Official Title: Multicenter, Randomized, Double-blind Placebo-controlled, Crossover Study to Investigate Effects of V117957 in Female Subjects with Interstitial Cystitis/Bladder Pain Syndrome

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Protocol Number:	OAG1050
Protocol Title:	Multicenter, Randomized, Double-blind Placebo-controlled, Crossover Study to Investigate Effects of V117957 in Female Subjects with Interstitial Cystitis/Bladder Pain Syndrome
Brief Title:	Study of V117957 in Interstitial Cystitis/Bladder Pain Syndrome
Compound:	V117957 Tosylate
Phase:	Phase 1b
Sponsor:	Purdue Pharma L.P. One Stamford Forum Stamford, CT 06901-3431 USA
Protocol Approval Date:	01-Aug-2021

Protocol Amendment Number: 5

GCP Statement:	This study is to be performed in compliance with International Conference on Harmonisation (ICH) and applicable Good Clinical Practices (GCPs) and federal and local regulations.
Confidentiality:	This document is confidential. It contains proprietary information of Purdue Pharma. Any viewing or disclosure of such information that is not authorized in writing by the sponsor (or designee) is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

1. Protocol Summary

1.1. Synopsis

Protocol Title:

Multicenter, Randomized, Double-blind Placebo-controlled, Crossover Study to Investigate Effects of V117957 in Female Subjects with Interstitial Cystitis/Bladder Pain Syndrome

Brief Title:

Study of V117957 in Interstitial Cystitis/Bladder Pain Syndrome

Rationale:

V117957 is a selective partial agonist of the nociceptin/orphanin-FQ peptide receptor. V117957 inhibits bladder afferents following systemic administration in rats leading to reduction in the frequency of rhythmic bladder contractions without affecting the magnitude of contraction. V117957 had mixed effects in standard models of overactive bladder in rats (spinal cord injury and bladder outlet obstruction) and was anti-nociceptive in a rat model of interstitial cystitis / bladder pain syndrome (intraperitoneal administration of cyclophosphamide). Based on these animal observations, it is hypothesized that V117957 may be effective in treating symptoms of interstitial cystitis and bladder pain syndrome in humans.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Evaluate effects of V117957 on bladder pain/discomfort in subjects diagnosed with interstitial cystitis/bladder pain syndrome (IC/BPS) compared to placebo	• Bladder pain/discomfort score. – Each evening and morning subject will respond to question "Please indicate the worst bladder pain/discomfort you have had overnight/over the day" using an 11-point numeric rating scale.
[redacted]	[redacted]

[redacted]	[redacted]
Safety	
Assess safety and tolerability of V117957	Adverse events, Clinical laboratory values, Electrocardiograms, Physical examination, Vital signs, Columbia-Suicide Severity Rating Scale (C-SSRS), Epworth Sleepiness Scale (ESS)

Overall Design:

Phase 1b, multicenter, randomized, double-blind, placebo-controlled, crossover study.

Brief Summary:

The purpose of this study is to investigate the effects of oral administration of 1 mg/day V117957 each evening in female subjects with interstitial cystitis/bladder pain syndrome as compared to placebo. The study will consist of a Screening/ Washout Period (up to 2 weeks), Single-blind Placebo Run-in Period (2 weeks), Double-blind Treatment Period (8 weeks), Single-blind Placebo Washout Period (1 week), and Follow-up Period (up to 1 week).

Number of Participants:

It is estimated that up to 150 subjects will be screened to yield approximately 75 subjects who will enter Single-blind Run-in Period to yield approximately 44 subjects who will enter the Double-blind Treatment Period. A sample size of 38 (completers) will have 81% power to detect a treatment difference of bladder pain/discomfort mean scores of 0.5, assuming a standard deviation of differences of 1.4, using a paired t-test with a 10% one-sided significance level. Assuming a 15% dropout rate, a sample size of 44 would be needed.

Treatment Groups and Duration:

V117957 (6-weeks) and Placebo (5-weeks).

Schema:

Phase	**Pre-randomization**			**Post-randomization**									
Period	Screening/ washout	Single-blind Run-in		Double-blind Treatment								Single-blind washout	Follow-up
Day	-28 to -16	-15	-1[A]	1	14	15	28	35	42	49	56	63	70
Clinic Visit	V1		V2		V3		V4		V5		V6	V7	V8
Phone call [B]				P1		P2		P3		P4			
Treatment		Placebo		V117957 or Placebo								Placebo	

[A] At visit 1 subject must meet all inclusion/exclusion criteria. At visit 2, if subject has met all randomization eligibility criteria they may be dispensed double-blind study-drug. [B] Phone contact between clinic visits to assess tolerability and review diary/dosing instructions.

1.2. Schedule of Assessments

Table 1. Schedule of Assessments: Pre-randomization Phase

Period	Screening/washout	Single-blind Run-in	
Day [A]	-28 to -16[H]	-15	-1
Clinic Visit	V1 [B]	V1	V2
Assessment			
Informed consent	X		
Medical history	X		
Demographics	X		
Inclusion/exclusion	X		
Physical exam, full	X		
Physical exam, brief		X [F]	X
Vital signs	X	X [F]	X
Clinical labs (chem/heme/urine)	X	X [F]	X
Urine culture test	X	X [F]	X
Urine drug screen	X		X
Serum pregnancy test	X		
Urine pregnancy test		X [F]	X
12-lead ECG	X	X [F]	X
Concomitant medications	X	X [F]	X
Adverse events	X	X [F]	X
ESS		X [F]	X
C-SSRS	X	X [F]	X
Cystoscopy [C]	X		
Hunner's Lesion Assessment [D]	X		
BPIC-SS	X	X [F]	X
ICSI	X	X [F]	X
ICPI	X	X [F]	X
SGRA			X
SISQ (diary)		Once daily, in morning	
Pain Diary assessment [E]		Twice daily, in morning and evening	
Void Diary assessment (includes PPIUS)		During the week prior to clinic visit (V2), subject will record micturition time, type, and urgency for each episode for a minimum of 3 and up to 7-days; and will *also record* urine volume during 2-day weekend (or other timeframe convenient to subject work/life schedule). *Note: The urine volume collection is mandatory during the Run-in Period and optional (but encouraged) during Double-blind Treatment period.*	
Study drug dosing (diary)		Once daily, in evening	
Diary/dosing instruction		X [F]	X
Dispensing study drug		X [F]	X
Drug accountability			X
IC/BPS Symptoms characterized		X [FG]	
Randomization criteria checklist			X
Randomization			X

BPIC-SS=Bladder Pain/ Interstitial Cystitis Symptom Score; CSSRS=Columbia-Suicide Severity Rating Scale; ECG=Electrocardiogram; ESS= Epworth Sleepiness Scale; ICSI=O'Leary-Sant Interstitial Cystitis Symptom Index; ICPI=O'Leary-Sant Interstitial Cystitis Problem Index; NSQS=Nocturia Sleep Quality Scale; PPIUS= Patient Perception of Intensity of Urgency Scale; SGRA=Subject Global Response Assessment; SISQ= Symptom Impact on Sleep Questionnaire.

[A] visit window is ±3 day. [B] Visit 1, Day -15, is end of Screening/Washout Period and start of the Single-blind Run-in Period. At this visit, a subject that has met all inclusion/exclusion criteria, has stopped current prohibited medications, and completed all study procedures, will be dispensed single-blind study-drug with instruction to ingest first dose that evening 30 minutes before bedtime. [C D] Cystoscopy not required for enrollment; however, ,if available cystoscopy results within last 5 years should be recorded on eCRF. [E] pain assessment to be completed every 12 hours. [F] Item must be completed at the clinic visit on the same day that study drug is dispensed to subject; the

subject will ingest first dose of study drug that evening. [G] [redacted] this must be completed at the clinic visit on the same day that study drug is dispensed to subject; the subject will ingest first dose of study drug that evening.[H]

Table 2 Schedule of Assessments: Post-randomization Phase

Period	Double-blind Treatment									Single-blind washout	Follow-up
Day	-1	1	14	15	28	35	42	49	56	63	70
Clinic visit [A]	V2 [B]		V3		V4		V5		V6	V7/ EOT/ET	V8/ EOS [C]
Phone call [D]		P1		P2		P3		P4			
Assessment											
Physical exam, brief	See Table 1, V2 Day -1		X		X		X		X	X	
Vital signs			X		X		X		X	X	
Clinical labs (chem/hem/urine)			X		X		X		X	X	
Urine culture test			X		X		X		X	X	
Urine drug screen										X	
Serum pregnancy test										X	
Urine pregnancy test			X		X		X		X		
12-lead ECG			X		X		X		X	X	
Concomitant medications		X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X
ESS			X		X		X		X	X	
C-SSRS			X		X		X		X	X	
[redacted]											
[redacted]		[redacted]									
Pain Diary assessment		Twice daily, in morning and evening [E]									
Void Diary assessment (includes PPIUS)		During the week prior to each clinic visit (V3, V4, V5, V6, and V7), subject will record micturition time, type, and urgency for each episode for a minimum of 3 and up to 7-days, and will *also record* urine volume during 2-day weekend (or other timeframe convenient to subject work/life schedule). *Note: The urine volume collection is mandatory during the Run-in Period and optional (but encouraged) during Double-blind Treatment period.*									
Study drug dosing (diary)		Once daily, in evening.									
Diary/dosing instruction	See Table 1, V2 day -1	X	X	X	X	X	X	X	X		
Dispensing Study Drug		X	X		X		X		X		
Drug accountability			X		X		X		X	X	

[redacted] *PPIUS= Patient Perception of Intensity of Urgency Scale;* [redacted] *. V=visit, P=phone.*

[A] Visit window is ±3 day.

[B] Visit 2, Day -1, is end of Single-blind Run-in Period and start of the Double-blind Treatment Period. At visit 2, a subject that has met all inclusion/exclusion criteria, has met all randomization eligibility criteria, and has completed all study procedures, will be dispensed double-blind study-drug with instruction to ingest first dose that evening 30 minutes before bedtime. [C] May be phone call instead of clinic visit if no safety issue identified. [D] Phone contacts to assess tolerability and review diary/dosing instructions. [E] Pain assessment to be completed every 12 hours.

1.3. Study population:

Enrolled population: The group of subjects who sign informed consent.

Randomized safety population: The group of subjects who are randomized and receive at least 1 dose of the study drug and have at least 1 safety assessment.

Full analysis population: The group of subjects who are randomized, receive study drug, and have at least 1 valid efficacy measurement.

Per protocol population: The group of subjects who are included in the full analysis population but excluding those with major protocol deviations and those who do not receive the actual treatment they were randomized to receive.

Subjects and profiles/metrics excluded from the analysis set will be documented in the statistical analysis plan.

1.4. Efficacy Analysis

Listings, tables, and figures of efficacy variables will be based on the full analysis population.

1.4.1. Primary Efficacy Analyses

The baseline, post-baseline and change from baseline for bladder pain/discomfort scores over last 12 hours (morning and night) will be summarized by treatment group using descriptive statistics and presented graphically. Changes from baseline to endpoint in mean bladder pain/discomfort scores will be analyzed by mixed model with treatment, period and sequence as fixed effects, subject within the sequence as a random effect and baseline as a covariate. Comparison of the active treatment to placebo will be tested at the one-sided significance level 0.10 by means of the corresponding contrast. Plots of the least square mean change from baseline and 90% confidence intervals will be produced by treatment group.

1.4.3. Safety Analyses

All safety data (adverse events [AEs], clinical laboratory results, vital signs, physical examinations, electrocardiograms, Columbia-Suicide Severity Rating Scale and Epworth Sleepiness Scale will be listed for subjects in the enrolled and randomized safety populations.

AEs will be categorized into Preferred Term (PT) and associated System Organ Class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (TEAEs) will be defined as AEs that start after or increase in intensity after the first dose of study drug. TEAEs will be summarized by presenting the incidence of AEs for each treatment group by the MedDRA PT, nested within SOC for the randomized safety population. Medical history will be coded to MedDRA terms. Coded medical history terms will be summarized for all subjects in the randomized safety population.

Laboratory evaluations and vital signs will be summarized by treatment and time point for the randomized safety population. Concomitant and prior medications will be coded using the latest version of the World Health Organization Drug Dictionary and presented in tables and listings