1	2	4	6	8	10	12				
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	
Visit Window (days)			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**-5/+2**			**+5**	
Withdrawal scale (Marijuana withdrawal checklist)		X							X	X		X	
Pharmacogenomics		X											[redacted] Samples that are not collected at Baseline may be drawn at any subsequent visit.
Blood draws for PK			X				X		X				Week 12 PK sample post-dose should be collected after the collection of the CAPS-5 assessment. Refer to Section 8.5 for details.
Blood draws for AEA levels		X	X				X		X			X	Refer to Section 8.7 for details.
Administration of study intervention in clinic[c]			X		X				X				
Administration of study intervention at home				X		X	X	X					

Procedure	Screening (up to 28 days)	Intervention Period (Weeks)								E/D[a]	Efficacy Follow-up[b] (Only conducted for participants that discontinue study intervention)	Safety Follow-up (14 days after last dose)	Notes
		Baseline/ Randomization -1[c]	1	2	4	6	8	10	12				
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	
Visit Window (days)			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**-5/+2**			**+5**	
Provide light meal or snack	X	X	X		X				X	X			
Dispense study intervention		X[c]	X		X		X						
Collect study intervention/assess compliance			X		X		X		X	X			
Dispense and train on digital tool and medication adherence application		X											
Read expectancies script (placebo mitigation)	X	X	X		X		X		X	X			
Medication adherence application		X	X	X	X	X	X	X	X	X			
Intent to attend assessment		X	X	X	X	X	X	X					
Schedule/confirm next visit and or phone call	X	X	X	X	X	X	X	X	X	X			

Procedure	Screening (up to 28 days)	Intervention Period (Weeks)								E/D[a]	Efficacy Follow-up[b] (Only conducted for participants that discontinue study intervention)	Safety Follow-up (14 days after last dose)	Notes
		Baseline/ Randomization -1[c]	1	2	4	6	8	10	12				
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	
Visit Window (days)			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**-5/+2**			**+5**	
Phone call check-in				X		X		X					
AE review		X	←==========→							X		X	For medical occurrences that begin before the start of study intervention, but after obtaining informed consent, details are provided in Section 8.4.1.
SAE review[e]		X	←==========→							X		X	
Prior and concomitant medication review	X	X	←==========→							X	X	X	Screening visit: assess prior and concomitant medications; all subsequent visits include concomitant medication review only

Abbreviations. AE = adverse event; AEA = anandamide; B-IPF = Brief Inventory of Psychosocial Functioning; E/D = Early Discontinuation; CAPS-5 = Clinician Administered PTSD Scale version 5; CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; E/D = Early Discontinuation; [redacted] HbA1c = glycosylated hemoglobin; ISI = Insomnia Severity Index; LEC = Life Events Checklist; [redacted] MINI = Mini International Neuropsychiatric Interview; PCL-5 = Posttraumatic Checklist-5; PGI-S = Patient Global Impression of Severity; PHQ-9 =Patient Heath Questionnaire-9; PK = pharmacokinetics; PSQI-A = Pittsburgh Sleep Quality Index with PTSD Addendum; PTSD = posttraumatic stress disorder; ReQoL = Recovering Quality of Life; SAE = serious adverse event; SDS = Sheehan Disability Scale; SIGH-A = Structured Interview Guide for the Hamilton Anxiety Rating Scale; TSH = thyroid stimulating hormone; WOCBP= women of childbearing potential.

[a] The E/D visit is conducted for participants who prematurely discontinue from the study intervention and the study.

[b] The efficacy follow-up visit is conducted for participants who discontinue study intervention but remain in the study to complete scheduled assessments. For participants who discontinue study intervention early, every effort should be made to obtain an efficacy follow-up 12 weeks after first dose. An additional efficacy follow-up at 4 weeks is encouraged for participants who discontinue study intervention prior to Week 4. For those participants who discontinue study intervention but who otherwise continue in the study, the assessments included in these visits may be performed during the participants' safety follow-up visit if that efficacy follow-up is scheduled to occur within 2 after last dose of study intervention. This is meant to limit participant burden.

[c] Participants will be instructed to start taking study intervention the day following their Baseline visit, which will be Day 1. Study intervention will be taken in the morning without regard for food.

[d] Participants are required to fast for safety laboratory tests at the Baseline Visit (Visit 2), Week 1 (Visit 3), Week 4 (Visit 5), Week 12 (Visit 9), Early Discontinuation (Visit 10), if applicable, and Safety follow-up Visit (Visit 12). Participants are not required to fast for laboratory tests at the Screening Visit or Week 8 (Visit 7).

[e] All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (Section 8.4.3).

2. INTRODUCTION

Fatty acid amide hydrolase (FAAH) is the primary enzyme responsible for catabolism of the endocannabinoid anandamide (AEA) (Cravatt 1996), an endogenous ligand for the type-1 cannabinoid receptor (CB1). Inhibition of FAAH protects AEA from degradation leading to elevated levels of AEA (Kathuria 2003), and reduces fear and anxiety-related behaviors in rodents (Kathuria 2003; Patel and Hillard 2006; Haller 2009; Hill 2013; Bluett 2014; Haller 2014; Lomazzo 2015; Carnevali 2017).

JZP150 (previously known as PF-04457845) is an orally available, highly selective and irreversible inhibitor of FAAH (Ahn 2011; Johnson 2011; Bonifacio 2020). A recent investigator-sponsored, placebo-controlled study showed that JZP150 enhanced recall of fear extinction memory and blunted negative affect in response to an aversive stimulus in healthy volunteers (Mayo 2020). Another study revealed that JZP150 significantly increased slow wave sleep as measured by polysomnography and improved self-reported overall self-reported sleep compared to placebo in men with cannabis use disorder (CUD) (D'Souza 2019).

Taken together, results from previous studies in animals and humans suggest that FAAH inhibition with JZP150 may positively influence many of the core symptoms experienced by patients with posttraumatic stress disorder (PTSD).

2.1. Study Rationale

This is a 12-week, double-blind, placebo-controlled, randomized, parallel-group study of the safety and efficacy of JZP150 in the treatment of adult participants with PTSD. JZP150 is an orally available, highly selective and irreversible inhibitor of FAAH.

The purpose of this phase 2 study is to provide an evaluation of the efficacy and safety of JZP150 in participants with PTSD, while evaluating a broad range of JZP150 doses to support pharmacokinetic (PK)/pharmacodynamics (PD) exposure-response analysis. Results from this study will be used to inform the study design, patient population, and dose selection for future studies in PTSD.

Multiple preclinical and clinical studies have demonstrated the association between the endocannabinoid system and the underlying pathophysiology of PTSD, which JZP150 directly targets (ie, augmentation of AEA levels).

A double-blind, placebo-controlled experimental study examined the effect of JZP150 on experimentally induced fear conditioning and extinction, and stress response among healthy volunteers. Study participants on 4 mg JZP150 once daily (QD) compared to placebo had improved recall of fear extinction 24 hours later, and did not have the typical reduction in AEA in response to acute stress. Furthermore, those participants who were randomized to JZP150 had decreased stress-induced reactivity to emotional pictures demonstrating an attenuation of negative affect.

Results from previous studies in animals and humans suggest that FAAH inhibition with JZP150 may positively influence many of the core symptoms experienced by patients with PTSD.

2.2. Background

Posttraumatic stress disorder is a common psychiatric condition that can result from direct or indirect exposure to actual or threatened death, serious injury or sexual violence (APA 2013). Approximately 70% of the global population will experience a traumatic event at some point during their lifetime, the majority of whom will recover in the days and weeks following trauma exposure (Kessler 2017). However, 4.7% to 6.1% will go on to develop PTSD in the US (Goldstein 2016), with similar rates observed across European Union countries (0.6 to 6.7%) (Burri and Maercker 2014). While men are more likely to experience a traumatic event, women are twice as likely to develop PTSD (Goldstein 2016; Kessler 2017).

Posttraumatic stress disorder is characterized by symptoms experienced after a potentially traumatic event (Hoffman 2018). Symptoms of PTSD are grouped into 4 symptom clusters: 1) recurrent intrusion/re-experiencing; 2) persistent avoidance; 3) negative alterations in mood and cognition; and 4) marked arousal/reactivity. A traumatic event is defined as exposure to actual or threatened death, serious injury, or sexual violence that is either directly experienced, witnessed, learned about the occurrence to a loved one, or extreme or repeated exposure to aversive details through work (ie, first responders) (APA 2013). In addition to increased risk for mortality, PTSD also has a significant impact on how patients feel and function. Posttraumatic stress disorder impacts all aspects of patients' lives including negative impacts on work, school, relationships, housing, legal problems, financial problems and an overall increase in healthcare utilization and healthcare costs (Kessler 2017; Watson 2019).

Various guidelines exist for the treatment of PTSD (APA 2004; NICE 2018; VA/DoD 2003; ISTSS 2018), most of which include guidance for both psychological and pharmacological treatments. There is an urgent need to address a critical gap in the advancement of pharmacotherapy treatment for PTSD (Krystal 2017). Food and Drug Administration (FDA) -approved medications for PTSD are limited to 2 selective serotonin reuptake inhibitors (SSRIs): sertraline and paroxetine. Both are thought to reduce symptom severity of PTSD through the same mechanism of action with many patients experiencing residual symptoms. Due to limited efficacy of approved medications, many providers turn to polypharmacy and off-label use of medications in order to address the range of debilitating symptoms that comprise PTSD. These medications and combinations of medications have not been adequately studied. The last 20 years have been marked by a dearth of research into pharmacotherapies for PTSD despite a massive unmet medical need for a condition that results in significant morbidity and mortality.

The endocannabinoid system is a neuromodulatory system comprised of 2 G-protein-coupled receptors (CB1 and type 2 cannabinoid receptor), 2 major endogenous lipid ligands (AEA and 2-arachidonoylglycerol), and the enzymes involved in the synthesis and degradation of these lipid ligands (FAAH and monoacylglycerol lipase) (Hill 2018). Preclinical and translational work implicates the endocannabinoid system in the pathophysiology of PTSD and suggests the endocannabinoid system plays a critical role in stress responsivity, anxiety and fear extinction. Since FAAH is the primary enzyme responsible for the active degradation of AEA (Cravatt 1996), inhibition of FAAH represents a novel mechanistic approach for augmenting AEA levels at relevant brain circuits. Fatty acid amide hydrolase inhibition has been shown to reduce stress-induced anxiety and enhance the extinction of fear memory in animals (Kathuria 2003; Patel and Hillard 2006; Haller 2014; Hill 2013; Bluett 2014; Haller 2009;

Lomazzo 2015; Carnevali 2017) and humans (Hill 2009; Gunduz-Cinar 2013; Hauer 2013; Dincheva 2015; Harfmann 2020).

The PK of JZP150 has been characterized in 3 phase 1 studies in a total of 76 healthy adult volunteers after single- (dose range 0.1 to 40 mg) and multiple-dose (dose range 0.5 to 8 mg QD) oral administration. Absorption of JZP150 was rapid, reaching maximal plasma concentrations within an average of 2 hours post dose. Plasma concentrations of JZP150 post maximum plasma concentration (C_{max}) followed a multiphasic decline, with an estimated terminal half-life ($t_{½}$) ranging from approximately 12 to 23 hours. The steady-state of plasma concentrations was attained by Day 7 following QD administration for 14 days with an approximate 2 to 3× accumulation in exposure between Days 1 and 14. The exposures of JZP150 at steady-state appeared dose-proportional over the dose range of 0.5 to 8 mg following multiple dose administration; but supra-proportional increases in exposure were noted over a similar dose range of 0.1 to 10 mg following single oral administration. Proportional increase of exposures was observed in the dose range of 10 to 40 mg following single dose administration. No major food effects on the PK of JZP150 were observed using a tablet formulation. Examination of the relationship between FAAH inhibition and JZP150 plasma concentration suggests that concentrations of at least 1 ng/mL is required to maintain FAAH inhibition by at least 97%.

JZP150 has been evaluated in 7 sponsor-initiated interventional clinical studies to date. In these studies, a total of 108 healthy volunteers, 37 subjects with osteoarthritis and 8 subjects with PTSD have been administered 4 mg JZP150, which is the high end of the therapeutic dose range. There have been no deaths, serious adverse events (SAEs) or severe adverse events (AEs) in the completed sponsor-initiated interventional clinical studies in subjects who have received JZP150. The overall incidence and severity of AEs observed during these studies has been comparable to placebo. No maximum tolerated dose has been identified. There were no safety concerns suggested by laboratory values, vital signs, or electrocardiogram (ECG) data. Based on this experience, the overall safety and tolerance of JZP150 supports further clinical testing.

In addition, 73 participants have been dosed with JZP150 in investigator-initiated research studies where the sponsor has provided compound to investigators. The longest duration study has been a 28-day study evaluating JZP150 4 mg QD in subjects with CUD. There have been no deaths, SAEs or severe AEs apart from 1 incidence each of severe fatigue, dizziness, and headache reported in these investigator-initiated research studies.

A detailed description of the chemistry, pharmacology, efficacy, and safety of JZP150 is provided in the IB.

2.3. Benefit/Risk Assessment

A summary of the benefit-risk assessment for conducting study JZP150-201 is provided in the subsections below.

2.3.1. Risk Assessment

Participants who enroll in this study may encounter the following potential risks:

- Adverse events for participants in JZP150-201 are expected to be similar to those seen in previously conducted clinical studies with the high end of the dose range of JZP150 (ie, 4 mg). The most common treatment-emergent adverse events (TEAEs) that have occurred in ≥ 2participants on JZP150 and greater than placebo included headache, back pain, and dizziness. To date, JZP150 has been well-tolerated with an AE profile that is comparable to placebo. No deaths or SAEs have been reported in clinical studies with JZP150.

- Participants will be asked to discontinue prohibited medications to enter the study, including those medications that could affect the evaluation of PTSD symptoms and those related to the pharmacology of JZP150. There may be risks associated with abrupt discontinuation of some of these medications.
- Study procedure-related risks, including risks and/or discomfort associated with blood collection, ECGs, physical examinations, and completion of questionnaires and other assessments.

2.3.2. Benefit Assessment

Participants who enroll in this study may experience the following benefits:

- Receiving JZP150 for the study duration may alleviate the significant symptom burden associated with PTSD.

- Contribution to the process of developing new therapies in PTSD.
- Participants will receive comprehensive clinical exams and clinical monitoring associated with the study.
- A future a long-term open-label study may become available for participants that complete this study.

2.3.3. Overall Benefit: Risk Summary

Benefits to participants include the potential to receive a therapy, which may alleviate symptoms of PTSD, contribute to the development of new therapeutics in PTSD, as well as receiving comprehensive physical examinations and clinical monitoring.

Risks to all participants include those related to JZP150 and to blood collection and completion of clinical assessments and questionnaires. [redacted] The risks to subjects are expected to be similar to those seen in prior clinical studies, which are summarized in Section 2.2.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of JZP150 may be found in the IB and the informed consent document.

3. OBJECTIVES AND ESTIMANDS/ASSESSMENTS

Objectives	Estimands/Assessments
Primary	
To evaluate the efficacy of JZP150 administered once daily for up to 12 weeks at doses of 0.3 mg and 4 mg compared to placebo in the treatment of adults with PTSD, as measured by the change in CAPS-5 total symptom severity score.	The primary estimand is defined as follows: • **Treatment:** 0.3 mg and 4 mg of JZP150, and placebo. • **Population:** Participants with PTSD (as defined in the eligibility criteria). • **Variable (endpoint):** Clinician Administered PTSD Scale (CAPS-5) total symptom severity score change from Baseline to Week 12. • **Intercurrent events (ICEs):** the "treatment policy strategy" will address all ICEs. • **Population-level summary:** The mean change from Baseline to Week 12 in CAPS-5 total symptom severity score for each treatment group and the difference in means between each randomized treatment group compared to placebo.
Key Secondary	
To evaluate the efficacy of JZP150 administered once daily for 12 weeks at doses of 0.3 mg and 4 mg compared to placebo on overall clinician and patient global impression of severity.	The two key secondary estimands are defined as follows: Key Secondary Estimand 1: • **Treatment:** 0.3 mg and 4 mg of JZP150, and placebo. • **Population:** Participants with PTSD (as defined in the eligibility criteria). • **Variable (endpoint):** Change in Clinical Global Impression of Severity (CGI-S) from Baseline to Week 12. • **Intercurrent events (ICEs):** the "treatment policy strategy" will address all ICEs. • **Population-level summary:** The mean change from Baseline to Week 12 in CGI-S for each treatment group and the difference in means between each randomized treatment group compared to placebo.

Objectives	Estimands/Assessments
	Key Secondary Estimand 2: • **Treatment:** 0.3 mg and 4 mg of JZP150, and placebo. • **Population:** Participants with PTSD (as defined in the eligibility criteria). • **Variable (endpoint):** Change in Patient Global Impression of Severity (PGI-S) from Baseline to Week 12. • **Intercurrent events (ICEs):** the "treatment policy strategy" will address all ICEs. • **Population-level summary:** The mean change from Baseline to Week 12 in PGI-S for each treatment group and the difference in means between each randomized treatment group compared to placebo.
Secondary	
To evaluate the efficacy of JZP150 administered once daily for 12 weeks at doses of 0.3 mg and 4 mg compared to placebo on functional outcomes and patient reported symptoms in adults with PTSD	All other secondary and exploratory estimands are defined using the same estimand attributes (treatment, population, ICEs, and population-level summary, difference in means or proportions between each randomized treatment and placebo, as appropriate) as described above. The variables (endpoints) for the estimands are: • Responder analysis defined in 3 separate ways: o Percent of participants with ≥ 30% improvement on the CAPS-5 total symptom severity score from Baseline to Week 12 o Percent of participants who are very much or much improved on the CGI-C at Weeks 4 and 12 o Percent of participants with ≥ 1 unit of improvement on the PGI-S from Baseline to Week 12 • CAPS-5 total symptom severity score change from Baseline to Week 4. • Change in functional outcomes measured by the Brief Inventory of Psychosocial

Objectives	Estimands/Assessments
	Functioning (B-IPF) and Sheehan Disability Scale (SDS) from Baseline to Week 12. • Change in patient-reported symptoms of PTSD as assessed by the PTSD Checklist (PCL-5) from Baseline to Week 1, 4, 8, and 12. • Change in patient and clinician-reported symptoms of PTSD as assessed by the PGI-S, and CGI-S from Baseline to Weeks 1, 4, and 8. • Change in self-reported sleep problems as measured by the Insomnia Severity Index (ISI) and Pittsburgh Sleep Quality Index-PTSD Addendum (PSQI-A) from Baseline to Week 12. • Change in PTSD symptom clusters (intrusive symptoms, avoidance symptoms, arousal/reactivity symptoms, and negative alterations in mood and cognition) as assessed by the change in the subscales of the CAPS-5 from Baseline to Week 4 and Week 12. • Change in mood and anxiety from Baseline to Weeks 1, 4, and 12 as assessed by the Patient Health Questionnaire (PHQ-9), and change from Baseline to Weeks 4, 8, and 12 on the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A). • Change in quality of life from Baseline to Week 12 as measured by the Recovering Quality of Life (ReQoL).
To evaluate the safety and tolerability of JZP150 administered once daily for up to 12 weeks at doses of 0.3 mg and 4 mg in adults with PTSD.	The safety of JZP150 will be evaluated by the following assessments: • AEs • Vital signs • Physical examinations [redacted] • 12-lead ECG

Objectives	Estimands/Assessments
	• Clinical laboratory tests (chemistry, hematology, urinalysis [redacted] • Columbia Suicide Severity Rating Scale (C-SSRS) • Withdrawal scale (marijuana withdrawal checklist)
To characterize the PK and PD of JZP150 in adults with PTSD using population PK modeling and simulation methodology.	Plasma concentration of AEA, JZP150 and its metabolites
[redacted]	
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a 12-week, multicenter, double-blind, placebo-controlled, randomized, parallel-group study of the safety and efficacy of JZP150 in the treatment of adult participants with PTSD.

Participants who meet Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for PTSD as confirmed by the Mini International Neuropsychiatric Interview (MINI), with a total PCL-5 score ≥ 33 at Screening and Baseline will be eligible for enrollment.

Following screening, eligible participants will be randomized (2:1:2) to 1 of 3 treatment arms: placebo, JZP150 0.3 mg QD, or JZP150 4 mg QD. Randomization will be stratified based on presence versus absence of use of stable selective SSRIs/ serotonin norepinephrine reuptake inhibitors (SNRIs) at Screening. The sponsor, study investigators, clinical raters, and participants will be blinded to treatment assignment.

The study will consist of the following periods:

- Screening period and washout of prohibited medications (up to 28 days).
- Baseline and randomization (Day -1).
- Double-blind Treatment Period (12 weeks).
- Safety follow-up (2 weeks).

Assessments of efficacy, safety, and PK will be conducted as indicated in Section 8.2 , Section 8.3, and Section 8.5, respectively, and as described in the Schedule of Activities (SoA) (Section 1.3). Study visits will be done in the clinic and with telephone call check-ins conducted between clinic visits.

An independent data safety monitoring committee is not planned. An internal safety data review committee will review the accumulating safety data in a blinded manner (see Section 10.1.5 for details).

4.2. Scientific Rationale for Study Design

A 12-week, placebo-controlled, parallel-group, fixed-dose design of placebo and 2 doses of JZP150 was selected for the following reasons: 1) data obtained from this study design will inform the development, design, and dose selection for a phase 3 trial; 2) this study design has the potential to identify a no-effect or minimally effective dose and will characterize the efficacy and safety at the highest dose intended for clinical use and inform exposure-response; 3) this study and choice of control is in accordance with ICH E6(R2) and E10 guidelines; 4) the use of only 2 active treatment arms is expected to minimize placebo-related expectancy effects; 5) the 12-week double-blind treatment duration was chosen to maximize active-placebo differences. The scientific rationale for key study design elements is provided below.

Stratification Elements

Randomization will be stratified by the presence or absence of concomitant use of SSRIs/SNRIs. Many PTSD patients are being treated with SSRI/SNRI medications and this enrollment strategy

is therefore reflective of the real-world patient populations. This enrollment strategy will permit assessment of safety and efficacy in both users and non-users of these antidepressants.

Posttraumatic stress disorder diagnosis and severity of condition

The PCL-5 cut score of ≥ 33 was selected for the following reasons: 1) The PCL-5 is a 20-item patient report measure that assesses the 20 DSM-5 symptoms of PTSD (Weathers 2013) and has a dynamic range of 0-80. The PCL is one of the most widely used self-report measures of PTSD and has strong internal consistency, test re-test reliability, and convergent and discriminant validity (Blevins 2015; Bovin 2016); 2) A PCL-5 total score ≥ 33 ensures patients are reporting significant symptoms especially as individuals may be enrolled that are currently on SSRIs/SNRIs and will minimize and potential "floor" effects; 3) The use of the PCL-5 limits the potential confounding factor of determining eligibility criteria using the same assessment that is used for the primary endpoints. The use of the PCL-5 to determine minimum symptom severity reduces this confound while using a measure that is valid and reliable with a strong correlation to total CAPS-5 scores (Weathers 2018); 4) Prior work has demonstrated that scores between 31 and 33 are optimally efficient for diagnosing PTSD (Bovin 2016). Based on this range, the specific cut of ≥ 33 was selected as a conservative score based on this prior work, and from feedback obtained from PTSD clinical experts. 5) Relative to the CAPS-5, the PCL-5 is anticipated to minimize therapeutic alliance placebo effects.

Study Duration

The 12-week duration was selected for 3 main reasons. First, review of prior PTSD studies using the CAPS (CAPS-2 and CAPS-IV) efficacy endpoint have demonstrated a substantial placebo response. The pattern of this response shows a rapid increase in the mean placebo response from baseline to Week 4. After Week 4, the slope (Change in CAPS score vs. time) of this placebo response decreases, but the response continues to increase through Week 8. Between Week 8 and Week 12 the placebo response slope plateaus and in some cases the response decreases. This pattern has been observed in PTSD trials with sertraline and paroxetine. Based on this pattern of placebo response observed in prior PTSD trials, 12 weeks of treatment provides the best chance to observe separation between placebo and JZP150. Second, pivotal confirmatory trials will require at least 12 weeks of treatment. Therefore, setting up a phase 2 study with the same treatment duration de-risks phase 3. Third, 12-week treatment duration allows for maximizing the time between CAPS-5 assessments.

Study Endpoints

The primary efficacy assessment of this study is the CAPS-5, a structured clinical interview of patient reported severity of symptoms. The CAPS-5 is a well-established and validated assessment that captures DSM-5 symptoms of PTSD and is sensitive to treatment change. In addition, the key secondary endpoints (CGI-S and PGI-S) and exploratory endpoints are included to support and corroborate the clinical relevance of the primary endpoint.

Clinic Visits/Telephone Calls and Study Assessments (Frequency of Collection)

The primary evaluation for efficacy will be at the end of Week 12. A clinic visit is planned at Week 1 in order to conduct an early in clinic safety assessment and to ensure participants are dosing appropriately. This Week 1 assessment will also provide insight into the onset of effect with the assessment of the CGI-S, PGI-S and PCL-5 at this time point. A clinic visit will be

conducted at the end of Week 4 in order to allow for an evaluation of efficacy (including CAPS-5) and safety. The timing and number of administrations of the CAPS-5 has been carefully considered. Due to the therapeutic alliance that occurs with the administration of the CAPS-5, and the effect this can have on an already high placebo response rate, we have developed a CAPS-5 administration schedule to minimize the number of CAPS-5 administrations during the study and to maximize the time between administrations. For this reason, the CAPS-5 is conducted only at Baseline, Week 4, and Week 12. A clinic visit at the end of Week 8 is also included for safety assessments, secondary efficacy assessments, sparse PK sampling and study intervention dispensation.

4.3. Justification for Dose

A low dose of 0.3 mg QD and high dose of 4 mg QD were selected for this phase 2 study. The selection of doses of JZP150 for use in PTSD was based on data assessing brain receptor occupancy in a positron emission tomography (PET) study conducted in healthy volunteers (Boileau 2015), PD data (ie, peripheral FAAH inhibition and elevation of plasma AEA concentrations) from clinical studies, and overall safety data. Clinical studies contributing data towards dose selection included single ascending and multiple ascending dose trials in healthy volunteers, a study conducted in participants with osteoarthritis of the knee, and a study in participants with CUD (D'Souza 2019).

The inclusion of the 4 mg JZP150 dose is based on data obtained from PET imaging studies, the multiple ascending dose study, healthy volunteer fear conditioning trial and clinical studies in patients with osteoarthritis of the knee and CUD and the safety data obtained in studies conducted to date. Positron emission tomography imaging studies using a selective radioligand for imaging of brain FAAH binding availability conducted in healthy volunteers have shown JZP150 exhibits good brain penetration and selectively binds to FAAH yielding > 95% FAAH inhibition at single doses of 1, 4, and 20 mg (Boileau 2015; Rusjan 2018). In the PET study, doses of JZP150 were administered after completion of the baseline scan and approximately 2 hours before the start of the blocking scan. JZP150 doses lower than 1 mg were not tested in this study and therefore the FAAH competitive binding dose-response was not established for doses lower than 1 mg.

The 4 mg dose has shown therapeutic effects on fear extinction learning in a fear condition model conducted in healthy volunteers and this study data supports dose selection for this phase 2 study. Data from studies conducted in participants with osteoarthritis of the knee, and participants with CUD (D'Souza 2019) at daily doses of 4 mg JZP150 showed average plasma AEA concentrations of 2.5 to 3 ng/mL. In the multiple ascending dose study in healthy volunteers, among those who received 4 mg JZP150 QD, individual plasma AEA concentrations at steady-state ranged from 2 to 4 ng/mL. A high dose of 4 mg JZP 150 QD is therefore selected for the planned phase 2 study and is expected to yield at least 97% FAAH inhibition and result in target plasma AEA concentrations higher than 2 to 2.5 ng/mL for the majority of participants. Moreover, based on the PET imaging study (Boileau 2015), doses higher than 4 mg are not expected to result in greater FAAH inhibition and subsequent higher plasma AEA levels. To date, single doses of JZP150 up to 40 mg, and repeated daily doses up to 8 mg, have been administered to healthy volunteers. Multiple daily doses of 4 mg have been administered for up to 30 days in patients with osteoarthritis and CUD. Overall JZP150 has been shown to be

well-tolerated with an AE profile comparable to placebo and no AEs suggesting a dose relationship were reported. In addition, no AEs related to abuse potential, cognitive impairment, or clinically meaningful changes in labs, vital signs, or ECGs were observed. Moreover, the exposure multiples across all the completed nonclinical safety studies indicate acceptable safety margins between the no-observed-adverse-effect levels (NOAELs) obtained in animals and the anticipated maximum human exposure at 4 mg QD.

In single dose administration of 0.3 mg, JZP150 plasma levels were not above 1 ng/mL during most of the 24 hour period post dose; however, multiple dose administration of 0.5 mg QD resulted in mean plasma concentration levels in the 1 to 2 ng/mL range. Thus, based on these data and the observed between-subject variability, the 0.3 mg dose administered QD is not expected to maintain JZP150 plasma concentrations consistently above the threshold of 1 ng/mL to sustain the AEA levels at the target concentration above 2 to 2.5 ng/mL in most study participants. Therefore, the 0.3 mg dose should provide a means to identify a no-effect or minimally effective dose. Additionally, PTSD patients may have increased activity of FAAH and reduced levels of baseline AEA, and therefore may require higher AEA elevations compared with healthy volunteers. The 0.3 mg dose will also provide a low end of a broad range of concentrations to explore exposure-response.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last visit of the last participant remaining in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 to 70 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants must be outpatients with a primary diagnosis of DSM-5 defined PTSD confirmed by the MINI at Screening.
3. PCL-5 total score ≥ 33 at Screening and Baseline.
4. PTSD must be the primary diagnosis. Participants with comorbid diagnoses of major depressive disorder (with the exception of current severe symptoms), persistent depressive disorder (previously known as dysthymia), generalized anxiety disorder, specific phobia, obsessive compulsive disorder (with the exception of severe symptoms), or social anxiety disorder, are eligible if PTSD is the primary diagnosis.
5. Participants prescribed an SSRI or SNRI must be on a stable dose for at least 8 weeks prior to screening with no plan to change dose or treatment regimen during the course of the trial. Those not on an SSRI/SNRI at screening may not start treatment with a SSRI/SNRI during the course of the study. See Section 6.8.1 for details.

Weight

6. Body Mass Index (BMI) from 18 to 40 kg/m^2 (inclusive).

Sex and Contraceptive/Barrier Requirements

7. Participant is male or female

a. Male participants:

Male participants are eligible to participate if they agree to the following during the study intervention period and for at least 30 days after the last dose of study intervention:

- Refrain from donating sperm

  PLUS, either**:**

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception as detailed below
  - Agree to use a male condom with female partner use of an additional highly effective contraceptive method with a failure rate of < 1% per year as described in Appendix 5 OR should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant during exposure to study intervention and for 30 days after the last dose. Male participants with female partners must agree to use double-barrier methods if the female is using oral contraception. Agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

b. Female participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
  - Is a woman of non-childbearing potential (WONCBP) as defined in Appendix 5.

    OR

  - Is a woman of childbearing potential (WOCBP) and using a contraceptive method that is highly effective, with a failure rate of < 1%, as described in Appendix 5 during the study intervention period and for at least 30 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention. Female participants must agree to use double-barrier methods if the female is using oral contraception.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) at Screening and Baseline before the first dose of study intervention, see Section 8.3.5.
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

8. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
9. Willing to provide contact information for at least 1 additional person the study team may contact.
10. Willing and able to comply with the study schedule and other requirements.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

Physical Health Conditions

1. History or presence of gastrointestinal (including prior bariatric bypass surgery), or any other condition that, in the opinion of the investigator, may interfere with absorption, distribution, metabolism, or excretion of drugs.
2. Evidence of unstable or clinically significant systemic illness at screening including, but not limited to, the following:
    a. Cardiovascular disease (eg, unstable angina or congestive heart failure, chronic ventricular arrhythmia, uncontrolled hypertension, systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 90 mmHg [at screening or baseline], or QT interval corrected using Fridericia's formula [QTcF] > 450 msec for men and > 470 msec for women);
    b. Respiratory disease (eg, chronic obstructive pulmonary disease requiring oxygen therapy or hospitalization in the last year);
    c. Neurologic disease (eg, adulthood seizure disorders);
    d. Hepatic disease (eg, hepatitis B or hepatitis C viral infection);
    e. Renal disease;
    f. Immunodeficiency (eg, human immunodeficiency virus infection);
    g. Malignancy diagnosed within 5 years prior to screening, with the exception of adequately treated localized skin cancer (basal cell or squamous cell carcinoma) or carcinoma in-situ of the cervix.
3. Female participants who are pregnant, trying to become pregnant, nursing, or lactating and/or have a positive serum/urine human chorionic gonadotropin (hCG) test at Screening/Baseline, respectively.

4. History or presence of acute or unstable medical condition, behavioral or psychiatric disorder (other than PTSD), or surgical history that could affect the safety of the participant or interfere with study efficacy, safety, PK assessments, or the ability of the participant to complete the trial based on the judgment of the investigator.

Mental Health Conditions

5. Any suicidal behavior in the past 2 years as assessed on the C-SSRS or active suicidal ideation in the past 6 months defined as endorsing item 4 or 5 on the C-SSRS.
6. History or current bipolar disorder, bipolar related disorders, active psychotic symptoms, schizophrenia, schizophrenia spectrum disorders, according to DSM-5 criteria.
7. A recent major depressive episode (onset within the past 6 months) by history or a diagnosis of current severe symptomatic Major Depressive Disorder as assessed by the MINI and a PHQ-9 score > 20 at Screening.

Trauma-related Factors

8. Ongoing exposure to a traumatic event or exposure to a traumatic event <3 months prior to Screening.
9. Index event that occurred > 12 years prior to screening.
10. Index event is combat trauma (combat within a war zone).
11. Receiving disability payments because of PTSD or any other psychiatric disorders.
12. Engaged in litigation whereby personal compensation could be gained from having prolonged symptoms of PTSD or any other psychiatric disorder.
13. Individual meets criteria for dissociative subtype of PTSD as defined by DSM-5.

Substance Use

14. Current or recent (within the past 6 months) diagnosis of a substance use disorder (including cannabis use disorder) based on DSM-5 criteria with the following exceptions and limitations
    a. Caffeine use disorder (limitation: see exclusion #16 below)
    b. Tobacco use disorder (limitation: see exclusion #17 below)
    c. Mild alcohol use disorder (as defined by DSM-5 criteria)
15. Current, recent (within the past 6 months), or seeking treatment for a substance-related disorder. The use of Narcotics Anonymous/ Alcoholics Anonymous is acceptable if being used for maintenance of sobriety.
16. Inability to limit caffeine use to ≤ 600 mg/day throughout the study.
17. Inability to abstain from nicotine products during normal sleep periods.
18. Current (past 6 months) regular use of cannabis is excluded. Sporadic recreational users of cannabis can complete a repeat urine drug screen during the Screening period.

If this is negative, the participant may be allowed to enter the study pending agreement to completely refrain from the use of cannabis during the course of the study.

Prior/Concomitant Therapy

19. Participants who plan to begin or are currently enrolled in, an evidence-based psychotherapy for the treatment of PTSD. Examples include: prolonged exposure; cognitive processing therapy; trauma-focused cognitive behavioral therapy; eye movement desensitization and reprocessing therapy; Skills training in affective and interpersonal regulation; Concurrent treatment of PTSD and substance use disorders using prolonged exposure, or an evidence-based digital therapeutic for the treatment of PTSD or associated symptoms (eg, Nightware).
20. Use of prohibited prescription and/or non-prescription drugs and other products. See Section 6.8 for details.

Prior/Concurrent Clinical Study Experience

21. Prior exposure to JZP150 (previously known as PF-04457845) or participation in a prior clinical trial of PF-04457845.
22. Received an investigational drug in the past 30 days or 5 half-lives prior to Screening (whichever is longer), or plans to use an investigational drug (other than the study intervention) during the study.

Diagnostic Laboratory Assessments

23. Clinically significant abnormal laboratory values as assessed by the investigator (clinical chemistry, hematology, and urinalysis), including creatinine clearance (CrCL) < 60 mL/min per Cockcroft-Gault Equation, total bilirubin > 1.5 × upper limit of normal (ULN) (isolated), alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 × ULN (isolated), or ALT or AST > 1 × ULN and have a total bilirubin > 1 × ULN. An isolated total bilirubin > 2 × ULN attributable to known Gilbert syndrome is not exclusionary. Note: Screening laboratory tests may be repeated 1 time.
24. Urine drug screen positive at screening for cocaine, amphetamines, methamphetamine, barbiturates, benzodiazepines, opioids, methadone, THC, MDMA, PCP, LSD, except for prescribed drugs at Screening that will be washed out prior to Baseline.
25. Positive alcohol breath test at screening.

Other Exclusions

26. Does not agree to refrain from consumption of food/food products containing seville oranges, grapefruit, pomelos, tangelos, or grapefruit hybrids from 2 weeks before the start of study intervention until after the final dose.

27. Allergy or sensitivity to any ingredients in the study intervention formulation or placebo.
28. Any other condition and/or situation that causes the investigator or medical monitor to deem the participant unsuitable for the study.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

1. Refrain from consumption of food/food products containing seville oranges, grapefruit, pomelos, tangelos, or grapefruit hybrids from 2 weeks before the start of study intervention until after the final dose.

5.3.2. Caffeine, Alcohol, and Tobacco

As noted in exclusion criteria 14 through 18 (Section 5.2), participants are excluded from the study for the following criteria:

1. Current or recent (within the past 6 months) diagnosis of a substance use disorder (including cannabis use disorder) based on DSM-5 criteria with the following exceptions and limitations
    a. Caffeine use disorder (limitation: see exclusion #16, above)
    b. Tobacco use disorder (limitation: see exclusion #17, above)
    c. Mild alcohol use disorder (as defined by DSM-5 criteria)
2. Current, recent (within the past 6 months), or seeking treatment for a substance-related disorder. The use of Narcotics Anonymous/ Alcoholics Anonymous is acceptable if being used for maintenance of sobriety.
3. Inability to limit caffeine use to ≤ 600 mg/day throughout the study.
4. Inability to abstain from nicotine products during normal sleep periods.
5. Current (past 6 months) regular use of cannabis is excluded. Sporadic recreational users of cannabis can complete a repeat urine drug screen during the Screening period. If this is negative, the participant may be allowed to enter the study pending agreement to completely refrain from the use of cannabis during the course of the study.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to receive study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (ie, reason for screen failure), eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Individuals may not rescreen for eligibility criteria related to PTSD diagnostic status or the severity of their PTSD (eg, PCL-5 score). Rescreened participants should be assigned a new participant number for every screening/rescreening event.

5.5. Criteria for Temporarily Delaying Administration of Study Intervention Administration

As indicated in Section 6.5 , dose modifications are not permitted. See Section 7.1 for details regarding temporary interruption of study intervention.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention/treatment is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s)/Treatment(s) Administered

Participants will be instructed to take study intervention in the morning QD without regard for food. The study interventions planned for use in this study are described in Table 4 below.

Table 4: Study Treatment/Intervention

Treatment Arm	Intervention/Treatment Name	Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Use	Sourcing	Packaging	Labeling	Storage Conditions
1	Placebo	Capsule	Placebo	QD	Oral	Placebo	Provided centrally by the Sponsor	Bottles with 30 capsules/ bottle	Double-blind	[redacted]
2	JZP150	Capsule	0.3 mg	QD	Oral	Experimental	Provided centrally by the Sponsor	Bottles with 30 capsules/ bottle	Double-blind	
3	JZP150	Capsule	4 mg	QD	Oral	Experimental	Provided centrally by the Sponsor	Bottles with 30 capsules/ bottle	Double-blind	

Abbreviations: mg = milligram; QD = once daily.

6.2. Preparation/Handling/Storage/Accountability

Further guidance and information for the final disposition of unused study interventions are provided in the Investigator Trial Site Binder.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. Details regarding dispensation and storage requirements for study intervention are provided in the pharmacy manual.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants who sign the ICF will receive a participant number. The participant number identifies the participant for all study procedures that occur throughout the study. This number is unique and once assigned, cannot be reassigned to another study participant.

Treatment allocation/randomization for this study will occur centrally through the use of an interactive response technology (IRT). Following screening, eligible participants will be randomized (2:1:2) to one of three treatment arms: placebo, JZP150 0.3 mg QD, or JZP150 4 mg QD. Randomization will be stratified based on presence versus absence of stable use of SSRIs/SNRIs at Screening. The sponsor, study investigators, study coordinators, site staff, clinical raters, and participants will be blinded to treatment assignment.

A double-blind approach will be used throughout the 12-week treatment period. During the study, the number of capsules taken each day will be the same for participants randomized to each treatment and JZP150 and placebo capsules will look and feel identical.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant.

If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable. The participant's treatment assignment may be unblinded for regulatory reporting purposes. Notification of the treatment assignment is only made known to those who require it for safety reporting and submission processes. All other individuals involved in the study, including the investigator, will

remain blinded to treatment assignment. Participants for whom the blind is broken for this reason will not be withdrawn from the study.

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

6.4. Study Intervention/Treatment Compliance

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned capsules, etc. during the site visits and documented in the source documents and case report form (CRF) or other electronic device as applicable. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of JZP150 dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for study intervention delays should also be recorded in the CRF or other electronic device as applicable.

This study will use a medication adherence monitoring platform for all participants in the study. The Platform is provided on a smartphone application to confirm ingestion of study intervention. Built-in reminders and a communication system allow real-time intervention in case of missed doses. Other features such as visit reminders, study-specific instructions, and questionnaires may be included.

6.5. Dose Modification

No dose adjustments or modifications will be allowed. Participants who cannot tolerate their assigned fixed dose of JZP150 will be discontinued from the study intervention (see Section 7.1).

6.6. Continued Access to Study Intervention After the End of the Study

No immediate long-term study is planned. A future a long-term open label study may become available for participants that complete this study.

6.7. Treatment of Overdose, Medication Errors, or Misuse

Any dose greater than the assigned QD dosing will be considered an overdose. In a case of an acute overdose, there is no specific antidote but treatment should consist of general supportive measures. See the JZP150 IB for further details.

In the event of an overdose, the investigator/treating physician should:

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until at least 14 days after the last dose of study intervention.

- Document the quantity of the excess dose as well as the duration of the overdose.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Psychoactive medications that could affect the evaluation of symptoms of PTSD (with the exception of insomnia symptoms) are prohibited within a time period prior to Baseline, corresponding to at least 5 half-lives of the drug(s) or planned use of such drug(s) at some point throughout the duration of the study. Psychoactive medications that do not affect the evaluation of PTSD symptoms (including psychoactive medications used to manage insomnia) should be stable for at least 6 weeks prior to Screening and remain stable over the course of the trial with the exception of SSRI/SNRIs which is described in detail in Section 6.8.1, below.

For details on prohibited and cautionary medications please refer to the Prohibited and Cautionary Medication document that has been provided.

Prohibited/cautionary medications and other products include the following. Note: An example list of prohibited/cautionary medications is provided in the Investigator Trial Site Binder:

Prohibited:

- Prescription or nonprescription drugs or other products (eg, St. John's Wort) known to be strong or moderate inducers of CYP3A4, which cannot be discontinued at least 4 weeks before baseline, or planned use at any time during the study.
- Use of prescription or nonprescription drugs or other products (eg, grapefruit, grapefruit juice, or Seville oranges) known to be strong or moderate inhibitors of CYP3A4, which cannot be discontinued 2 weeks or 5 half-lives, whichever is longer, before baseline or planned use at any time during the study.

Cautionary:

- Use of prescription drugs that are CYP3A4 substrates at any time during the study.

6.8.1. Use of Concomitant SSRIs/SNRIs

Participants who are stable on SSRI/SNRIs as well as those not on concomitant SSRI/SNRIs at Screening may be enrolled in the study, as follows:

- Participants on an SSRI/SNRI at Screening may stay on the SSRI/SNRI as long as the following criteria are met: (1) the SSRI/SNRI is not a prohibited medication (eg,

fluvoxamine; see the prohibited medication list in the Investigator Trial Site Binder), (2) the dosing regimen remains stable with no plans to change during the course of the trial, and (3) the PTSD severity criteria outlined in the eligibility criteria (Section 5) are still met. The use of tricyclic antidepressants are prohibited.

- Participants not on an SSRI/SNRI at screening will also be enrolled as long as treatment with an SSRI/SNRI is not initiated during the course of treatment.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation from study intervention does not represent discontinuation from the study (Section 7.2). Participants may discontinue from study intervention at any time for any reason, or at the discretion of the investigator. In addition, a participant may be withdrawn from study intervention by the investigator or sponsor for safety, behavioral, compliance, and/or administrative reasons.

For participants that discontinue study intervention, all effort should be made to complete the procedures listed in the Early Discontinuation Visit, Efficacy Follow-up Visit (if applicable), and Safety Follow-up Visit (Section 1.3). If the participant does not withdraw from the study, continue to follow the participant as detailed in the SoA (Section 1.3).

7.1. Discontinuation of Study Intervention

In some instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will be requested to remain in the study and be asked to complete a 12-week efficacy follow-up. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed. Every effort should be made to have the participant attend an Early Discontinuation Visit and the Week 12 efficacy follow-up. For those participants who discontinue study intervention prior to Week 4, every effort should be made to have the participant complete the efficacy follow-up at Week 4 and Week 12 (see Section 1.3).

A participant must be discontinued from study intervention for any of the following reasons, or if they meet protocol stopping criteria:

- The participant requests to discontinue study intervention.
- The participant has an AE that may compromise the participant's continued participation.
- The participant has a suicide risk reported or assessed by the C-SSRS that requires intervention (Section 8.3.6).
- The participant has a positive pregnancy test (Appendix 5 and Section 8.4.5).
- The participant is noncompliant with study intervention or procedures.
- The participant meets the liver chemistry stopping criteria (Section 7.1.1).
- The participant meets the QTc stopping criteria (Section 7.1.2).
- [redacted]
- The sponsor decides to terminate the study prior to completion.
- The investigator determines the participant should not continue on study intervention.

7.1.1. Liver Chemistry Stopping Criteria

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in Appendix 7 or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

7.1.2. QTc Stopping Criteria

If a clinically significant finding is identified in a particular study participant (including, but not limited to a measured QT interval corrected using QTcF of > 500 msec) after enrollment and confirmed with a repeat (second) ECG, the investigator or qualified designee will discontinue the participant from the study and arrange for appropriate follow-up, including repeat ECGs as indicated. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.3. [redacted]

[redacted]

7.1.4. Temporary Discontinuation/Study Intervention Interruption

If a participant must temporarily interrupt study intervention for any reason, the Medical Monitor should be consulted to determine whether the participant will continue in the study.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.

If the participant is discontinued from study intervention, they will be asked to continue with follow-up efficacy visits. In this case, the participant will undergo the efficacy follow-up, as shown in the SoA (Section 1.3) and described in Section 7.1.

If the participant is discontinued both from the study intervention, which will be returned to the clinical site, and from the study, an early discontinuation visit should be conducted (if possible) at the time of discontinuation, as shown in the SoA (Section 1.3). Refer to the SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible.
- The site must counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). After trying to contact the participant, the investigator should reach out to the contact provided by the participant. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study and lost to follow-up.
  - The participant is not considered lost to follow-up until the last scheduled visit for that individual participant.
  - The amount of missing data for an individual participant will be managed via the data handling guidelines for the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Study and Site Start and Closure Section 10.1.9.

8. STUDY ASSESSMENTS AND PROCEDURES

Efficacy, safety, PK/PD sampling will be collected during clinic visits as outlined in the SoA. In addition, telephone calls will be conducted between clinic visits in order to (1) assess safety and (2) maintain engagement with the participants to mitigate attrition rates which are high in this patient population.

Study procedures and their timing are summarized in the SoA (Section 1.3).

For clinic visits, participants should check-in to the study site in the morning, with the exception of the Week 8 visit, which should be scheduled for the afternoon/ evening. Participants should dose at home in the morning on the day of the Week 8 clinic visit. The investigator may opt to have the participant attend an unscheduled visit, if deemed necessary, at any time during the study. Some clinic visits may be shortened and/or conducted remotely, if required due to the COVID-19 (or other) pandemic, and with approval from the Sponsor's Medical Monitor, as noted in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

All screening evaluations must be completed by the principal investigator (PI) or sub-investigator and reviewed to confirm that potential participants meet all eligibility criteria. The investigator should maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

After screening procedures have been completed and eligibility criteria have been confirmed, eligible participants will be provided with instructions on how to discontinue any excluded medications. It should be documented that the investigator has determined that discontinuation is safe and medically appropriate, and the discontinuation is medically supervised. The medical monitor should be contacted if there are any questions regarding discontinuation of excluded medications.

For clinical outcome assessment measures that are rated by specially qualified and trained interviewers/raters, the same person should perform each assessment for the same participant throughout the duration of the study, whenever possible.

The CAPS-5 assessment will be administered and scored by a trained rater at the site throughout the study. Raters are defined as clinical site personnel (eg, a physician, clinical psychologist, or nurse) who must have undergone the required training in administration and scoring of the CAPS-5 and received certification to administer the CAPS-5. Appropriate training for rating scales will be provided by the rater training vendor. Documentation of how and when data are filed, stored and transmitted to or from the study site will be provided in the Investigator Trial Site Binder.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Pharmacokinetic results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded. The maximum amount of blood collected from each participant over the duration of the study (18 weeks) will be 108 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

8.1. General Administrative Procedures

8.1.1. Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant prior to participation in this study. A signed copy of ICF should be given to the participant and the original should be placed in the participant's medical records.

8.1.2. Assignment of Participant Number

Each participant who signs the ICF will be assigned a unique number that will identify the participant throughout the study. Once a number has been assigned, it cannot be reassigned to another study participant.

8.1.3. Medical History

A medical history will be obtained by the investigator or a medically qualified designee (consistent with local regulations). All active conditions should be recorded and any condition diagnosed within the participant's lifetime that the investigator deems clinically significant. The information will include, but is not limited to, symptoms of PTSD (current and past, including symptoms experienced prior to any PTSD treatment); history and treatment (if any) of cardiovascular, pulmonary, gastrointestinal, [redacted] hepatic, renal, immunologic, neurologic, or psychiatric disease; reproductive status; current contraceptive method (if appropriate); smoking status (current/past), and confirmation of relevant inclusion and exclusion criteria.

8.1.4. Medication Review (Prior and Concomitant Medications)

The investigator or medically qualified designee should review the participant's prior medication use within 30 days, with the exception of SSRI/SNRIs which will be assessed per eligibility criteria (Section 5). Medication that is required to be washed out prior to the study should also be recorded. All medication currently taken by the participant should be recorded.

COVID-19 vaccination information will be collected as a concomitant medication, if the vaccine was obtained in the past 12 months.

Additional information related to any medications or psychological treatment taken for the treatment of PTSD since diagnosis (eg, treatment duration, satisfaction) should be collected.

8.1.5. Inclusion and Exclusion Criteria Review

All inclusion and exclusion criteria should be reviewed by the PI (MD/DO) or sub-investigator (MD/DO) to ensure that the participant qualifies for the study.

8.1.6. Timing of Study Intervention Dosing

Participants will be instructed to take study intervention in the morning QD without regard for food, with the exception of days of clinic visit where they will dose in clinic. The Week 8 visit is an afternoon visit and participants will take study intervention at home as normal on this visit day.

8.1.7. Mini International Neuropsychiatric Interview (MINI)

The Mini International Neuropsychiatric Interview (MINI) is a short, structured, clinician administered, diagnostic interview for psychiatric disorders (Sheehan 1998). This assessment will be used to confirm PTSD diagnosis at Screening.

A sample MINI can be found in the Investigator Trial Site Binder.

8.1.8. Life Events Checklist (LEC)

The Life Events Checklist (LEC) is a measure designed to screen for potentially traumatic events in a respondent's lifetime (Gray 2004). The LEC assesses exposure to events known to potentially result in PTSD or distress. This assessment will be used at the Screening visit only.

A sample LEC can be found in the Investigator Trial Site Binder.

8.2. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3).

8.2.1. Clinician Administered PTSD Scale (CAPS-5)

The CAPS-5 is a structured, clinician administered, clinical interview wherein participants report on their symptoms of PTSD (Weathers 2018). The CAPS-5 will be administered by qualified medical personnel (ie, PI, clinical rater). It is a well-established, widely used, and validated assessment that captures PTSD symptom frequency and intensity over the past week using a 5-point Likert-type rating scale. Its distinctive features include standardized prompts, assessment of symptom frequency, intensity, severity and behaviorally anchored ratings.

A sample CAPS-5 can be found in the Investigator Trial Site Binder.

8.2.2. Clinical Global Impression of Severity (CGI-S)

The CGI-S will be assessed by qualified medical personnel (ie, PI, clinical rater) to evaluate the severity of participants' PTSD.

The CGI-S is a 7-point Likert-type rating scale and a widely used assessment in clinical psychopharmacology trials to assess severity of illness (Guy 1976). The responses to this investigator-completed scale range from 1 (Normal, not at all ill) to 7 (Among the most extremely ill patients). The qualified medical personnel will rate his/her impression of the severity of the participant's current ability to function due to their PTSD relative to his/her experience with this patient population.

A sample CGI-S can be found in the Investigator Trial Site Binder.

8.2.3. Clinical Global Impression of Change (CGI-C)

The CGI-C will be assessed by qualified medical personnel (ie, PI, clinical rater). The CGI-C is a 7-point Likert-type rating scale and a widely used assessment to assess efficacy in clinical drug trials (Guy 1976). Investigators or trained raters will rate their impression of any change in the severity of the participant's condition since Baseline on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Ratings will focus on the participants' change in their ability to function due to PTSD.

A sample CGI-C can be found in the Investigator Trial Site Binder.

8.2.4. Patient Global Impression of Severity (PGI-S)

The PGI-S is a 5-point Likert-type rating scale and a widely used assessment in clinical psychopharmacology trials to assess severity of illness. The responses of this patient-completed scale range from 1 = none to 5 = very severe. Participants will report on the severity of their PTSD symptoms.

A sample PGI-S can be found in the Investigator Trial Site Binder.

8.2.5. Brief Inventory of Psychosocial Functioning (B-IPF)

The B-IPF is a 7-item self-reported questionnaire that assesses PTSD-related psychosocial functional impairment (Kleiman 2020). Questions regarding functional impairment are rated on a 7-point scale from 0 (Not at all), 1 to 5 (Somewhat), to 6 (Very much).

A sample B-IPF can be found in the Investigator Trial Site Binder.

8.2.6. Sheehan Disability Scale (SDS)

The SDS is a brief, 5-item self-reported tool that assesses functional impairment in work/school, social life, and family life (Leon 1997). The total score is 0 to 30 (0 unimpaired, 30 highly impaired). High scores are associated with significant functional impairment.

A sample SDS can be found in the Investigator Trial Site Binder.

8.2.7. PTSD Checklist (PCL-5)

The PCL-5 is a 20-item self-reported measure that assesses the 20 DSM-5 symptoms of PTSD. It can be used for monitoring symptom change during and after treatment (Blevins 2015).

A sample PCL-5 can be found in the Investigator Trial Site Binder.

8.2.8. Insomnia Severity Index (ISI)

The ISI is a 7-item self-reported questionnaire assessing the nature, severity, and impact of insomnia (Morin 2011). The dimensions evaluated are: severity of sleep onset, sleep maintenance, and early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. A 5-point Likert scale is used to rate each item.

A sample ISI can be found in the Investigator Trial Site Binder.

8.2.9. Pittsburgh Sleep Quality Index with PTSD Addendum (PSQI-A)

The PSQI-A is a 19-item self-report questionnaire evaluating sleep quality and disturbances over the past month (Insana 2013). The PSQI-A is comprised of seven different sleep disturbance items that are commonly reported by adults with PTSD (eg, hot flashes, memories or nightmares of the traumatic experience, and episodes of terror during sleep). Items are rated on a 0 (not in the past month) to 3 (three or more times a week) point scale and can be summed to create a total score. The total scores can range from 0 (normal) to 21 (severe).

A sample PSQI-A can be found in the Investigator Trial Site Binder.

8.2.10. Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a component of the longer Patient Health Questionnaire and is a concise, self-administered tool for assessing depression (Kroenke 2001). It incorporates DSM depression criteria with other leading major depressive symptoms into a brief self-report instrument that is commonly used for screening and diagnosis, as well as selecting and monitoring treatment.

A sample PHQ-9 can be found in the Investigator Trial Site Binder.

8.2.11. Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A)

The SIGH-A is a clinician administered rating scale developed to measure the severity of anxiety symptoms (Hamilton 1959). The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety).

A sample SIGH-A can be found in the Investigator Trial Site Binder.

8.2.12. Recovering Quality of Life (ReQoL)

The ReQoL-10 is a patient reported outcome that has been developed to assess the quality of life for people with different mental health conditions (Keetharuth 2018). It is suitable for use across all mental health populations including common mental health problems.

A sample ReQoL can be found in the Investigator Trial Site Binder.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. Physical Examinations

A complete PE will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal (including liver), neurological systems [redacted]. Height and weight will also be measured and recorded as indicated in the SoA (Section 1.3).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Any abnormalities identified at the screening PE should be recorded as medical history.

[redacted]

8.3.2. Vital Signs

Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed at each clinic visit, as indicated in the SoA (Section 1.3).

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Respiratory rate and body temperature will be assessed after the participant has been resting and seated (or supine) for at least 5 minutes.

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded. The triplicate blood pressure measurements may be repeated once at Screening and Baseline.

8.3.3. Electrocardiograms

Triplicate 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc) intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

Electrocardiograms will be reviewed, initially interpreted, signed, and dated by the investigator or a designated physician after each ECG collection. All ECGs (with the exception of ECGs for participants who are screen failures) will be transmitted to a designated central ECG laboratory. A cardiologist at the central ECG laboratory will conduct a full over-read. A report based on data from this over-read will be issued to the site.

8.3.4. Clinical Safety Laboratory Assessments

See Appendix 3 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with abnormal values considered clinically significant during participation in the study (and considered by the investigator to be related to study intervention) should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory tests, as defined in Appendix 3, must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).

8.3.5. Pregnancy Testing

Refer to Section 5.1 for pregnancy testing entry criteria.

Pregnancy testing (urine or serum as required by local regulations) should be conducted as specified in the SoA (Section 1.3). Urine pregnancy testing will be done by dipstick at the site. At Screening, clinical sites will also do a serum pregnancy that will be sent to the central lab. At all other visits, a serum pregnancy can be conducted as needed (ie, if the site obtains a positive urine pregnancy test).

Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during participation in the study.

8.3.6. Suicidal Ideation and Behavior Risk Monitoring

Participants being treated with JZP150 should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of intervention. Participants who experience signs of suicidal ideation or behavior should undergo a risk assessment. All factors contributing to suicidal ideation or behavior should be evaluated, and consideration should be given to discontinuation of the study intervention.

When informed consent has been given, families and caregivers of participants being treated with JZP150 should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior and to report such symptoms immediately to the study investigator.

Baseline assessment of suicidal ideation and behavior/ intervention emergent suicidal ideation and behavior will be monitored during JZP150-201 using the C-SSRS. At the Screening Visit, the Baseline/Screening Version of the C-SSRS will be administered to participants to exclude any individuals with active suicidal ideation or behavior.

The Since Last Visit Version of the C-SSRS will be administered to participants at every clinic visit after their Screening visit, including the Baseline and Follow-up visits, as well as during telephone calls conducted between clinic visits. At the Screening Visit, any participant who reports active suicidal ideation (eg, a positive response to Question 4 or 5 on the C-SSRS) or behavior (eg, a positive response to any suicidal behavior question on the C-SSRS) will be excluded. At post-baseline visits, active suicidal ideation or behavior must be recorded as an AE and reported to the sponsor or designee within 24 hours of first knowledge of the event by study personnel. Please refer to Appendix 4 for details on reporting other reportable experiences (OREs).

8.3.7. Marijuana Withdrawal Checklist

The Marijuana Withdrawal Checklist will be conducted per the SoA (Section 1.3). The checklist is a 22-item measure developed to assess the incidence and severity of marijuana withdrawal symptoms. Individuals can choose from the following responses for presence of each symptom: 0 = Not at all; 1 = Mild; 2 = Moderate; and 3 = Severe (Budney 1999).

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 4.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Section 7). The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.3).

All SAEs that occur after the consent form is signed but before study intervention/treatment must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure**.**

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and within 24 hours of first knowledge of the event by study personnel, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator should promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.4.6) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 4.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Investigator safety reports will be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

The Reference Safety Information for the determination of expectedness of JZP150 can be found in the IB.

8.4.5. Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 30 days after the last dose of study intervention.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant /pregnant female partner and the neonate, and the information will be forwarded to the sponsor. The pregnancy of a participant or a female partner of a male participant will be followed until the

outcome of the pregnancy is known and, in the case of a live birth, for 6 months following the birth of the child. The Infant Follow-up Form should be used to report information regarding the status of the infant.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

8.4.6. Adverse Events of Special Interest

Adverse events of special interest (AEOSI) for this study are based on observations from the clinical studies that have been conducted with BIA 10-2474, another FAAH inhibitor (Kerbrat 2016). Death and severe neurological symptoms, signs, and MRI findings were reported only in participants taking BIA 10-2474, and have not been reported in those participants taking JZP150 or other FAAH inhibitors to date. Findings from the study of BIA 10-2474 suggest the possibility of an off-target effect associated with BIA 10-2474 or its metabolites. As no specific off-targets that attribute to these AEs have been identified, caution will be taken with JZP150 and the neurological AEs that are listed as AEOSI, including headache, dizziness, gait disturbance, slurred speech, blurred vision, amnesia, cerebellar syndrome, such as limb ataxia, gait ataxia, postural ataxia, dysarthria, and nystagmus; and altered consciousness, such as somnolence and coma. Prompt neurological examination and necessary tests or procedures should be performed as necessary based on the investigator's clinical judgment. If associated signs or symptoms are identified to suggest increased intracranial pressure, stroke, intracranial bleed, cerebral edema, or any type of progressive central nervous system disorder, the investigator should provide emergency treatment and submit the ORE/AEOSI Reporting form, as described in Appendix 4. If the event also meets the criteria for an SAE submit the SAE form (rather than the ORE form) as described in Appendix 4. Participants who experience neurological AEs that are severe or serious and related to the study intervention as judged by the investigator should discontinue study intervention.

8.4.7. Overdose, Medication Errors, and Misuse

Overdose (defined as any dose administered or received that was higher than the intended dose), medication errors (defined as any unintentional error in the dispensing or administration of the study intervention), and misuse of the study intervention are considered reportable experiences. The method for completing and transmitting reports of these experiences are provided in Appendix 4.

If any overdose, medication error, or misuse of the study intervention results in an AE, this must be recorded. If the AE is serious, it must also be reported as described in Appendix 4.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Blood samples for measurement of plasma concentration of JZP150 and its metabolites will be collected at the visits noted in the Schedule of Assessments (Section 1.3). Blood samples of 4 mL will be drawn at predose and 1 sample at 2 (± 15 minutes) hours postdose on Week 1 and Week 12, 5 (± 15 minutes) and 8 (± 15 minutes) hours post dose on Week 8. Week 12 post-dose sample should be collected after completion of the CAPS-5 assessment. Blood samples will be taken as directed in the Laboratory Manual. The actual collection time points will be noted in the CRF.

Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. Samples will be used to evaluate the PK of JZP150 and its metabolites, if applicable. Each plasma sample will be divided into 2 aliquots (1 each for primary plasma PK and a back-up). All blood samples for PK assessments will be collected and processed according to the PK sample preparation instructions provided in the Laboratory Manual. The bioanalysis will be performed by the central laboratory as noted in the Laboratory Manual.

A population PK model may be used to estimate PK parameters of JZP150 and its metabolites, if applicable. Pharmacokinetic parameters may be reported in a separate report. The exposure-response analysis may be conducted and reported separately.

Study intervention concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6. Pharmacogenomics

A 10 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study at the time points noted in the Schedule of Assessments (Section 1.3). Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 6 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Investigator Trial Site Binder.

8.7. Biomarkers

Blood samples of approximately 4 mL will be collected to examine plasma AEA concentration at the visits noted in the Schedule of Assessments (Section 1.3). When AEA draws are taken on days with PK draws, a single 4 mL sample will be drawn for both PK and AEA levels. In addition to being collected at every PK blood sample, AEA will also be drawn at Baseline and at the safety follow-up.

On the days that include PK analysis, the sample will be processed and split into 2 aliquots, one for JZP150 levels and one for AEA levels. At Baseline and safety follow-up, the entire sample (4 mL) will be processed for AEA.

8.8. Immunogenicity Assessments

Immunogenicity assessments will not be performed in this study.

8.9. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The pairwise comparisons of interest are between each JZP150 dose and placebo for the primary efficacy and key secondary efficacy variables, resulting in up to six separate null hypotheses to be tested.

The null and alternative hypotheses for the primary estimand variable are:

$$H0: u_{JZP150} = u_{control}$$

$$H1: u_{JZP150} \neq u_{control}$$

where JZP150 represents either the high or low dose, as appropriate

Specifically, the null hypothesis states that there is no difference in the mean change in CAPS-5 total symptom severity score from Baseline to Week 12 between the indicated JZP150 dose level and placebo treatment groups. The alternative hypothesis states that the mean change in CAPS-5 is not equal between the indicated JZP150 dose level and placebo.

The null and alternative hypotheses for each key estimand variable, (CGI-S and PGI-S), are defined similarly as described above for the primary efficacy estimand variable.

9.2. Sample Size Determination

Approximately 270 participants will be randomized (2:1:2) to receive placebo, 0.3 mg JZP150, or 4 mg JZP150. Participants will be stratified by the presence or absence of concomitant use of SSRIs/SNRIs.

The sample size was determined based on ensuring at least 80% marginal power to detect a difference of 6 between placebo and each dose of JZP150 for the mean change in CAPS-5 total symptom severity score from Baseline to Week 12. The sample sizes for the estimated 70% of subjects completing the 12-week dosing period for each arm (placebo [n = 75], 0.3 mg JZP150 [n = 38], and 4 mg JZP150 [n = 75]) provides a marginal power of 80.9% and 93.4% for comparing the low dose vs placebo and high dose vs placebo, respectively. Calculations are based on assuming a common standard deviation of 10.5, using a two-sample t-test, and two-sided significance level of 0.05. To account for a 30% dropout, the sample size will be 270 participants to ensure that a minimum of 188 participants have 12 weeks of treatment data.

9.3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled Analysis Set	The Enrolled Analysis Set will include all participants who provide informed consent for this study. This analysis set will be used to summarize participant disposition, including number of screened, screen failures, and randomized participants. Summaries will be presented overall and by the randomization group for those randomized.

Participant Analysis Set	Description
Safety Analysis Set	The Safety Analysis Set will include all participants who took at least one dose of study medication. Participants will be analyzed according to the treatment received rather than randomized. If a participant receives more than one randomized treatment, they will be analyzed according to the treatment they received the most.
Full Analysis Set (FAS)	The FAS will include all participants who are randomized and took at least one dose of study medication. Participants are analyzed according to randomized treatment.
Modified FAS	The mFAS population will include all participants who are randomized, took at least one dose of study medication, and have baseline and any post- baseline assessment of CAPS-5 total score, CGI-S, or PGI-S score, excluding ineligible participants that were randomized. Participants are analyzed according to randomized treatment. The mFAS analysis set will be the primary analysis set for all efficacy analyses.
PK Analysis Set	The PK Analysis Set will include all participants who receive at least 1 dose of study intervention and have at least 1 pre-dose or 1 post-dose evaluable PK concentration. All PK analyses will be based on the PK analysis set.
PD Analysis Set	The PD Analysis Set will include all participants who receive at least 1 dose of study intervention and have at least 1 pre-dose and 1 post-dose evaluable PD (AEA) level. The PD set will be used to summarize the PD data.

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.4.1. General Considerations

In general, results will be summarized by treatment group. Categorical variables will be reported as frequency and percent. Continuous variables will be reported as the number of participants, mean, SD, or SE, median, minimum, and maximum. All summaries, statistical analyses, and individual participant data listings described below will be completed using Version 9.3 or later of the SAS Statistical Analysis System (SAS Institute, Inc. Cary, NC).

9.4.1.1. Multiplicity Adjustments

A fixed sequence hierarchical testing strategy will be implemented for the primary and key secondary endpoints (as illustrated in Table 5) to preserve the family-wise Type 1 error rate at the significance level of 0.05. Testing will begin with the comparison of the JZP150 4 mg dose vs Placebo for the primary efficacy variable followed by sequential testing of the key secondary efficacy variables in the order of CGI-S and then PGI-S. If all three null hypotheses are rejected,

then similar hierarchical sequential testing of the endpoints will be performed for comparing JZP150 0.3 mg dose vs placebo. The testing will stop when the p-value exceeds the significance level of 0.05. All tests will be conducted at a 2-sided significance level of 0.05.

Table 5: Hierarchical Testing Strategy

Gatekeeper Family	Endpoint	Null Hypothesis	Effect Size	Power
1	CAPS-5	H_1: JZP150 4 mg = Placebo	0.57	93.4%
2	CGI-S	H_2: JZP150 4 mg = Placebo	0.50	86%
3	PGI-S	H_3: JZP150 4 mg = Placebo	0.50	86%
4	CAPS-5	H_4: JZP150 0.3 mg = Placebo	0.57	80.9%
5	CGI-S	H_5: JZP150 0.3 mg = Placebo	0.50	70%
6	PGI-S	H_6: JZP150 0.3 mg = Placebo	0.50	70%

9.4.1.2. Intercurrent Event Strategies

The ICE of treatment discontinuation will be handled using two different strategies as defined below:

- The treatment policy strategy will be used to address the ICE of treatment discontinuation. It is defined as the effect of the randomized treatment over the study period regardless of whether randomized treatment is continued.
- The supplemental estimand of interest will address the ICE of treatment discontinuation using the hypothetical approach. This estimand is defined as the pharmacologic effect of JZP150 compared to placebo assuming continuation of randomized treatments for the duration of the study. Analysis of this estimand will be conducted using only data collected at time points that are obtained at or prior to participants discontinuing from randomized treatment will be utilized.

Other possible ICEs include: study intervention non-compliance, significant protocol deviations, new trauma, or initiation or adjustment of concomitant medications for PTSD, which are not permitted per protocol, but nevertheless can still occur. It is anticipated that the occurrence of these events will be rare; therefore, both estimands use the treatment policy approach to address these ICEs.

9.4.1.3. Pooling of Investigational Centers

Data from all investigational centers will be pooled for presentation of the main results (eg, demographics, safety, PK, and efficacy).

9.4.1.4. Dropouts and Missing Data

Every effort will be undertaken to limit premature discontinuation and ascertain completeness of the data collection. The main estimator for the primary and key secondary estimands is based on a mixed effect model with repeated measures (MMRM) which can handle missing outcomes and produces an estimate of the treatment effect via restricted maximum likelihood estimation. For

the main estimator of the estimands, the data are assumed to be missing at random (MAR). This assumes that participants with missing data would have efficacy outcomes similar to those participants in their treatment group, randomization strata, and initial trajectory who completed the trial.

In order to evaluate the robustness of the primary and key secondary variables, sensitivity analyses will be performed for both estimands to estimate the overall treatment effect under an alternative assumption of missing data - missing not at random (MNAR).

Sensitivity analyses that are planned include:

- Time-dependent Multiple Imputation
- A two-dimensional tipping point analysis to study the sensitivity of the study conclusion affected by missing data

Details of analyses will be included in the SAP.

9.4.2. Primary Estimand

Refer to Section 3 for the primary estimand attributes.

The CAPS-5 total symptom severity score is derived by summing scores for items 1-20. Each item is rated with a single severity score on a five-point rating scale (0-4) corresponding to the following categories: 0 Absent, 1 Mild/ subthreshold, 2 Moderate/ threshold, 3 Severe/ markedly elevated, and 4 Extreme/ incapacitating. The CAPS-5 total symptom severity score can range from 0 to 80.

A MMRM will be used to analyze the primary efficacy variable, change in CAPS-5 total symptom severity score from baseline at each time point. The model will include treatment group, week (as a discrete factor), baseline-by-week, treatment-by-week interaction, randomization stratum, stratum-by-week interaction, and the CAPS-5 total symptom severity score at baseline as fixed effects. An unstructured variance-covariance matrix will be used to model the correlation among repeated measurements.

For participants meeting criteria for the mFAS population who prematurely discontinue the study and refuse to return for the Week 12 visit, but who do return to the study site at the time of discontinuation to complete the protocol-specified assessments (the early discontinuation visit), the efficacy data from this early discontinuation visit will be included in the primary analysis using the prespecified visit windows (± 4 weeks) around Week 4, and Week 12 visits.

Refer to Section 9.4.1.2 and Section 9.4.1.4 for further details on the ICE strategies and missing data, respectively.

9.4.3. Key Secondary Estimands

Each key secondary efficacy estimand variable (eg, CGI-S and PGI-S) will be analyzed as a continuous variable using a similar method as described above for the primary efficacy variable.

9.4.4. Secondary and Exploratory Estimands

All other secondary and exploratory analyses will be further described in the SAP.

9.4.5. Safety Analyses

All safety analyses will be made on the Safety Population. All safety analyses will be descriptive; no formal statistical testing will be performed and are further described in the SAP.

Adverse Event Analyses:

Adverse events will be mapped to system organ classes (SOC) and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). The participant incidence of AEs, AEs related to study intervention, SAEs, AEs leading to discontinuation, and fatal AEs will be summarized. This overall summary will also provide AEs by maximum severity.

The participant incidence of AEs, AEs related to study intervention, AEs, and AEs leading to discontinuation will also be presented by SOC and preferred term (PT). Preferred term summaries may also be provided.

The participant incidence of an AE will be summarized; if a participant has multiple events with the same PT occurring in different periods, the event will be reported for each of those periods. If an AE continues from one period to the next without increase in severity, the event will be reported only for the period of the AE onset. Changes in the severity of an AE within a period will only be counted as one AE with the worst severity.

Vital Signs:

For each vital sign parameter, summary statistics will be provided for observed and change from baseline values by scheduled visit.

Physical Examinations:

Observed and change from baseline values for weight will be summarized descriptively by scheduled visit. [redacted]

12-lead ECG:

Observed and change from baseline values for ECG intervals will be summarized descriptively. The number and percent of participants with values or change from baseline values in QT/QTcF exceeding certain thresholds will be tabulated.

Clinical Laboratory Evaluations:

Observed and change from baseline laboratory evaluations will be summarized descriptively.

C-SSRS:

Columbia Suicide Severity Ratio Scale parameters will be summarized by scheduled visit.

Marijuana Withdrawal Checklist

Marijuana Withdrawal Checklist parameters will be summarized by scheduled visit.

9.4.6. Other Analyses

Subgroup analyses for the efficacy and safety assessments will be provided by baseline presence or absence of concomitant use of SSRIs/SNRIs. Subgroup analyses by gender or other

characteristics as defined in the SAP will be provided for efficacy and safety assessments as appropriate.

9.4.7. Pharmacokinetic/ Pharmacodynamic Analyses

Plasma concentrations of JZP150 and its metabolites will be listed by visit and dose. Pharmacodynamic markers (eg, AEA concentration) will be measured and listed by visit and dose.

The results of the population PK and population PK/PD analysis may be presented separately from the study data.

9.5. Interim Analysis

An interim analysis is not planned.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC and national regulatory authority (as applicable), before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and national regulatory authority (where required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require IRB/IEC and national regulatory authority approval prior to initiation, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial

certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

If participants will be asked to consent to optional exploratory research using the remainder of mandatory samples, include text that addresses the use of remaining mandatory samples for optional exploratory research.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for [redacted] research. The investigator or authorized designee will explain to each participant the objectives of the [redacted] research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for [redacted] research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

Internal Safety Data Review Committee

Participant safety will be continuously monitored by the sponsor's internal safety data review committee (ISDRC) in a blinded manner, which includes safety signal detection at any time during the study.

This committee will be composed of the following members:

- Safety Physician
- Clinical Safety Scientist
- Biostatistics Lead
- Sponsor Medical Monitor
- Clinical Research Organization Medical Monitor

Blinded safety data from the study will be reviewed on an ongoing basis as part of routine safety data review with regular review of aggregate blinded safety information within monthly JZP150 ISDRC meetings. The ongoing review of safety data will include the following elements:

- Abnormal, clinically significant changes in the physical examination [redacted], will be recorded as TEAEs and reviewed.
- Changes from Baseline in vital signs.
- Clinical laboratory tests (chemistry, complete blood count, urinalysi [redacted].
- ECG data, to include an evaluation of clinically relevant changes from Baseline.
- TEAEs with attention to the development and frequency of previously unidentified TEAEs as well as identified TEAEs and the following AEOSIs:
  - Severe neurological events
  - Psychiatric events (eg, behavioral/cognitive changes, suicidal ideation or behavior)
  - Vision changes (eg, blurred vision)
  - Hepatic-related events (new right upper quadrant pain, hepatomegaly, tenderness, jaundice, serum chemistry abnormalities)
  - [redacted]

All blinded safety data collected will be summarized and reviewed by ISDRC for agreement of next steps.

If adverse safety trends are detected that may constitute a risk to study participants prior to the monthly ISDRC meetings, an ad hoc Safety Management Team (SMT) meeting will be urgently

convened to evaluate the information and determine actions that should be undertaken up to and including termination of the clinical study (Section 10.1.9.2).

Case unblinding may be performed for above reviews if necessary, including but not limited to participants meeting protocol participant stopping criteria (see Section 7). The SMT will include membership distinct and separate from the blinded study team and its structure and standard operating procedures will be specified in a charter in accordance with Jazz Pharmacovigilance policies.

10.1.6. Dissemination of Clinical Study Data

As the sponsor of the study, Jazz Pharmaceuticals is solely responsible for disclosing results on ClinicalTrials.gov, EudraCT, and other public registries in accordance with applicable global laws and regulations. By signing this protocol, the investigator acknowledges that all posting requirements are solely the responsibility of the sponsor and agrees not to submit any information about the study or its results.

10.1.7. Data Quality Assurance

Investigators and site staff will be trained on protocol procedures and electronic case report form (eCRF) completion prior to enrolling participants in the study.

All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in data handling and entry guidelines.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues, and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator or institution/site as applicable, for the period of time established in the clinical study agreement entered into by the investigator's study site unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in data handling and entry guidelines.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

10.1.9.1. First Act of Recruitment

The study start date is the date on which the first participant has the first visit.

10.1.9.2. Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

Administration of the study agent will be temporarily suspended by the SMT upon the occurrence of any of the following:

- Unexpected SAEs within the same SOC or similar in nature are reported by 2 or more participants on active study intervention with a plausible relationship to study intervention administration.
- 1 or more participants on active study intervention meets Hy's Law Criteria as defined in Appendix 7.

Based on the sponsor review and evaluation of the aforementioned safety events, the study may be restarted or terminated.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Sponsor makes a business decision to stop the study.
- Study stopping criteria are met and following investigation, the sponsor decides to stop the study.
- Ongoing evaluation of study safety data suggests that the benefit-risk profile suggests stopping the study.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

Please refer to individual site contracts for specific contractual obligations and requirements.

All information concerning JZP150, Jazz Pharmaceuticals' operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by Jazz Pharmaceuticals to the investigator and not previously published, are considered confidential and remain the sole property of Jazz Pharmaceuticals. eCRFs also remain the property of Jazz Pharmaceuticals. The investigator agrees to use this information only to complete this study and will not use it for other purposes without written consent of Jazz Pharmaceuticals as further detailed in the Clinical Study Agreement signed by the investigator and/or institution.

It is understood by the investigator that Jazz Pharmaceuticals will use the information obtained in this clinical trial in connection with the study of JZP150, and therefore may disclose this information as required to other Jazz Pharmaceuticals investigators; appropriate international regulatory agencies; or others. In agreeing to participate in this study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this trial to Jazz Pharmaceuticals. Jazz Pharmaceuticals requires that permission to publish details of this study must be obtained in writing as further detailed in the Clinical Study Agreement signed by the investigator and/or institution. It is intended that the results of this trial will be published in scientific literature. The conditions noted here are intended to protect commercial confidential materials (patents, etc.) and not to restrict publication.

APPENDIX 1. ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AEA	Anandamide
AEOSI	Adverse events of special interest
ALT	Alanine aminotransferase
APA	American Psychiatric Association
AST	Aspartate aminotransferase
B-IPF	Brief Inventory of Psychosocial Functioning
CAPS	Clinician Administered PTSD Scale
CB1	Type 1 cannabinoid receptor
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum plasma concentration
CRF	Case report form
C-SSRS	Columbia Suicide Severity Rating Scale
CUD	Cannabis use disorder
CYP	Cytochrome P450
DoD	Department of Defense
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
eCRF	Electronic case report form
E/D	Early Discontinuation
FAAH	Fatty acid amide hydrolase
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICE	Intercurrent Events
ICF	Informed Consent Form

Abbreviation	Definition
ICH E6(R2)	International Council for Harmonization Guideline for Good Clinical Practice
IEC	Independent ethics committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
ISDRC	Internal safety data review committee
ISI	Insomnia Severity Index
ISTSS	International Society for Traumatic Stress Studies
LEC	Life Events Checklist
LH	Luteinizing hormone
mFAS	Modified Full Analysis Set
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed Effect Model Repeated Measures
N/A	Not Applicable
ng/mL	Nanograms per Millitre
NICE	National Institute for Health and Care Excellence
NOAELs	No-observed-adverse-effect levels
PCL-5	PTSD Checklist
PD	Pharmacodynamics
PE	Physical examination
PET	Positron emission tomography
PGI-S	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire-9
PI	Principal investigator
PK	Pharmacokinetic
PSQI-A	Pittsburgh Sleep Quality Index - PTSD Addendum
PT	Preferred term
PTSD	Posttraumatic stress disorder
QD	Once daily
QTc	Corrected QT interval
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
ReQoL	Recovering Quality of Life

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical analysis plan
SDS	Sheehan Disability Scale
SIGH-A	Structured Interview Guide for the Hamilton Anxiety Rating Scale
SMT	Safety Management Team
SNP	Single Nucleotide Polymorphism
SNRI	Serotonin norepinephrine reuptake inhibitor
SOC	System organ class
SSRI	Selective serotonin reuptake inhibitor
TEAE	Treatment-emergent adverse event
WOCBP	Women of Childbearing Potential
WONCBP	Women of Non-childbearing Potential

APPENDIX 2. REFERENCES

Ahn K, Smith SE, Limatta MB, et al. Mechanistic and pharmacological characterization of PF-044578845: a highly potent and selective fatty acid amide hydrolase inhibitor that reduces inflammatory and noninflammatory pain. Journal or Pharmacology and Experimental Therapeutics. 2011;338(1):114-124.

American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders. 5th Edition. American Psychiatric Publishing; 2013.

American Psychiatric Association (APA). Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder. Arlington, VA. 2004.

Blevins CA, Weathers FW, Davis MT, et al. The posttraumatic stress disorder checklist for DSM-5 (PCL-5): Development and initial psychometric evaluation. Journal of Traumatic Stress. 2015;28(6):489-98.

Bluett RJ, Gamble-George JC, Hermanson DJ, et al. Central anandamide deficiency predicts stress-induced anxiety: behavioral reversal through endo cannabinoid augmentation. Translational Psychiatry. 2014;4(7):e408.

Boileau I, Rusjan PM, Williams B, et al. Blocking of fatty acid amide hydrolase activity with PF-04457845 in human brain: a positron emission tomography study with the novel radioligand [11C] CURB. Journal of Cerebral Blood Flow and Metabolism. 2015;35(11):1827-35.

Bonifacio MJ, Sousa F, Aires C, et al. Preclinical pharmacological evaluation of the fatty acid amide hydrolase inhibitor BIA 10-2474. British Journal of Pharmacology. 2020;177(9):2123-42.

Bovin MJ, Marx BP, Weathers FW, et al. Psychometric properties of the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (PCL-5) in veterans. Psychological Assessment. 2016;28(11):1379-91.

Budney AJ, Novy PL, Hughes JR. Marijuana withdrawal among adults seeking treatment for marijuana dependence. Addiction. 1999;94(9):1311-21.

Burri A and Maercker A. Differences in prevalence rates of PTSD in various European countries explained by war exposure, other trauma and cultural value orientation. BMC Research Notes. 2014;7(407):1-11.

Carnevali L, Rivara S, Nalivaiko E, et al. Pharmacological inhibition of FAAH activity in rodents: A promising pharmacological approach for psychological-cardiac comorbidity? Neuroscience and Biobehavioral Reviews. 2017;74:444-52.

Cravatt BF, Giang DK, Mayfield SP, et al. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. Nature. 1996;384(6604):83-7.

Dincheva I, Drysdale AT, Hartley CA, et al. FAAH genetic variation enhances fronto-amygdala function in mouse and human. Nature Communications. 2015;6(1):1-9.

D'Souza DC, Cortes-Briones J, Creatura G, et al. Efficacy and safety of a fatty acid amide hydrolase inhibitor (PF-04457845) in the treatment of cannabis withdrawal and dependence in med: a double-blind, placebo-controlled, parallel-group, phase 2a single-site randomized controlled trial. The Lancet Psychiatry. 2019;6(1):35-45.

Goldstein RB, Smith SM, Chou SP, et al. The epidemiology of DSM-5 posttraumatic stress disorder in the United States: results from the National epidemiologic Survey on Alcohol and Related Conditions-III. Social Psychiatry and Psychiatric Epidemiology. 2016;51(8):1137-48.

Gray MJ, Litz BT. Hsu JL, et al. Psychometric properties of the Life Events Checklist. Assessment. 2004;11(4):330-41.

Gunduz-Cinar O, MacPherson KP, Cinar R, et al. Convergent translational evidence of a role for anandamid in amygdala-mediated fear extinction, threat processing and stress-reactivity. Molecular Psychiatry. 2013;18(7):813-23.

Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, US Department of Health, Education, and Welfare.

Haller J, Aliczki M, Pelczer KG, et al. Effects of the fatty acid amide hydrolase inhibitor URB597 on coping behavior under challenging conditions in mice. Psychopharmacology. 2014;231(3):593-601.

Haller J, Barna I, Barsvari B, et al. Interactions between environmental aversiveness and the anxiolytic effects of enhanced cannabinoid signaling by FAAH inhibition in rates. Psychopharmacology. 2009;204(4):607-16.

Hamilton M. The assessment of anxiety states by rating. British Journal of Medical Psychology. 1959;31:50-5.

Harfmann EJ, McAuliffe TL, Larson ER, et al. Circulating endocannabinoid concentrations in grieving adults. Psychoneuroendocrinology. 2020;120:104801.

Hauer D, Schelling G, Gola H, et al. Plasma concentrations of endocannabinoids and related primary fatty acid amides in patients with posttraumatic stress disorder. PLos One. 2013;8(5):e62741.

Hill MN, Bierer LM, Makotkine I, et al. Reductions in circulating endocannabinoid levels in individuals with post-traumatic stress disorder following exposure to the World Trade Center attacks. Psychoneuroendocrinology. 2013a;38(12):2952-61.

Hill MN, Campolongo P, Yehuda R, et al. Integrating endocannabinoid signaling and cannabinoids into the biology and treatment of posttraumatic stress disorder. Neuropsychopharmacology. 2018;43(1):80-102.

Hill MN, Miller GE, Carrier EJ, et al. Circulating endocannabinoids and N-acyl ethanolamines are differentially regulated in major depression and following exposure to social stress. Psychoneuroendocrinology. 2009a;34(8):1257-62.

Hoffman V, Middleton JC, Feltner C, et al. Psychological and Pharmacological Treatments for Adults with Posttraumatic Stress Disorder: A Systematic Review Update Comparative Effectiveness Review No. 207. (Prepared by the RTI International -University of North Carolina at Chapel Hill Evidence-based Practice Center under Contract No. 290-2015-00011-1 for AHRQ and PCORI.) AHRQ Publication No. 18-EHC011-EF. PCORI Publication No. 2018-SR-01. Rockville, MD. Agency for Healthcare Research and Quality; May 2018.

Insana SP, Hall, M, Buysse DJ, et al. Validation of the Pittsburgh Sleep Quality Index Addendum for posttraumatic stress disorder (PSQI-A) in male military veterans. Journal of Traumatic Stress. 2013;26(2):192-200.

International Society for Traumatic Stress Studies (ISTSS) Guidelines Committee. Posttraumatic stress disorder prevention and treatment guidelines methodology and recommendations. 2018.

Johnson DS, Stiff C, Lazerwith SE, et al. Discovery of PF-04457845: a highly potent, orally bioavailable, and selective urea FAAH inhibitor. ACS Medicinal Chemistry Letters. 2011;2(2):91-6.

Kathuria S, Gaetani S, Fegley D, et al. Modulation of anxiety through blockage of anandamide hydrolysis. Nature Medicine. 2003;9(1):76-81.

Keetharuth AD, Brazier J, Connell J, et al. Recovering Quality of Life (ReQoL): a new generic self-reported outcome measure for use with people experiencing mental health difficulties. The British Journal of Psychiatry. 2018;212:42-9.

Kerbrat A, Ferré J-C, Fillatre P, et al. Acute neurologic disorder from an inhibitor of fatty acid amide hydrolase. New England Journal of Medicine. 2016;375(18):1717-25.

Kessler RC, Aguilar-Gaxiola S, Alonso J, et al. Trauma and PTSD in the WHO world mental health surveys. European Journal of Psychotraumatology. 2017;8(sup5):1353-83.

Kleiman SE, Bovin MJ, Black SK, et al. Psychometric properties of a brief measure of posttraumatic stress disorder-related impairment: The Brief Inventory of Psychosocial Functioning. Psychological Services. 2020;17(2):187-194.

Kroenke K, Spitzer RL, Williams JB. The PHQ-9: Validity of a brief depression severity measure. Journal of General Internal Medicine. 2001;16:606-13.

Krystal JH, Davis LL, Neylan TC, et al. It is time to address the crisis in the pharmacotherapy of posttraumatic stress disorder: a consensus statement of the PTSD psychopharmacology working group. Biological Psychiatry. 2017;82(7):e51-9.

Leon AC, Olfson M, Portera L, et al. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. International Journal of Psychiatry in Medicine. 1997;27(2):92-105.

Lomazzo E, Bindila L, Remmers F, et al. Therapeutic potential of inhibitors of endocannabinoid degradation for the treatment of stress-related hyperalgesia in an animal model of chronic pain. Neuropsychopharmacology. 2015;40(2):488-501.

Mayo LM, Asratian A, Linde J, et al. Elevated anandamide, enhanced recall of fear extinction, and attenuated stress responses following inhibition of fatty acid amide hydrolase: a randomized, controlled, experimental medicine trial. Biological Psychiatry. 2020;87(6):538-47.

Morin CM, Belleville G, Belanger L, et al. The Insomnia Severity Index: Psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep. 2011;34(5):601-8.

National Institute for Health and Care Excellence (NICE). Posttraumatic stress disorder. 05 December 2018. Accesses 25 January 2021. www.nice.org.uk/guidance/ng116.

Patel S and Hillard CJ. Pharmacological evaluation of cannabinoid receptor ligands in a mouse model of anxiety: further evidence for an anxiolytic role for endogenous cannabinoid signaling. Journal of Pharmacology and Experimental Therapeutics. 2006;318(1):304-11.

Rusjan PM, Knezevic D, Bioleau I, et al. Voxel level quantification of [11C] CURB, a radioligand for fatty acid amide hydrolase, using high resolution positron emission tomography. PloS One. 2018;13(2):e0192410.

Sheehan DV, Lecrubier Y, Harnett Sheehan K, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. Journal of Clinical Psychiatry. 1998;59(suppl 20):22-33.

Suliman S, Anthonissen L, Carr J, et al. Posttraumatic stress disorder, overweight, and obesity: a systematic review and meta-analysis. Harvard Review of Psychiatry. 2016 Jul 1;24(4):271-93.

Veterans Affairs (VA) and the Department of Defense (DoD). Clinical Practice Guideline Working Group. Management of posttraumatic stress. Washington, DC. VA Office of Quality and Performance. 2003.

Watson P. PTSD as a public health priority. Current Psychiatry Reports. 2019;21(7):1-2.

Weathers FW, Bovin MJ, Lee DJ, et al. The Clinician Administered PTSD Scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. Psychological Assessment. 2018;30(3):383.

Weathers FW, Litz BT, Keane TM, et al. The PTSD Checklist for DSM-5 (PCL-5). 2013. Available at www.ptsd.va.gov.

APPENDIX 3. CLINICAL LABORATORY TESTS

The tests detailed in Table 6 will be performed by the central laboratory, with the exception of urine pregnancy, urine dipstick for drug screen (with the exception of the screening visit during which urine drug screen will be done by the central lab), and breath alcohol tests, which will be performed locally.

Participants are required to fast for safety laboratory tests at the Baseline Visit (Visit 2), Week 1 (Visit 3), Week 4 (Visit 5), Week 12 (Visit 9), Early Discontinuation (Visit 10), if applicable, and Safety Follow-up Visit (Visit 12). Participants are not required to fast for laboratory tests at the Screening Visit or Week 8 (Visit 7).

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of each laboratory report.

Table 6: Protocol-Required Safety Laboratory Tests

Laboratory Tests	**Parameters**			
Hematology[a]	Platelet Count	RBC Indices: MCV MCH Reticulocytes (count, absolute)	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	RBC Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry[ab]	Albumin	ALP[c]	ALT/ SGPT	AST/ SGOT
	BUN	Calcium	CO_2	Chloride
	Creatinine	Creatine kinase	GGT	Glucose
				HbA1c (Screening and Week 12 only)
	Lactate dehydrogenase	Phosphorus	Potassium	Sodium
	TSH (Screening only)	Total and direct bilirubin	Total cholesterol	Total protein

Laboratory Tests	**Parameters**			
	Triglycerides	Uric acid	High-density lipoprotein cholesterol	Low-density lipoprotein cholesterol
	LH (males only)	FSH (collected at Screening only for WONCBP when needed; collected at [redacted])	Serum testosterone (males only)	
Routine Urinalysis	• Appearance, color • Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase (by dipstick) • Microscopic examination (if blood or protein is abnormal) • Urinalysis will always be conducted by the central laboratory.			
Pregnancy testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for WOCBP)[d]			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed for WONCBP) • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines). Note: The urine drug screen will be conducted by the central laboratory at Screening and the urine drug screen at subsequent visits after screening will be conducted locally at the site. In the case of a positive urine drug screen at the site, samples can be sent to the central laboratory for confirmation. • Breath alcohol test			

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; HbA1c = glycosylated hemoglobin; hCG = human chorionic gonadotropin; LH = luteinizing hormone; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; MDMA = 3, 4,-methylenedioxymethamphetamine; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TSH = thyroid stimulating hormone; WBC = white blood cell; WOCBP = woman of childbearing potential; WONCBP = woman of non-childbearing potential.

[a] Participants are required to fast for safety laboratory tests at the Baseline Visit (Visit 2), Week 1 (Visit 3), Week 4 (Visit 5), Week 12 (Visit 9), Early Discontinuation (Visit 10), if applicable, and Safety follow-up Visit (Visit 12). Participants are not required to fast for laboratory tests at the Screening Visit or Week 8 (Visit 7).

[b] All events of ALT (or AST) ≥ 3 × upper limit of normal (ULN) and total bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT (or AST) ≥ 3 × ULN and international normalized ratio (INR) >1.5, (if INR measured) which may indicate severe liver injury (possible Hy's Law), must be reported to the sponsor or designee in an expedited manner.

[c] If alkaline phosphatase is elevated, consider fractionating.

[d] Urine pregnancy testing will be done by dipstick at the site. At Screening, clinical sites will also do a serum pregnancy that will be sent to the central lab. At all other visits, a serum pregnancy can be conducted as needed (ie, if the site obtains a positive urine pregnancy test).

APPENDIX 4. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of Unsolicited and Solicited AE
• An unsolicited AE is an AE that was not solicited using a Participant Diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. • Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by participant will be collected during interview with the participants and by review of available medical records at the next visit. • Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

Events Meeting the AE Definition
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence SAE that, at any dose:
Results in death
Is life-threatening • The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

An SAE is defined as any untoward medical occurrence SAE that, at any dose:
Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Is a suspected transmission of any infectious agent via an authorized medicinal product.
Other situations: Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information. • It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the required form. • There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant

AE and SAE Recording

number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:
  - Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only, intervention not indicated.
  - Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
  - Severe: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. An AE/SAE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
  - Life-threatening: life-threatening consequences; urgent intervention indicated.
  - Fatal: death related to AE.

    * These categories are based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 or higher.

When the severity of an AE increases over time, the increase in the severity will be recorded as a new AE and the original AE will stop when the new AE starts.

An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the Investigator’s Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.

Assessment of Causality
• For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor (or designee) to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to Sponsor or Designee via an Electronic Data Collection Tool
• SAEs must be reported to the sponsor (or designee) using an SAE Reporting Form within 24 hours of first knowledge of the event by study personnel. • The site will enter the SAE data into the electronic system as soon as it becomes available. • The form, instructions on completion, and contact information can be found in the Investigator Trial Site Binder. • The SAE Reporting Form should be completed as much as possible before transmittal. • Contacts for SAE reporting can be found in the Investigator Trial Site Binder.

Reporting of Other Reportable Experiences (OREs) and Adverse Events of Special Interest (AEOSI)

• Other reportable experiences (OREs, including suicidal ideation, overdose, medication error or abuse, and elevated LFTs) and AEOSI requiring expedited reporting, as described in Section 8.4.6,

must be reported to the sponsor or its designee using an ORE/AEOSI Reporting Form within 24 hours of first knowledge of the event by study personnel.

- The form, instructions on completion, and contact information can be found in the Investigator Trial Site Binder.
- The ORE/AEOSI Reporting Form should be completed as much as possible before transmittal.
- Contacts for ORE reporting can be found in the Investigator Trial Site Binder.

APPENDIX 5. CONTRACEPTIVE AND BARRIER GUIDANCE

Definitions

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
     - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
   - Permanent sterilization methods (for the purpose of this study) include:
     - Documented hysterectomy
     - Documented bilateral salpingectomy
     - Documented bilateral oophorectomy
     - For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

       Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
   - If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o oral o intravaginal o transdermal o injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

[b] Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c] Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together due to risk of failure from friction.

APPENDIX 6. GENETICS

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact intervention absorption, distribution, metabolism, and excretion; mechanism of action of the intervention; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to JZP150 or PTSD and related diseases. They may also be used to develop tests/assays including diagnostic tests related to JZP150. Genetic research may specifically consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or targeted candidate gene analysis (as appropriate).
- [redacted]
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to JZP150 or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on JZP150 continues but no longer than 15 years or other period as per local requirements.

APPENDIX 7. LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Table 7: Phase 2 Liver Chemistry Stopping Criteria and Follow-up Assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 5 × ULN
ALT Increase	ALT ≥ 3 × ULN persists for ≥ 4 weeks
Total bilirubin[a,b]	ALT ≥ 3 × ULN **and** total bilirubin ≥ 2× ULN (> 35% direct bilirubin)
INR[b]	ALT ≥ 3 × ULN **and** INR >1.5, if INR measured
Cannot Monitor	ALT ≥ 3 × ULN and cannot be monitored weekly for 4 weeks
Symptomatic[c]	ALT ≥ 3 × ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions, Monitoring and Follow-up Assessments	
Actions	**Follow-up Assessments**
Immediately discontinue study intervention. Record the Liver Stopping Events as an AE, and report to the sponsor or designee as an ORE, as described in Appendix 4. If the Liver Stopping Event also meets the criteria for an SAE, record and report to the sponsor or designee as an SAE, as described in Appendix 4. Perform follow-up assessments as described in the Follow-Up Assessment column. Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**). **MONITORING:** **<u>If ALT ≥ 3 × ULN AND total bilirubin ≥ 2 × ULN or INR > 1.5:</u>** Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within **24 hours.** Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline.	Viral hepatitis serology.[d] Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend. Obtain blood sample for PK analysis.[e] Obtain serum creatine phosphokinase, lactate dehydrogenase, GGT, glutamate dehydrogenase, and serum albumin. Fractionate bilirubin, if total bilirubin ≥ 2 × ULN. Obtain complete blood count with differential to assess eosinophilia Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity as an AE. Record use of concomitant medications (including acetaminophen, herbal remedies, recreational drugs and other over-the-counter medications) and provide information via email to Aereporting@jazzpharma.com. **<u>If ALT ≥ 3 × ULN AND total bilirubin < 2 × ULN or INR > 1.5</u>** obtain the following in addition to the assessments listed above**:** Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G or gamma globulins.

Liver Chemistry Stopping Criteria	
A specialist or hepatology consultation is recommended. **<u>If ALT ≥ 3 × ULN AND total bilirubin < 2 × ULN and INR ≤ 1.5:</u>** Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours.** Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline. Permanently discontinue study intervention and continue participant in the study for any protocol-specified follow-up assessments.	Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week. Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease. Provide liver imagine results via email to Aereporting@jazzpharma.com. Liver biopsy may be considered and discussed with local specialist if available: In participants when serology raises the possibility of autoimmune hepatitis. In participants when suspected drug-induced liver injury progresses or fails to resolve on withdrawal of study intervention. In participants with acute or chronic atypical presentation If liver biopsy conducted, provide liver imaging results via email to Aereporting@jazzpharma.com.

[a] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT ≥ 3 × ULN **and** total bilirubin ≥ 2 × ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick which** is indicative of direct bilirubin elevations suggesting liver injury.

[b] All events of ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT ≥ 3 × ULN **and** INR > 1.5 may indicate severe liver injury **(possible "Hy's Law") and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria met.** The INR stated threshold value will not apply to participants receiving anticoagulants.

[c] New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

[d] Includes: Hepatitis A immunoglobulin M (IgM) antibody; hepatitis B virus surface antigen (HBsAg) and hepatitis B core antibody (HBcAb); hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

[e] PK sample may not be required for participants known to be receiving placebo. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Investigator Trial Site Binder.

Table 8: Phase 2 Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

Liver Chemistry Increased Monitoring Criterion and Actions With Continued Study Intervention	
Criterion	**Actions**
ALT ≥ 3 × ULN and < 5 × ULN **and** total bilirubin < 2 × ULN or INR < 1.5**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	Notify the sponsor within **24 hours** of learning of the abnormality to discuss participant safety. Participant can continue study intervention. Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin) until the abnormalities resolve, stabilize or return to baseline. If at any time, the participant meets liver chemistry stopping criteria, proceed as described in Section 7.1. If, after 4 weeks of monitoring, ALT < 3 × ULN and total bilirubin < 2 × ULN, monitor participants twice monthly until liver chemistry tests resolve, stabilize, or return to baseline.

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