A PHASE 4, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, PLACEBO- AND ACTIVE-CONTROLLED, SINGLE-DOSE, FIVE-WAY CROSSOVER STUDY EVALUATING THE ABUSE POTENTIAL OF THREE DOSES OF NEURONTIN® TAKEN ORALLY IN HEALTHY, NON-DRUG DEPENDENT PARTICIPANTS WITH SEDATIVE DRUG ABUSE EXPERIENCE

Investigational Product Number:	PF-00345043
Investigational Product Name:	Neurontin® (gabapentin)
United States (US) Investigational New Drug Application (IND) Number:	28,454 and 57,813
European Clinical Trials Database (EudraCT) Number:	Not Applicable (N/A)
Protocol Number:	A9451181
Version Number	5.0
Phase:	4
Short Title: Evaluating the Abuse Potential of Neurontin® When Taken Orally in Healthy Non-drug Dependent Participants with Sedative Drug Abuse Experience	

Sponsor:	**Viatris Specialty LLC** 3711 Collins Ferry Road Morgantown, WV 26505
Sponsor Contacts:	[redacted]

NCT Number: NCT04570436

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title	A phase 4, randomized, double-blind, double-dummy, placebo- and active-controlled, single-dose, five-way crossover study evaluating the Abuse Potential of three Doses of Neurontin® taken orally in healthy, non-drug dependent participants with sedative drug abuse experience
Protocol Number	A9451181
Version No.	5.0
Protocol Date	29 Apr 2022

Protocol accepted and approved by:

[redacted]
[redacted] Global Clinical Operations

[redacted]

Signature Date

[redacted]
Clinical Development [redacted]
Global Clinical Development

[redacted]

Signature Date

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Protocol Version 5.0	29 Apr 2022	• Change of Sponsor name from Upjohn US 1 LLC to Viatris Specialty LLC • Increasing the number of subjects enrolled • Modifying the definition of the Completer Population (upon which other analysis sets are defined) to specify the minimum required post-dose responses required within the Tmax time periods specific to the two study drugs, in line with FDA guidance on assessing abuse potential of drugs • Addition of the Modified Completer Population as the primary analysis population • Clarification that the Evaluation Population will be the subset of the Modified Completer Population who do not have major protocol deviations • Redefining the permitted time windows for vital signs assessments and PK sampling • Reducing the number of residential nights from 4 to 3 per treatment period, at the investigator's discretion, to facilitate subject enrollment • Adding "multi-center" in the study description • Clarification that subjects must abstain from using THC while resident in the clinic • Addition of further forms of acceptable female contraception • Clarifications and corrections to the statistics sections with respect to the null- and alternative-hypothesis equations, handling of missing pre-dose VAS values, and addition of "site" as a fixed effect • Updating the time period for making trial data available to reflect the change of Sponsor Complete summary of changes is provided in Appendix 13 (Section 10.13)

Protocol Version 4.0	04 Aug 2021	• Modified three inclusion/exclusion criteria, including the definition of an experienced recreational sedative user, in order to facilitate subject enrolment. • Administrative changes to update Sponsor contact details and table numbering change in Appendix 13 Complete summary of changes is provided in Appendix 13 (Section 10.13)
Protocol Version 3.0	26 Feb 2021	• Couple of typographic changes for harmonization within the protocol were implemented. Complete summary of changes is provided in Appendix 10.13
Protocol Version 2.0	11 Dec 2020	• The sponsor for this study is changed from 'Pfizer' to 'Upjohn US 1 LLC' • The responsibility of an Interactive Response Technology (IRT) was transferred to a CRO. • Administrative and typographic changes for harmonization within the protocol were implemented. Complete summary of changes is provided in Appendix 10.13
Original Protocol	14 May 2020	Not applicable (N/A)

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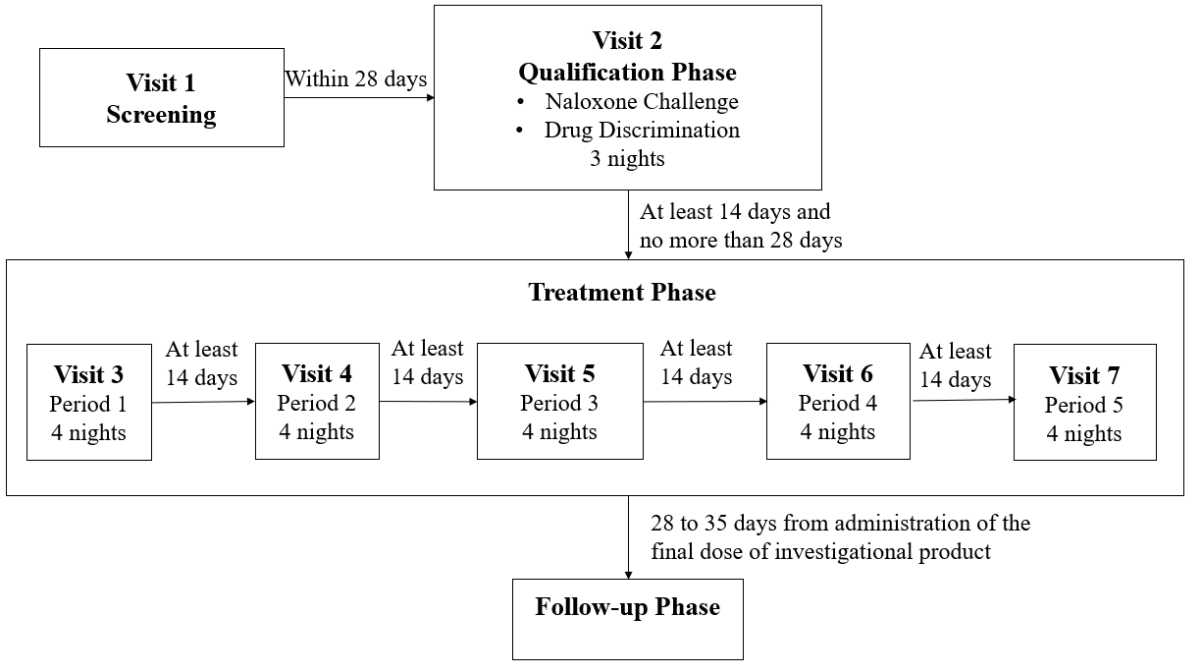
1. PROTOCOL SUMMARY

1.1. Synopsis (Not Applicable)

1.2. Schema

The participants will be screened, undergo a naloxone challenge to ensure that they are not drug dependent and a drug discrimination test to demonstrate that they can differentiate between a positive control and placebo. Once the participant has passed these tests, they may be enrolled into the Treatment Phase of the study. The Treatment Phase of the study will use a Williams square study design involving approximately 50 participants (5 participants in each sequence) to ensure at least 32 participants meeting the definition of the Modified Completer Population complete the treatment phase of the study as shown in Figure 1. Drop-out participants in the treatment phase for non-safety reasons may be replaced at the discretion of investigator in consultation with the sponsor.

Figure 1. Schematic of Study Visits



1.3. Schedule of Activities (SoA)

The SoA tables (Table 1 and Table 2) provide an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, to conduct evaluations or assessments required to protect the well-being of the participant.

Table 1. Schedule of Activities for Screening, Naloxone Challenge and Qualification Phase

	Visit 1 Screening	Visit 2 (Qualification Phase)												
		Naloxone Challenge	Drug Discrimination											
Study Day	Within 28 Days	Day -1	Days 1 and 2											Day 3[p]
Hours Post Dose			Pre-dose	0	0.25	0.5	1	1.5	2	2.5	3	3.5	4	5	24
Clinical Research Unit (CRU) admission		X[a]	→	→	→	→	→	→	→	→	→	→	→	→	
Informed consent	X[b]														
Inclusion/Exclusion	X														
Demographics	X														
Medical history (including drug abuse)	X	X													
Ongoing eligibility review	X	X													X
Prior/Concomitant medication (including past year recreational drug history)	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Physical examination[c]	X	X													X
Safety laboratory tests	X	X													
HIV, HBsAg, HBcAb, HCVAb, HAV IgM, HAV IgG	X														
Urine drug testing	X	X													
Serum Pregnancy test (Woman Of Childbearing Potential [WOCBP] only)	X[d]														
Follicular stimulating hormone (FSH) testing	X[e]														
Urine Pregnancy test (WOBCP only)		X[f]													
Contraception check	X														
Alcohol breathalyzer	X	X													

Table 1. Schedule of Activities for Screening, Naloxone Challenge and Qualification Phase

	Visit 1 Screening	Visit 2 (Qualification Phase)												
		Naloxone Challenge	Drug Discrimination											
Study Day	Within 28 Days	Day -1	Days 1 and 2											Day 3[p]
Vital signs[g]	X	X[h]	X		X	X	X	X	X					
Pulse oximetry, SpO_2			X		X	X	X	X	X	X	X	X	X	
Respiratory rate			X		X	X	X	X	X	X	X	X	X	
12-lead Electrocardiogram[i]	X	X												
Randomization for Qualification Phase, Day 1			X											
Pharmacodynamic (Instrument) training		X												
Cardiac telemetry[j]			X	→	→	→	→	→	→	→	→	→	→	X	
Study treatment administered		X[k]		X										
Visual Analogue Scales (VAS)[l]			X[l(a)]		X	X	X	X	X	X	X	X	X	X	
Take Drug Again, VAS, Overall "Drug Liking"														X
Clinical Opiate Withdrawal Scale (COWS)		X[m]												
Serious and non-serious adverse event monitoring[n]	X	X	→	→	→	→	→	→	→	→	→	→	→	→	X
Columbia Suicide-Severity Rating Scale	X	X													X
Evaluate to proceed[o]		X													X
Discharge from CRU															X

Abbreviations: COWS = Clinical Opiate Withdrawal Scale; CRU = Clinical Research Unit; FSH = follicle stimulating hormone; HAV IgG = hepatitis A virus immunoglobulin G; HAV IgM = hepatitis A virus immunoglobulin M; HBsAg = hepatitis B surface antigen; HCVab = hepatitis C antibody; HIV = human immunodeficiency virus; SpO_2 = saturated oxygen; VAS = Visual Analogue Scale; WOCBP = women of childbearing potential.

a. Admission should occur in the morning to ensure adequate time for pre-dose review of clinical laboratory results.

b. Assign a single participant identifier number.

c. Complete physical examination (PE) (including height and weight) only needs to be done once, ie, at Screening or at Day -1 of Visit 2. However, height and weight must be performed at Screening to obtain BMI for determination of eligibility. A brief symptom-directed physical examination will be conducted as needed on Day -1 and prior to discharge on Day 3.

d. Review of results are required prior to dosing on Visit 2 (ie, Naloxone Challenge).

e. For confirmation of postmenopausal status only.

f. Must be reviewed and confirmed as negative prior to dosing on Day -1.

Table 1. Schedule of Activities for Screening, Naloxone Challenge and Qualification Phase

	Visit 1 Screening	Visit 2 (Qualification Phase)		
		Naloxone Challenge	Drug Discrimination	
Study Day	Within 28 Days	Day -1	Days 1 and 2	Day 3[p]

g. Includes pulse rate, systolic and diastolic blood pressures. Temperature (oral or with a temporal infrared scanner) will be measured at Screening and upon admission on Day -1 of the Naloxone Challenge Phase. Vital signs are measured after a resting period of approximately 5 minutes in a sitting position.

h. Vital signs will be recorded at pre-dose (first naloxone dose) and at 5 minutes, 0.25, 0.5, 1, 1.5, and 2 hours following the second dose of naloxone. Vital signs will be recorded at nominal time points ± 5 minutes.

i. Conducted after a resting period of at least 10 minutes in a supine position.

j. Continuous cardiac telemetry (heart rate, cardiac rhythm, and oxygen saturation) will be monitored for approximately 5 hours post-dose or longer at the discretion of the clinical research unit.

k. Naloxone (0.2 mg IV) is administered first. If there are no signs of withdrawal apparent within 30 seconds after administration, another 0.6 mg naloxone IV is administered.

l. Include VASs for Drug Liking, High, Sleepy, Dizzy, Nausea, and Feel Sick.

l(a); Only for High, Sleepy, Dizzy, Nausea, and Feel Sick are administered at pre-dose.

m. COWS is collected and recorded at pre-dose, and at 30 seconds following the first naloxone dose and 5 minutes after the second dose is administered.

n. Assessed throughout and collected using open-ended questions. Symptoms of withdrawal following naloxone administration (Naloxone Challenge Phase) will not be collected as adverse events unless they meet the criteria for an SAE. Adverse events and serious AEs will be collected from the time the informed consent is signed through and including 28 calendar days after the last administration of the investigational product. During the Drug Discrimination Phase, AEs are collected at pre-dose and 0.25, 0.5, 1, 1.5, 2,2.5, 3, 3.5, 4, 5 and 24 hours post-dose.

o. Evaluation to proceed must occur prior to next scheduled time and event.

p. If participants fail to qualify, all AEs will be reported with no further SoA testing.

Table 2. Schedule of Activities for Treatment Phase

Study Day	Visits 3 to 7 Treatment Phase Periods 1 to 5[a]																		Follow-up	Early termination/discontinuation (DC)
	Day -1 Baseline	Day 1													Day 2		Day 3	Day 4	28 - 35 Days[n]	
Hours Post Dose		**Pre-dose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4**	**6**	**8**	**12**	**24**	**36**	**48**	**72**		
CRU admission	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		
Medical history update	X																		X	
Continuing eligibility check[b]	X																			
Concomitant medication	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X
Physical examination[c]	X																	X[m]		X
Safety laboratory tests[d]	X																	X[m]		X
Urine drug testing[e]	X																			
Urine Pregnancy test (WOCBP only)[f]	X																			
Serum Pregnancy test (WOCBP only)[f]																		X[m]		X
Contraception check	X																		X	X
Alcohol breathalyzer	X																			
Vital signs[g]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Pulse oximetry, SpO_2		X	→	→	→	→	→	→	→	→	→	→	→	→	X	X					X
Respiratory rate		X	→	→	→	→	→	→	→	→	→	→	→	→	X	X					
Tidal volume		X	→	→	→	→	→	→	→	→	→	→	→	→	X	X					
End-tidal carbon dioxide		X	→	→	→	→	→	→	→	→	→	→	→	→	X	X					
Randomization		X[h]																			
Pharmacodynamic (Instrument) training	X																			
Cardiac telemetry[i]		X	→	→	→	→	→	→	→	→	→	→	→	→							
Study treatment administration			X																		
VAS[j]		X[j] (a)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
VAS for Overall Drug Liking and "Take Drug Again"																X	X	X	X		X
VAS for Good Drug Effect, Bad Drug Effect, and Any Drug Effect				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Observer-rated assessment of alertness/sedation		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Table 2. Schedule of Activities for Treatment Phase

Study Day	Visits 3 to 7 Treatment Phase Periods 1 to 5[a]																		Follow-up	Early termination/discontinuation (DC)
	Day -1 Baseline	Day 1														Day 2		Day 3	Day 4	28 - 35 Days[n]	
Hours Post Dose		Pre-dose	0	0.25	0.5	1	1.5	2	2.5	3	3.5	4	6	8	12	24	36	48	72		
Viatris Prep D1 Banked biospecimen[k]	X																				
Pharmacokinetic blood sampling		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Serious and non-serious adverse event monitoring[l]	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X
Columbia Suicide-Severity Rating Scale	X																		X	X	X
ECG[o]	X																		X		
Discharge from CRU																		X[p]	X		
Discharge from Study																				X	

Table 2. Schedule of Activities for Treatment Phase

Study Day	Visits 3 to 7 Treatment Phase Periods 1 to 5[a]																			Follow-up	Early termination/discontinuation (DC)
	Day -1 Baseline	Day 1														Day 2		Day 3	Day 4	28 - 35 Days[n]	
Hours Post Dose		Pre-dose	0	0.25	0.5	1	1.5	2	2.5	3	3.5	4	6	8	12	24	36	48	72		

a. Treatment Periods will be separated by at least of 14 days between dosing.

b. Continuing eligibility checks will include checks of UDS, ethanol breath test, pregnancy tests, compliance with Lifestyle guidelines, and any changes to medical conditions that may require participant rescheduling or discontinuation.

c. Physical examinations will be brief and symptom-directed (if a change in medical history is reported). Symptom-directed physical examinations may be performed at admission to each visit at the discretion of the Investigator. A complete physical examination will be conducted at End of Study or early termination (ET).

d. See Appendix 2.

e. Urine drug screens may be repeated for confirmatory purposes at the discretion of the Investigator or designee.

f. For all female participants, urine pregnancy tests will be obtained upon admission to each Treatment Visit and a serum pregnancy test will be obtained at the End of Study Visit.

g. Vital signs (including pulse rate, systolic and diastolic blood pressures are measured at the nominal time points after a resting period of at least 5 minutes in a sitting position. Temperature (oral or with a temporal infrared scanner) will be measured on Day -1 of each Treatment Visit only. Vital signs will be recorded at nominal time points ±5 min for time points up to and including 4 h post-dose, within ±15 minutes for time points from 6-12 h post-dose, and within ±60 minutes for the remaining time points up to and including 72 h post-dose.

h. Visit 3 pre-dose only.

i. Continuous cardiac telemetry (heart rate, cardiac rhythm, and oxygen saturation) will be monitored from pre-dose for approximately 8 hours post-dose or longer at the discretion of the clinical research unit.

j. Include VASs for Drug Liking, High, Sleepy, Dizzy, Nausea, and Feel Sick.

J(a); Only VASs for High, Sleepy, Dizzy, Nausea, and Feel Sick are administered at pre-dose.

k. Visit 3 pre-dose only on Day -1. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

l. Spontaneous AE reporting will occur throughout study; however, AEs will also be elicited using non-leading questions during the Treatment Phase at pre-dose and post-dose at the indicated times. AEs and SAEs will be collected from the time the informed consent is signed through and including 35 calendar days after the last administration of the investigational product.

m. End of study only.

n. Contact may occur via telephone contact and must occur 28 to 35 days from administration of the final dose of investigational product.

o. 12-lead Electrocardiogram measurements (conducted after a resting period of at least 10 minutes in a supine position) at Day -1 (baseline) and Day 4 during Treatment Phase

p. Subjects may be discharged after completion of Day 3 assessments and return for Day 4 assessments, at the discretion of the investigator.

2. INTRODUCTION

2.1. Study Rationale

Neurontin® (gabapentin) is indicated for postherpetic neuralgia in adults, adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization in adults and pediatric patients 3 years and older with epilepsy.

Gabapentin does not exhibit affinity for benzodiazepine, opiate (mu, delta or kappa), or cannabinoid 1 receptor sites; however, gabapentin abuse has been reported at increasing rates. Individuals abusing gabapentin describe experiences such as euphoria, improved sociability, relaxation and a marijuana-like "high".[1-8]

There are post-marketing reports of abuse and individuals experiencing withdrawal symptoms shortly after discontinuing higher than recommended doses of gabapentin used to treat illnesses for which the drug is not approved. Such symptoms included agitation, disorientation and confusion after suddenly discontinuing gabapentin that resolved after restarting gabapentin. Most of these individuals were taking higher than recommended doses of gabapentin for unapproved uses and had a history of poly-substance abuse or used gabapentin to relieve symptoms of withdrawal from other substances.

Epidemiological studies have shown that gabapentin may have abuse potential, particularly among individuals with a history of opioid abuse. Gabapentin abuse is reported both alone (*ie*, without other drugs), and in conjunction with opioids to enhance the 'high' obtained from opioids.[1,4] Further, published data suggest that gabapentin is recorded on death certificates suggesting drug overdose, both as the primary and contributory causes of death, and reported with and without other drugs like opioids, benzodiazepines, and alcohol.[1,5-7] As a consequence, the FDA requires this post-authorization safety study (PASS) to evaluate gabapentin in a cross-over design with comparison to placebo and a positive control, diazepam, regarding abuse-related subjective responses, physiological responses (including an assessment of respiratory depression), and drug pharmacokinetics in a healthy non-drug dependent population with drug abuse experience with sedative drugs.

2.2. Background

The precise mechanisms by which gabapentin produces its analgesic and antiepileptic actions are unknown. Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but has no effect on GABA binding, uptake, or degradation. *In vitro* studies have shown that gabapentin binds with high-affinity to the $\alpha 2\delta$ subunit of voltage-activated calcium channels; however, the relationship of gabapentin binding to its therapeutic effects or potential abuse is unknown.

Approximately 1.1% of the general population and 22% of those attending addiction facilities have a history of abuse of gabapentin[8,9] and there have been deaths from gabapentin use with benzodiazepines and opioids.[1-7] The purpose of the present study is to assess prospectively the abuse potential of gabapentin compared to placebo and diazepam.

2.2.1. Clinical Overview

Neurontin® formulations are available in strengths of 100 mg, 300 mg, 400 mg capsules and 600 mg and 800 mg tablets and in an oral solution containing 250 mg/5 mL of gabapentin. Gabapentin is rapidly absorbed following oral administration. Peak concentrations were observed within 2 to 3 hours. Gabapentin bioavailability is not dose proportional; ie, as dose is increased, bioavailability decreases. Bioavailability of gabapentin is approximately 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day given in 3 divided doses, respectively. Food has only a slight effect on the rate and extent of absorption of gabapentin (14% increase in area under the curve [AUC] and maximum observed concentration [C_{max}]). Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans. Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance.[10]

Valium® (diazepam) is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety. After oral administration >90% of diazepam is absorbed and the average time to achieve peak plasma concentrations is 1 – 1.5 hours with a range of 0.25 to 2.5 hours. Absorption is delayed and decreased when administered with a moderate fat meal. In the presence of food, mean lag times are approximately 45 minutes as compared with 15 minutes when fasting. Diazepam is N-demethylated by Cytochrome P450 (CYP)3A4 and 2C19 to the active metabolite N-desmethyldiazepam and is hydroxylated by CYP3A4 to the active metabolite temazepam. N-desmethyldiazepam and temazepam are both further metabolized to oxazepam. Temazepam and oxazepam are largely eliminated by glucuronidation.[11] Metabolites have 25% to 33% of diazepam's anticonvulsant activity. As a result of extensive first-pass metabolism, the unchanged diazepam in the urine is only 1–3%.[12] The initial distribution phase is followed by a prolonged terminal elimination phase (half-life up to 48 hours). The terminal elimination half-life of the active metabolite N-desmethyldiazepam is up to 100 hours. Diazepam and its metabolites are excreted mainly in the urine, predominantly as their glucuronide conjugates. The clearance of diazepam is 20 to 30 mL/min in young adults.

2.3. Benefit/Risk Assessment

Neurontin® and diazepam are not expected to provide any clinical benefit to healthy participants in this study. This study is designed to assess the effect of Neurontin® compared to diazepam when taken orally in healthy non-dependent recreational drug abusers on the pharmacokinetics of each drug and the potential for abuse.

More detailed information about the known and expected benefits and risks and expected adverse events (AEs) of gabapentin and diazepam may be found in the single reference safety document (SRSD) for this study. The SRSDs for gabapentin and diazepam are their respective United States Package Inserts (USPI).[10,11]

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To assess the potential abuse liability of orally administered Neurontin® taken alone compared to placebo in a healthy non-drug dependent participants with drug abuse experience under fasted condition.	• Bipolar visual analog scale (VAS) for "Drug Liking" maximum effect (E_{max}).
Secondary:	**Secondary:**
• To evaluate additional pharmacodynamic (PD) effect, pharmacokinetics (PK), and safety of Neurontin® or diazepam taken alone in a healthy non-drug dependent participants with drug abuse experience under fasted condition.	**PD endpoints:** • Bipolar VAS for "Drug Liking" (Time for E_{max} [TE_{max}], area under the effect-time profile from time 0 to the time of the last quantifiable concentration [$AUEC_{last}$], and partial AUECs [$AUEC_1$, $AUEC_2$, $AUEC_3$, $AUEC_4$, $AUEC_8$]). • Unipolar VAS for "High" (E_{max}, TE_{max}, $AUEC_{last}$, and partial AUECs [$AUEC_1$, $AUEC_2$, $AUEC_3$, $AUEC_4$, $AUEC_8$]). • Bipolar VAS for "Take Drug Again" at 24, 36, 48, and 72 hour post-dose. • Bipolar VAS for "Overall Drug Liking" at 24, 36, 48, and 72 hours post-dose. • Unipolar VAS for "Good Drug Effect". • Unipolar VAS for "Bad Drug Effect". • Unipolar VAS for "Any Drug Effect". • Observer-rated assessment of alertness/sedation. **PK endpoints:** • C_{max}, time for C_{max} (T_{max}), area under the effect-time profile from time 0 to the time of the last quantifiable concentration (AUC_{last}) of gabapentin and, if deemed necessary for diazepam and its active metabolite (N-desmethyldiazepam). • Area under the plasma concentration-time profile from time 0 extrapolated to infinity time (AUC_{inf}), and terminal half-life ($t_{½}$), if data permits, of gabapentin and, if deemed necessary

Objectives	Endpoints
	for diazepam and its active metabolite (N-desmethyldiazepam). • Partial AUCs (AUC_1, AUC_2, AUC_3, AUC_4, and AUC_8) of gabapentin and, if deemed necessary for diazepam and its active metabolite (N-desmethyldiazepam). **Safety endpoints:** • Vital signs (respiratory rate [RR], blood pressure [BP], pulse rate [PR]). • Oxygen saturation of hemoglobin (SpO_2). • Physical examination. • 12-lead electrocardiogram (ECG). • Clinical lab and AEs.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• Exposure-response relationship between drug (gabapentin or diazepam) concentrations and selected PD effect. • To enable exploratory research through collection of banked biospecimens, unless prohibited by local regulations or ethics committee decision.	• Correlation between drug (gabapentin or diazepam) concentrations and selected PD endpoints (Bipolar VAS for "Drug Liking", Unipolar VAS for "High"), as data permit. • Potential results from exploratory analysis of banked biospecimens (these results may or may not be generated in the context of the present study).

4. STUDY DESIGN

4.1. Overall Design

This will be a multi-center, randomized, double-blind, double-dummy, placebo- and active-controlled, 5-treatment, 10-sequence, 5-period crossover single-dose, Williams square design study in healthy adult, non drug-dependent male and female participants with drug abuse experience with sedative drugs. The study includes Screening, a Qualification Phase, a Treatment Phase and Follow-up. This study will randomize approximately 50 participants to ensure at least 32 participants meeting the definition of the Modified Completer Population complete the Treatment Phase of the study. Dropouts in the treatment phase for non-safety reasons may be replaced at the discretion of investigator in consultation with the sponsor.

The following study visits are required, see Figure 1 and the SoA (Table 1 and Table 2):

- Visit 1, Screening will occur within 28 days prior to Visit 2.

- Visit 2, Qualification Phase will require inpatient stay at the clinical research unit (CRU) for 3 nights:
    - Naloxone Challenge Phase, Day -1.
    - Drug Discrimination, Days 1 and 2 will require inpatient stay at the CRU for 2 nights.
    - End of Drug Discrimination requires an inpatient stay at the CRU overnight to ensure discharge occurs 24 hours after receiving diazepam or placebo.
    - Participant will proceed to Visit 3 after at least 14 and no more than 28-day washout.
- Visits 3 to 7, Treatment Phase:
    - Each visit will require an inpatient stay at the CRU of 3 or 4 nights. Subjects may be discharged after completion of 48 h postdose assessments and return for 72 h postdose assessments on an ambulatory basis, at the discretion of the investigator.
    - Each visit will be separated by a washout period of at least 14 days.
    - End of Study Assessments will be at the CRU 72 hours after completing the last study drug dosing at the end of period 5 or at the time of early withdrawal.
    - For the entire study, 18 - 23 overnight inpatient stays will be required.

4.1.1. Screening

As shown in the SoA (Table 1), all participants will complete a Screening Visit with a standard medical screening to determine eligibility for this study. This visit (Visit 1) will occur within 28 days of the Qualification Phase of the study (Visit 2).

4.1.2. Qualification Phase (Visit 2; Days -1 to 3)

4.1.2.1. Naloxone Challenge (Day -1)

As shown in the SoA (Table 1), eligible participants who successfully complete the Screening Visit will return to the study center to complete the naloxone challenge. The naloxone challenge (Day -1) will be performed to ensure the participant is not physically dependent on opioids.

During the Naloxone Challenge, all participants will receive intravenous (IV) naloxone 0.2 mg dose as an IV bolus, followed by an assessment for signs of opioid withdrawal. If there are no signs of opioid withdrawal within 30 seconds after administration, a second dose of 0.6 mg IV will be administered within 5 minutes of the first dose, followed by another assessment for signs of opioid withdrawal 5 minutes after the second naloxone dose. Only participants who do not have signs and symptoms of opioid withdrawal, as assessed by the

Clinical Opioid Withdrawal Scale (COWS score <5), [Appendix 8] will be eligible to proceed to the Drug Discrimination Phase.

Any participant demonstrating evidence of withdrawal (COWS score ≥5) on any assessment will not be eligible for further participation in the trial. The participant will be released from the study center when medically stable, as determined by the investigator. Symptoms reported in the COWS as a consequence of opioid withdrawal will not be collected as AEs unless they meet the criteria for a new AE or serious adverse event (SAE).

4.1.2.2. Instrument Training

After successful completion of the Naloxone challenge, all eligible participants will undergo training on proper completion of the VAS instrument used to collect the PD endpoints. This will be done to ensure that participants fully understand how to perform the test, that they feel comfortable with the testing methods used for PD assessment and have attained a stable level of performance on the various performance-based measures. Detailed instructions for participant training will be provided in a separate study specific document.

4.1.2.3. Drug Discrimination (Days 1 to 3)

Following completion of the instrument training, the eligible participants will be evaluated for drug discrimination. The purpose of this phase is to select participants who can discriminate between the subjective effects of diazepam 20 mg and placebo when administered orally.

The drug discrimination will be performed over 2 consecutive days. The treatments will be double blind. The participants will be randomly assigned to receive one of the blinded treatments (diazepam 20 mg or placebo) on the first day and then receive the alternate treatment the next day according to a Williams square design (Table 3).

Table 3. Schema for Qualification Phase

Treatment Periods 1 and 2	
Day 1	**Day 2**
A	B
B	A

Treatment A: diazepam 20 mg.
Treatment B: placebo.

Pharmacodynamic (VAS) and safety assessments (vital signs, pulse oximetry and respiratory rate) will be conducted at pre-dose and up to 5 hours post dosing. Continuing eligibility will be based on the participant's ability to:

- Assess "Drug Liking" using the bipolar VAS of 0-100 such that the administration of placebo produces a score between 40-60 points;
- Have a diazepam VAS score outside of the placebo range of at least 15 points;
- Tolerate study treatments safely; ie, SpO_2 ≥90%, no episodes of vomiting within the first 2 hours post-dose;

- Demonstrate general behavior suggestive that the participant could successfully complete the study, as judged by the study center staff.

Only those participants who produce these results may be enrolled in the study.

Participants will be discharged from the clinic on Day 3 of the drug discrimination phase, approximately 24 hours after the last dose of either diazepam or placebo.

Following completion of Day 2 procedures, the study data for each participant will be unblinded and a determination will be made by the sponsor and investigator (and/or designee) if the participant is eligible to continue in the study.

4.1.3. Treatment Phase (Visits 3 to 7)

As shown in the SoA (Table 2), participants who successfully complete the Naloxone Challenge and the Drug Discrimination Phase and who meet all the Randomization Criteria will be randomized into the Treatment Phase of this randomized, double-blinded, placebo- and active-controlled, crossover study.

On Day 1 of each of the 5 periods, which will be separated by a washout of at least 14 days, participants will receive an oral dose of either gabapentin 600 mg, 1200 mg or 1800 mg or 20 mg dose of diazepam or placebo. Study treatments will be administered under fasted conditions (overnight fast and no food until 4 hours after dosing). Water will be allowed without restriction until 1 hour prior to dosing and 1 hour after dosing.

Physiological and subjective scales will be used to assess the potential for abuse of 3 doses of gabapentin compared to single dose of diazepam monotherapy and placebo. The blood samples for the analysis of gabapentin and diazepam (including its major active metabolite: N-desmethyldiazepam) in plasma will be obtained pre-dose (immediately prior to dosing) and post-dose as outlined in the SoA (Table 2). Vital signs including pulse rate (PR), blood pressure (BP), respiratory rate (RR), and pulse oximetry will be evaluated, and tolerability and safety will be assessed for all treatments by monitoring AEs.

4.2. Scientific Rationale for Study Design

There is a need to systematically evaluate the abuse potential of gabapentin with comparison to placebo and a positive control (such as diazepam), investigating a range of gabapentin dose (the highest therapeutic and supra-therapeutic) in a healthy non-drug dependent population with sedative drug abuse experience. Therefore, the study design will employ a 10-sequence, 5-period, cross-over design which will include the placebo, positive control, and three doses of gabapentin alone to allow for the various comparisons to be systematically evaluated. The washout period will be least 14 days minimizing the carry-over effects of the treatments. PK will be evaluated to allow for an exploratory correlation of pharmacodynamic effects.

Banked biospecimens will be collected for exploratory pharmacogenomic/genomic/biomarker analyses and retained in the Biospecimen Banking System (BBS), which makes it possible to better understand the investigational product's

mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

4.3. Justification for Dose

The highest therapeutic single dose of Neurontin® in adults for postherpetic neuralgia is 600 mg, 3 times a day (TID) (1800 mg/day). Doses above 1800 mg/day did not demonstrate additional clinical benefit. The recommended maintenance dose of Neurontin® for epilepsy is between 300 mg to 600 mg, TID. Therefore, three doses of Neurontin®, 600 mg (highest therapeutic single dose), 1200 mg (2 times of the highest therapeutic single dose), 1800 mg (3 times of the highest therapeutic single dose) were selected to adequately explore a range of doses to determine the abuse potential of Neurontin® when administered orally alone and diazepam monotherapy in this study.

The prescribing dose of diazepam in the management of anxiety disorders and relief of symptoms of anxiety is 2 mg to 10 mg, 2 to 4 times daily upon severity of symptoms. According to the literature,[13-15] studies using recreational sedative users have obtained significant results with doses of diazepam ranging from 10 to 40 mg. Diazepam showed dose-dependent increases in participant- and observer-rated sedation and drug liking within the range (eg, 10 mg, 20 mg, and 40 mg). A single dose of diazepam 20 mg produced significant positive subjective effects compared to the placebo group in human abuse potential studies. In the previous Pfizer human abuse potential study (Pregabalin clinical study 1008-098[16]), a single dose of diazepam 15 mg or 30 mg in a cross-over design was given in a moderately heavy sedative/alcohol-using population and produced positive psychoactive effects indicative of abuse potential. Thus, a single dose of diazepam 20 mg was selected as a positive control for this study.

Neurontin® formulations are available in capsule, tablet, and oral solution. The marketed Diazepam formulations are also available in tablet and oral solution.

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 visit.

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

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a participant is suitable for this protocol.

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 the following criteria apply:

Age and Sex:

1. Male and female participants must be 18 to 65 years of age, inclusive, at the time of screening.

2. Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

3. Male and female participants who are overtly healthy. Healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, complete physical examination, vital signs, 12-lead electrocardiogram (ECG), and/or clinical laboratory tests.

4. Participants must be recreational sedative users, defined as those reporting using a sedative agent (eg, barbiturates, benzodiazepines) for its intoxicating effects on at least 10 lifetime occasions and at least once in the 12 weeks before the Screening Visit (Visit 1), but who have no signs of dependence and are not seeking treatment for their sedative use.

5. Participants must satisfactorily complete both the Naloxone Challenge and the Drug Discrimination phases.

6. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

Weight:

7. Body mass index (BMI) of 17.5 to 34 kg/m^2, inclusive; and a total body weight >50 kg (110 lb).

Informed Consent:

8. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions:

1. Participants with current or past diagnosis of any type of drug dependence within the past year. Diagnosis of substance and/or alcohol dependence (excluding caffeine and nicotine) will be assessed by the Investigator using the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria performed at Screening. Current drug use will be allowed if the candidate can produce a negative urine sample and are free of any signs/symptoms of withdrawal. The candidate will be informed if they have a positive breathalyzer test.

2. Participants are heavy smokers or users of other types of nicotine products (>20 cigarettes equivalents per day)

3. Participants are unable to abstain from smoking for at least 2 hours before and at least 8 hours after study drug administration.

4. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

5. Participants with any history of sleep apnea, myasthenia or glaucoma.

6. Any condition possibly affecting drug absorption (eg, gastrectomy) excluding cholecystectomy within 1 year prior to study.

7. Clinical or laboratory evidence of active hepatitis A infection or a history of human immunodeficiency virus (HIV) infection, hepatitis B, or hepatitis C, and/or positive testing for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody (HCVAb).

8. Participants with active suicidal ideation or suicidal behavior within 5 year prior to Screening as determined through the use of the Columbia-Suicide Severity Rating Scale (C-SSRS) or active ideation identified at Screening or on Day -1.

9. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

Prior/Concomitant Therapy:

10. Use of prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of investigational product. (Refer to Section 6.5 for additional details).

11. Herbal supplements and herbal medications must be discontinued at least 28 days prior to the first dose of study medication.

Prior/Concurrent Clinical Study Experience:

12. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives (whichever is longer) preceding the first dose of investigational product used in this study.

Diagnostic Assessments:

13. Positive urine drug screen (UDS) for substances of abuse at each admission in Qualification and Treatment Phase, excluding tetrahydrocannabinol (THC). If a participant presents with a positive UDS excluding THC at any admission or any visit, the investigator, at his/her discretion, may reschedule a repeat UDS until the UDS is negative, excluding THC, before the participant is permitted to participate in any phase of the study.

14. Participants unable to abstain from using THC during the inpatient stays in the Qualification and Treatment Phases of the study.

15. Has participated in, is currently participating in, or is seeking treatment for substance-and/or alcohol-related disorders (excluding nicotine and caffeine).

16. Has a positive alcohol breathalyzer test at Screening or upon admission to the study center at Visits 2-6. Positive results may be repeated and/or participants re-scheduled at the Investigator's discretions.

17. Screening sitting BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility. Repeated BP tests should be spaced at least 5 minutes apart.

18. Baseline (screening) 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline corrected QT (QTc) interval >450 msec, complete left bundle branch block [LBBB], signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree atrioventricular [AV] block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT

interval is >450 msec, this interval should be rate-corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants.

19. Participants with ANY of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed to be clinically significant in the opinion of the investigator:

    - Aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) level ≥1.5 × upper limit of normal (ULN);

    - Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

Other Exclusions:

20. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.

21. History of sensitivity to heparin or heparin-induced thrombocytopenia.

22. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.

23. History of hypersensitivity to gabapentin or diazepam or any of the components in the formulation of the study products.

24. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Sponsor employees, including their family members, directly involved in the conduct of the study.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the pre-dose PK sample for fasted treatment.

- Water is permitted until 1 hour prior to investigational product administration. Water may be consumed without restriction beginning 1 hour after dosing. Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices-see below) may be consumed with meals and the evening snack.

- Lunch will be provided approximately 4 hours after dosing.

- Dinner will be provided approximately 9 to 10 hours after dosing.

- An evening snack may be permitted.

- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of investigational product until collection of the final PK blood sample.

- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeinecontaining products for 24 hours prior to the start of dosing until collection of the final PK sample of each study period.

- Participants will abstain from alcohol for 24 hours prior to admission to the clinical research unit (CRU) and continue abstaining from alcohol until collection of the final PK sample of each study period. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Participants will not be permitted to smoke from at least 2 hours before until at least 8 hours after dosing in the Qualification and Treatment Phases. At all other times while housed in the study center, smoking may be permitted in short breaks at the study center staff's discretion. The use of oral or chewed tobacco and/or nicotine-containing products (including topical patches) is not permitted from at least 2 hours before and at least 8 hours after study drug administration.

5.3.3. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

5.3.4. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its

consistent and correct use. At time points indicated in the schedule of activities (SoA), the investigator or designee will inform the participant of the need to use effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the Qualification Phase. Screen failure data are collected and remain as source and are not reported to the clinical database.

6. STUDY INTERVENTION

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

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

6.1. Study Interventions Administered

For this study, the investigational products are Neurontin® and diazepam.

Neurontin® and diazepam will be provided by Viatris Specialty LLC.

6.1.1. Administration

Following an overnight fast of at least 10 hours, participants will receive investigational product at approximately 08:00 hours (±2 hours). Detailed instructions on preparation of all study treatments, including steps to maintain the double blind, will be provided separately in Drug Administration Instructions (DAI).

In order to standardize the conditions on PK sampling days, all participants will be required to refrain from lying down (except when required for ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing. Water may only be consumed 1 hour following dosing.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

3. 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). All study interventions will be accounted for using an investigational product accountability form/record.

4. Further guidance and information for the final disposition of unused study interventions are provided in the investigational product (IP) manual.

5. Any storage conditions stated in the single reference safety document (SRSD) will be superseded by the storage conditions stated on the product label.

6. Study interventions should be stored in their original containers and in accordance with the labels.

7. Deviations from the storage requirements, including any actions taken, must be documented and reported to Sponsor upon discovery. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Sponsor provides permission to use the study intervention. It will not be considered a protocol deviation if Sponsor approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Sponsor approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

8. The sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Sponsor , and all destruction must be adequately documented.

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the investigational product ready for administration or dispensing to the participant/caregiver

by qualified staff. Dispensing is defined as the provision of investigational product, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, participant, or caregiver in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

Investigational products will be prepared at the CRU in the individual dosing containers by 2 operators, at least 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The investigational products will be provided in appropriate containers and labeled in accordance with Sponsor regulations and the clinical site's labeling requirements.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

At screening, participants will be assigned a subject screening identification number (SSID)via an automated Interactive Response Technology (IRT) or equivalent system.

Following screening the participants will be randomly assigned a qualification randomization number (QRN) via the IRT or equivalent system using a 1:1 randomization.
The QRN will be retained throughout the study and will correspond to the blinded qualification phase.

After satisfactory completion of the qualification phase, participants will randomly be assigned a study randomization number (SRN) via the IRT or equivalent system using a 1:1 randomization for the treatment phase. The SRN will be retained throughout the study and will correspond to the blinded treatment sequence.
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6.3.2. Breaking the Blind

The investigator site, study monitor(s), and Sponsor personnel will be blinded to study treatment. The site will have an unblinded pharmacist for preparation of the study drugs. The unblinded pharmacist or unblinded designee at the study center will be responsible for ensuring blinding procedure oversight at the study center, according to the study center guidelines. The unblinded pharmacist will not be able to perform any other duties for this study outside of the requirements of ensuring the blind.

At the completion of the Drug Discrimination Phase, the investigator and/or designee will un-blind the subject's treatment sequence in order for the investigator and Sponsor personnel to assess participant eligibility to continue to the Treatment Phase of the study. Additional information regarding the criteria for Drug Discrimination can be found in Section 4.1.2.3. Treatment data during the Treatment Phase of the study will remain blinded throughout the course of treatment until the study database has been locked. Unblinding during the Treatment Phase will not occur unless medically necessary for participant safety.

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 treatment 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 or medical monitor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment 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 data collection tool (DCT).

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

Investigational product will be administered under the supervision of investigator site personnel. The oral cavity of each participant will be examined following dosing to ensure the investigational product was taken.

6.5. Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of investigational product. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

Females using hormonal contraceptives or taking hormone replacement therapy are eligible to participate in this study.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of investigational product will be documented as a prior treatment. Treatments taken after the first dose of investigational product will be documented as concomitant treatments.

6.6. Dose Modification

Dose modification will not be allowed in this single dose study.

6.7. Emergency Intervention

- The investigational site shall have a fully equipped "crash cart" and advanced cardiac life support (ACLS) certified staff present during the entire study.

- Acute gabapentin and/or diazepam toxicity can be manifested as drowsiness, respiratory depression, and somnolence progressing to stupor, coma or death. In the

event that acute gabapentin and/or diazepam toxicity occurs, primary attention shall be given to re-establishment and/or maintenance of an open airway including assisted or controlled ventilation.

- Other supportive measures including the use of oxygen and vasopressors should be employed in the standard management of circulatory shock if it occurs in the event of gabapentin and/or diazepam toxicity, or other/further treatments as appropriate.

6.8. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue investigational product. If investigational product is permanently discontinued, the participant will not remain in the study. See the SoA for data to be collected at the time of discontinuation of investigational product.

ECG Changes

If the ECG of a participant meets the bulleted criteria below, then 2 more ECGs will be performed. If the average of the three ECGs meets the bulleted criteria below, the participant is to be withdrawn from the study.

- QTc, corrected QT using Bazett's method (QTcB), corrected QT using Fridericia's method (QTcF) >500 msec.

- Change from baseline: QTc >60 msec.

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. 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.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Potential Cases of Acute Kidney Injury

Abnormal values in serum creatinine (SCr) concurrent with presence or absence of increase in blood urea nitrogen (BUN) that meet the criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events.

An increase of ≥0.3 mg/dL (or ≥26.5 µmol/L) in SCr level relative to the participant's own baseline measurement should trigger another assessment of SCr as soon as practically feasible, preferably within 48 hours from awareness.

If the second assessment (after the first observations of ≥0.3 mg/dL [or ≥26.5 µmol/L] in SCr relative to the participant's own baseline measurement) is ≥0.4 mg/dL (or ≥35.4 µmol/L), the participant should be discontinued from the study and adequate, immediate, supportive measures taken to correct apparent acute kidney injury.

Participants should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, laboratory tests should include serum BUN, serum creatine kinase, and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr. If ≥2 healthy participants in a given period are noted to have 2 *consecutive* SCr results of ≥0.3 mg/dL (or ≥26.5 µmol/L), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

Pregnancy

In the case of a positive confirmed pregnancy, the participant will be withdrawn from 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, compliance, or administrative reasons.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples, but data already generated from the samples will continue to be available and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

If the participant withdraws from the study and withdraws consent (see below) for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Clinical Trial (CT) SAE Report.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

Withdrawal of Consent:

Participants who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

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 and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether 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). 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.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Participants will be screened within 28 days prior of the Qualification Phase to confirm that they meet the study population criteria for the study. The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. In addition, other clinical assessments or specimen collections, eg, banked biospecimens, may be used without repeat collection, as appropriate.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

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.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate and BP) should be collected prior to the insertion of the catheter.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 479 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Sponsor, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations and Concomitant Therapy sections of the protocol.

8.1. Efficacy Assessments (Not applicable)

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant-reported symptoms.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and weight will also be measured and recorded as per the SoA. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

8.2.2. Vital Signs

Sitting BP will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) should be used throughout the study. Participants should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP is acceptable. Pulse rate and oxygen saturation will be measured with a pulse oximeter. When the timing of these measurements coincides

with a blood collection, BP, pulse oximetry and respiratory rate should be obtained prior to the nominal time of the blood collection.

Pulse and respiratory rates, oxygen saturation, diastolic and systolic blood pressure will be monitored post-drug (See SoA). These measures are done in abuse liability testing to ensure safety.

Additional collection times, or changes to collection times, of BP, pulse oximetry and respiratory rates will be permitted, as necessary, to ensure appropriate collection of safety data.

If the participant develops orthostatic hypotension, the procedure for collecting postural or orthostatic data will be:

- Assess BP after the participant is in the supine position for a minimum of 5 minutes;
- Have the participant stand up for 2 minutes;
- Assess BP after the participant is in the standing position for approximately 2 minutes.

Orthostatic hypotension is defined as a decrease of ≥20 mm Hg for systolic BP or ≥10 mm Hg for diastolic BP 2 minutes after standing from a supine position. Orthostatic hypotension may be symptomatic or asymptomatic. Symptoms of orthostatic hypotension are those that develop upon assuming the erect posture from a supine position and may include: lightheadedness, dizziness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache, and/or neck ache.

If a participant has symptoms suggestive of orthostasis, but not documented orthostatic hypotension, repeated measurements of supine/standing BP should be obtained. Lesser degrees of BP reduction may still be considered clinically significant if the participant becomes symptomatic upon standing, especially in the presence of a significant increase in pulse rate (≥30 beats per minute [bpm]).

8.2.2.1. Respiratory Monitoring

Respiratory rate (RR, breaths/min), pulse oximetry, tidal volume (VT, mL) and end-tidal carbon dioxide (ETCO2, mmHg) will be measured continuously, pre-dose to 8 hours and then for 5 minutes at 12 hours and 24 hours post-dose during the Treatment Phase (see SoA).

8.2.2.2. Temperature

Temperature will be measured orally or with a temporal infrared scanner. No eating, drinking, or smoking is allowed for 15 minutes prior to the oral measurement.

8.2.3. Electrocardiograms

Twelve (12)-lead ECGs should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures

pulse rate (PR), QT, and QTc intervals and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) a post-dose QTc interval is increased by ≥30 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTc values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a post-dose QTc interval remains ≥30 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator), or QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 7.

8.2.3.1. Continuous Cardiac Monitoring by Telemetry

Continuous cardiac monitoring will be performed as noted in the SoA. The time, duration, and description of any clinically significant abnormal rhythm will be reported as an adverse event.

8.2.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 to 35 days after the last dose of 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 such 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 assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

Participants may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for participants to receive investigational product.

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

8.2.5.1. Columbia Suicidality Severity Rating Scale (C-SSRS)

The Columbia Suicide-Severity Rating Scale (C-SSRS) will be collected at timepoints on the SoA. The C-SSRS is being used in the current study to provide a summary measure of suicidal ideation and behavior risks. This scale is to be completed by trained staff. Training materials on the scale will be provided to investigator sites by Sponsor .

8.2.5.2. Risk Assessment During Screening

The Investigator will review the results of the C-SSRS (baseline), and medical history. The following criteria would indicate a potential suicide risk:

- Suicidal ideation associated with actual intent and/or method and/or plan and/or action (eg, selfharming behaviors) in the past year based on CSSRS assessment ("yes" answers on items 4 or 5 of the CSSRS).
- Any previous history of suicide behaviors reported or documented within the past 10 years.
- For events that occurred within the past 5 years, an answer of "yes" to any of the suicidal behavior items of the CSSRS).
- Investigator's judgment.

If any of these criteria are met and the participant is being considered for study participation, a risk assessment must be completed to determine whether it is appropriate for the participant to be enrolled.

Risk assessments should be done by a qualified mental health professional (MHP). In the United States, a qualified MHP is a psychiatrist or a licensed PhD level clinical psychologist. In other countries a qualified MHP is a clinically-qualified professional with appropriate training in the assessment of suicide risk (according to the local clinical practice standards and regulations) and who would normally evaluate the risk for suicide for a participant.

The MHP may be a member of the study site team. If an MHP is not available within the study team, the Investigator should make the necessary referral.

The Investigator must obtain and review the risk assessment prior to the participant being randomized. A written copy of the risk assessment should be included in the participant's clinical record (source documentation).

8.2.5.3. Risk Assessment During the Study

Beginning with Period 1, if there are any "yes" responses on items 4, 5 or on any behavioral question of the C-SSRS (since last visit), a risk assessment should be done by a qualified MHP to determine whether it is safe for the participant to continue to participate in the trial. Suicidal risk should be managed appropriately by the Investigator together with a qualified MHP (or the Investigator alone if the Investigator is a qualified MHP). In addition, the Investigator should consult with the Sponsor medical monitor to determine whether the participant can continue in the trial.

A narrative should be prepared for participants who have undergone any post-baseline risk assessment, using information from the C-SSRS.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in woman of childbearing potential (WOCBP) at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the study treatment. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. 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 if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs 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 to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE or that caused the participant to discontinue the study (see Section 7).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the investigational product.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

Follow-up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AE or SAE 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, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

SAEs occurring in a participant after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

8.3.1.2. Recording Non-serious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

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 3.

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

8.3.3. 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. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. 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, IRBs/ECs, and investigators.

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

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During 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 28 calendar days after the last administration of the investigational product.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

An Exposure During Pregnancy (EDP) occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention or by other possible routes of exposure, eg, ingestion or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention or by other possible routes of exposure, eg, ingestion or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 calendar days after the last administration of the investigational product.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable

8.3.8. Adverse Events of Special Interest

Not applicable

8.3.8.1. Lack of Efficacy

Not applicable since this is an abuse liability study in healthy participants.

8.3.9. Medical Device Deficiencies

Not applicable

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if

applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of Neurontin® >1800 mg or diazepam >20 mg within a 24-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until gabapentin and diazepam can no longer be detected systemically (at least 3 days).
3. Obtain a blood sample for PK analysis within 3 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
5. Overdose is reportable to Safety **only when associated with an SAE.**

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 of approximately 5 mL, to provide a total of approximately 2 mL of plasma volume, will be collected for measurement of plasma concentrations of gabapentin and diazepam as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 5 minutes or 10% of the nominal time (eg, within 6 minutes of a 60-minute sample), whichever is greater, relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF). Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as

long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF).

Samples will be used to evaluate the PK of gabapentin and diazepam (including its major active metabolite, N-desmethyldiazepam). Samples collected for analyses of gabapentin and diazepam plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

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

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.6. Pharmacodynamics

8.6.1. Subjective Effects

The questionnaire described below is used in drug abuse as well as clinical efficacy and toxicity evaluation of pharmacologic agents, and its usefulness is widely accepted. Furthermore, previous results indicate that the instrument is sensitive, reliable, and valid.

8.6.2. Visual Analog Scale (VAS)

The VAS consists of horizontal 100-mm lines, each labeled with an adjective such as “Drug Liking” or “High”, etc. Participants will be instructed to place a mark on each line indicating how they feel at the moment. For example, measuring “Drug Liking” on the bipolar VAS, the participant will be asked: Do you like the drug effect you are feeling now? The participant will then rate on the 0 to 100 scale, where: Strong disliking = 0; Neither like or Dislike = 50; and Strong Liking = 100. Further information on follow-up procedures is given in Appendices 10 and 11. All VAS testing will be administered at the nominal time points ±5 minutes for time points up to and including 4 h post-dose, within ±15 minutes for time points from 6-12 h post-dose, and within ±60 minutes for the remaining time points up to and including 72 h post-dose.

Primary Endpoints:

- VAS for Drug Liking presented on a bipolar 0 to 100 scale.

Secondary Endpoints:

- VAS for High presented on a unipolar 0 to 100 scale.
- VAS for Take Drug Again presented on a bipolar 0 to 100 scale.
- VAS for Overall Drug Liking presented on a bipolar 0 to 100 scale.
- VAS for Any Drug Effects, Good Effects, and Bad Effects presented on unipolar 0 to 100 scales.

Additional Secondary Endpoint:

- Modified Observer's Assessment of Alertness/Sedation scale or comparable scale.

8.7. Genetics

8.7.1. Specified Genetics

Specified genetics are not evaluated in this study.

8.7.2. Banked Biospecimens for Genetics

A 4-mL blood sample optimized for deoxyribonucleic acid (DNA) isolation Prep D1 will be collected as local regulations and IRBs/ECs allow.

Banked biospecimens may be used for research related to drug response. Genes and other analytes (eg, proteins, ribonucleic acid (RNA), nondrug metabolites) may be studied using the banked samples.

Unless prohibited by local regulations or IRB/EC decision, participants will be asked to indicate on the consent document whether they will allow their banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients. This component of the sampling banking is optional for participants; they may still participate in the study even if they do not agree to the additional research on their banked biospecimens. The optional additional research does not require the collection of any further samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the Lab Manual.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

Statistically, the study will be evaluated as a safety study. Consequently, the null hypothesis for gabapentin will be constructed on the presumption that these treatments produce abuse potential similar to placebo. To demonstrate that these treatments have no abuse potential the null hypothesis will be statistically rejected.

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data.

9.1. Statistical Hypotheses

To assess the abuse potential of gabapentin the following tests will be performed in the order they are given:

Study Validation:

The sensitivity and integrity of the study will be validated by comparing the mean responses of diazepam, the positive control (C), to the placebo (P):

$$H_0: \mu_C - \mu_P \leq \delta_1 \text{ versus } H_a: \mu_C - \mu_P > \delta_1 \text{ where } \delta_1 = 15.$$

Gabapentin versus diazepam:

1. Does gabapentin (T) produce mean responses that show less abuse potential than diazepam?

$$H_0: \mu_C - \mu_T \leq \delta_2 \text{ versus } H_a: \mu_C - \mu_T > \delta_2 \text{ where } \delta_2 = 0.$$

Gabapentin versus placebo (Primary):

2. Does gabapentin (T) produce mean responses that show abuse potential similar to placebo?

$$H_0: \mu_T - \mu_P \geq \delta_3 \text{ versus } H_a: \mu_T - \mu_P < \delta_3 \text{ where } \delta_3 = 11.$$

For each of the gabapentin hypotheses, the statistical significance of the test will be assessed for all doses of gabapentin.

9.2. Sample Size Determination

An 11-point VAS E_{max} "Drug Liking" difference between the treatment and the placebo is being selected as the cutoff for demonstrating abuse. This criterion is clinically meaningful for oral drug discrimination and is within the range used by previous studies to assess potential abuse liability.[17-20] This assumes no difference in Bipolar VAS for "Drug Liking" E_{max} for the comparison of gabapentin to placebo and a standard deviation of 18 points. Under these assumptions, 32 completed participants will provide at least 90% power for the comparison of gabapentin to placebo at the 1-sided significance level of 0.05. This study will randomize approximately 50 participants to ensure at least 32 participants who meet the definition of the Modified Completer Population complete the Treatment Phase of the study. Among the 50 participants, at least 20% will be females to ensure that the findings are valid across different populations.

9.3. Populations for Analysis

The following populations are planned for this study:

- The Safety Population will include all participants who receive at least one dose of study drug, beginning with the Naloxone Challenge. This population will be analyzed as treated.

- The PK population will include all enrolled participants treated who have at least 1 concentration in the Treatment Phase. The PK parameter analysis population will include all enrolled participants treated who have at least 1 of the PK parameters of interest.

- The Completer Population will include all randomized participants who complete all 5 periods of the Treatment Phase and who contribute post-dose PD data from each period. These participants must have at least one post-dose response on the VAS for Drug Liking within 2 hours of Tmax for each treatment group: ie, at least one VAS response within the interval 0-3h postdose (assuming the Tmax of 20 mg diazepam is 1h) and at least one VAS response within the interval 1-5h postdose (assuming the Tmax of 600/1200/1800 mg gabapentin is 3h). This population will be analyzed as randomized.

- The Modified Completer Population will include all randomized participants in the Completer Population, but will exclude any participant who meet either or both of the following criteria for Drug Liking VAS:

    1. Emax scores are within a 5 point difference across all five treatments (ie, Maximum Emax score – Minimum Emax score $\leq$5);

    2. Emax(P) > 60 AND Emax(P) - Emax(Dia) $\geq$5;

where Emax(P) and Emax(Dia) are the VAS Emax scores for placebo and diazepam 20 mg, respectively.

This population will be analyzed as randomized.

- The Evaluable Population will include all randomized participants in the Modified Completer Population who do not have major protocol violations or adverse events that would interfere with drug absorption such as vomiting within 4 hours of study drug administration. Major protocol violations, including deviations related to study drug intake are defined as those that could potentially affect the PD conclusions of the study. Prior to unblinding the Treatment Phase data, the sponsor (or designee) will identify protocol violations or adverse events that would disqualify a participant from the evaluable population and determine which participants or participant visits will be excluded. This population will be analyzed as randomized.

All PD analyses will be performed using the Modified Completer Population and all available post-dose data; these will be the primary PD analyses. Key PD analyses may be repeated on the Evaluable Population using all available post-dose data.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study.

9.6. Endpoint Analysis

The following parameters will be calculated for VAS for "Drug Liking" (primary endpoint) and VAS for "High" (secondary endpoint) during the Treatment Period:

- Maximum (peak) effect (E_{max}); calculated as maximum change from pre-dose response if pre-dose assessment is performed; the neutral VAS point (50 for Drug liking, 0 for High) will be used as pre-dose response when VAS not performed or missing.

- Time of maximum (peak) effect (TE_{max});

- Area under the effect curve to the last measurement ($AUEC_{last}$);

- Area under the effect curve to 1 hour ($AUEC_1$);

- Area under the effect curve to 2 hours ($AUEC_2$);

- Area under the effect curve to 3 hours ($AUEC_3$);
- Area under the effect curve to 4 hours ($AUEC_4$);
- Area under the effect curve to 8 hours ($AUEC_8$).

The additional endpoints of VAS for "Overall Drug Liking", "Take Drug Again", "Good Drug Effect", "Bad Drug Effect", and "Any Drug Effect" and the observer-rated assessment of alertness/sedation will be summarized by timepoints.

9.7. Study Validity Analysis of Endpoints

Study validity will first be confirmed through the comparison of mean E_{max} for Drug Liking between diazepam 20 mg and placebo administered during the Treatment Phase. This comparison will be made using a mixed-effect model with treatment, period, and sequence as fixed effects, and participant nested within the sequence as a random effect. If the treatment comparison of diazepam 20 mg vs. placebo is statistically significant by a margin of 15 (ie, one-sided $p \leq 0.05$) in the appropriate direction, it will confirm the sensitivity of the study. If study validity is not confirmed, comparisons between gabapentin and diazepam will not be performed.

9.8. Analysis of Primary and Secondary Endpoints

A linear mixed-effects model that includes site, period, sequence, and treatment as fixed effects, and the participant as a random effect will be used. The primary analyses of abuse potential will be based on testing the differences between the means from the primary measure(s) at the peak of drug response effects (VAS E_{max}) produced by gabapentin, diazepam and placebo at a significance level of 0.05 (1-sided).

The primary PD endpoint is the Emax of bipolar VAS for "Drug Liking".

The principal parameters for the primary and secondary endpoints will be summarized by treatment using descriptive statistics (mean, standard deviation [SD], median, first and third quartiles, minimum and maximum). These parameters will be analyzed using a mixed-effect model with treatment, period, and sequence as fixed effects, and participant nested within the sequence as a random effect. Analyses of endpoints with baseline (pre-dose) measurements will include the baseline measurement as a covariate in the model. Least squares means, standard errors, and 90% confidence intervals will be provided for each treatment and for the difference between treatments. Data will be summarized graphically, where appropriate.

The treatment comparison to test for study validity will be:

- diazepam 20 mg vs. placebo; (This comparison is used for validation of the study and adjustments for multiple comparisons will not be applied for this treatment comparison).

Comparisons of gabapentin versus diazepam will be:

- gabapentin 600 mg vs. diazepam 20 mg;
- gabapentin 1200 mg vs. diazepam 20 mg;
- gabapentin 1800 mg vs. diazepam 20 mg.

Comparisons of gabapentin versus placebo will be (Primary):

- gabapentin 600 mg vs. placebo;
- gabapentin 1200 mg vs. placebo;
- gabapentin 1800 mg vs. placebo.

Statistical significance of all treatment differences will be reported. All statistical tests will be conducted using one tailed significance criteria. These comparisons will be used to assess the primary study objective.

Regression diagnostics will be performed to verify model assumptions and adequacy of the fitted linear models for the primary endpoints. Levene's test will be used to diagnose potential heterogeneity of variance and the Shapiro–Wilk test will be used to diagnose potential non-normality of the model residuals.

If the resulting p-value from Levene's test is ≤0.05, the null hypothesis of equal variances is rejected and it will be concluded that there is a difference between the treatment group variances. An unequal variance model will then be applied using the Satterthwaite method in order to produce an accurate F-approximation.

If the resulting p-value from the Shapiro-Wilk test is ≤0.05, symmetry of the distribution of paired differences will be tested using the Triples Test and either the t-test (symmetry) or sign test (asymmetry) will be performed.

9.8.1. Pharmacodynamic Analysis

PD parameter values that will be evaluated are listed in Table 4. The pre-dose psychometric measurements of each period will be the baseline for calculating the changes in these parameters post dose. Descriptive statistics for the changes from baseline will be reported by treatment and by hours postdose. The changes from baseline will be analyzed with an analysis of variance (ANOVA) model consisting of: Site, Sequence, Site*Sequence, Period, Treatment, Time, Period*Time, Site*Treatment and Treatment*Time terms as fixed effects, and a participant (Site*Sequence) term as a random effect for testing Site, Sequence, and Site*sequence effect. Site*Treatment interaction will be evaluated and this interaction term will be dropped from the final model if it is not significant. To accommodate the repeated measures aspect of the design, a compound symmetric covariance matrix will be employed, with the participant set to Period*Participant (Sequence). The Treatment*Time least-squares means and differences among them will be assessed for trends likely to be of clinical relevance.

Descriptive statistics of the mean, standard error, and other summary statistics such as minimum, first quartile (Q1), median, third quartile (Q3) and maximum for each subjective measure, each treatment and each paired difference among treatments will be calculated and used to create tables and graphs.

As an exploratory analysis, the time course of the different subjective measures in relation to each other (and to abuse-related AEs) will evaluate the outcome of positive or negative assessments of the drug before, during and after the peak of drug effects. The physiological effects such as pulse rate, blood pressure and respiratory rate will be monitored over the course of the study session and correlated to both the drug dose administered and the PK of the drug.

9.8.2. Derivation of Pharmacodynamic Parameters

PD parameters for VAS "Drug Liking" and "High" will be derived from the concentration-time profiles as shown in Table 4.

Table 4. Derivation of Pharmacodynamic Parameters

Parameter	Definition	Method of Determination
E_{max}	Maximum effect	Observed directly from data
TE_{max}	Time for E_{max}	Observed directly from data as time of first occurrence
$AUEC_{last}$	Area under the effect-time profile from time 0 to the time of the last quantifiable effect (E_{last})	Linear trapezoidal method
$AUEC_1$	Area under the effect-time profile from time 0 to 1 hour postdose	Linear trapezoidal method
$AUEC_2$	Area under the effect-time profile from time 0 to 2 hour postdose	Linear trapezoidal method
$AUEC_3$	Area under the effect-time profile from time 0 to 3 hour postdose	Linear trapezoidal method
$AUEC_4$	Area under the effect-time profile from time 0 to 4 hour postdose	Linear trapezoidal method
$AUEC_8$	Area under the effect-time profile from time 0 to 8 hour postdose	Linear trapezoidal method

9.8.3. Pharmacokinetic Analysis

Blood samples will be collected throughout a study session in order to assess drug PK. Samples from gabapentin treatment will be analyzed using a validated analytical method in compliance with Viatris standard operating procedures. If deemed necessary, samples of placebo and diazepam (including its major active metabolite; N-desmethyldiazepam) will be analyzed. This will be done to primarily confirm that plasma levels of the drug are equivalent between participants and to evaluate whether subjective measures and AEs can be correlated with drug levels over time. Typically, blood will be drawn immediately after the collection of subjective measures are completed at each time point. If an analysis shows that a participant had low plasma levels of a drug, it may account for a lack of subjective responses in a drug session.

9.8.3.1. Pharmacokinetic Parameters

The PK parameter values for gabapentin and, if deemed necessary, for diazepam (including its major active metabolite as data permit: N-desmethyldiazepam) will be calculated for each non-placebo treatment and each participant using noncompartmental analysis of concentration-time data. PK parameter values that will be evaluated are listed in Table 5.

The PK parameters (AUC_{inf}, AUC_{last}, C_{max}, t_{max}, $t_{½}$, partial AUCs [AUC_1, AUC_2, AUC_3, AUC_4, AUC_8]) will be derived for each participant/period/analyte and will be summarized by treatment and analyte. Individual participant PK parameters, as well as summary statistics (eg, group averages, SD, geometric means, coefficient of variation [CV], and geometric CV%) by treatment will be reported for PK parameters, as appropriate. Plasma concentration-time profiles of gabapentin, diazepam and its metabolite (N-desmethyldiazepam) will be presented. Concentrations will be listed and summarized by PK sampling time and treatment for each analyte.

9.8.3.2. Derivation of Pharmacokinetic Parameters

PK parameters will be derived from the concentration-time profiles as shown in Table 5.

Table 5. Derivation of Pharmacokinetic Parameters

Parameter	Definition	Method of Determination
C_{max}	Maximum plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}[a]	Area under the plasma concentration-time profile from time 0 extrapolated to infinity time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
AUC_1	Area under the plasma concentration-time profile from time 0 to 1 hour postdose	Linear/Log trapezoidal method
AUC_2	Area under the plasma concentration-time profile from time 0 to 2 hour postdose	Linear/Log trapezoidal method
AUC_3	Area under the plasma concentration-time profile from time 0 to 3 hour postdose	Linear/Log trapezoidal method
AUC_4	Area under the plasma concentration-time profile from time 0 to 4 hour postdose	Linear/Log trapezoidal method
AUC_8	Area under the plasma concentration-time profile from time 0 to 8 hour postdose	Linear/Log trapezoidal method

Table 5. Derivation of Pharmacokinetic Parameters

Parameter	Definition	Method of Determination
$t_{½}$[a]	Terminal elimination half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression

a. If data permit.

9.9. Efficacy Analyses

An efficacy analysis is not applicable to this study.

9.10. Safety Analyses

All safety analyses will be performed on the safety population.

The safety data will be described and summarized in accordance with the sponsor's Data Standards.

AEs, ECGs, BP, RR, PR, SpO2, continuous cardiac monitoring, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination and neurological examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.10.1. Electrocardiogram Analyses

Electrocardiogram results collected at Screening will be listed.

9.11. Exploratory Analyses

Exploratory analysis will be conducted to evaluate the correlation between drug (gabapentin or diazepam) concentrations and selected PD endpoints (Bipolar VAS for "Drug Liking" and Unipolar VAS for "High"), as data permit.

9.12. Data Monitoring Committee

This study will not use a data monitoring committee (DMC).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 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 International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, USPIs, and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, 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/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC 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/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Sponsor should be informed immediately.

In addition, the investigator will inform Sponsor immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators 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 or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative 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/EC or study center.

The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

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.

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/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

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 ICD.

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

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 28 days from the previous ICD signature date.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Viatris fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and other public registries in accordance with applicable local laws/regulations. In addition, Viatris reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

In all cases, study results are reported by Viatris in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Viatris posts clinical trial US Basic Results on www.clinicaltrials.gov for Viatris-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Viatris posts European Union (EU) Basic Results on EudraCT for all Viatris-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

Documents within marketing authorization packages/submissions

Viatris complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Viatris provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Viatris will make available data from these trials 12 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF 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.

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

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic form and are password protected to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

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.

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.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion 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. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate

with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. 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 site.

Data reported on the CRF or entered in the electronic CRF (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 the Clinical Monitoring Plan.

10.1.8. Study and Site Closure

The sponsor 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.

The investigator may initiate study-site closure at any time upon notification to the sponsor if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Viatris-intervention related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by agreement.

Authorship of publications for the overall study results will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the team SharePoint site.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests (Table 6) will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 6. Protocol-Required Safety Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/urea and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	FSH[b] Urine drug screening[c] Alcohol breathalyzer β-hCG[d] Hepatitis B surface Antigen Hepatitis B core Antibody Hepatitis C core Antibody Human Immunodeficiency Virus
	Additional Tests (Needed for Hy's Law)		HAV IgM HAV IgG
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin CK GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels		

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; FSH = follicle stimulating hormone; GGT = gamma glutamyl transferase; HAV IgG = hepatitis A virus immunoglobulin G; HAV IgM = hepatitis A virus immunoglobulin M; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blod cell; WBC = white blood cell.

Table 6. Protocol-Required Safety Laboratory Tests

Hematology	Chemistry	Urinalysis	Other

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.

b. For confirmation of postmenopausal status only.

c. The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).

d. Serum or urine β-hCG for female participants of childbearing potential.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigator sites or other blinded personnel until the study has been unblinded.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. Upon completion of the study, these retained safety samples may be used for the assessment of exploratory safety biomarkers or unexpected safety findings. These data will not be included in the CSR. Samples to be used for this purpose will be shipped to either a Viatris-approved Biospecimen Banking System (BBS) facility or other designated laboratory and retained for up to 1 year following the completion of the study.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or 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.
Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• 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 drug-drug 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.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which 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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. 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 that, at any dose:
a. Results in death
b. 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 that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (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 preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent 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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but 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 in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and exposure during pregnancy [EDP] supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- 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: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category

utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

- 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.
- 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. 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.**
- 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.
- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the

investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE 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 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 healthcare providers.
- If a participant dies during participation in the study or during a recognized followup period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 93 days after the last dose of study intervention, which corresponds to the time needed to eliminate study intervention(s) ***plus*** an additional 90 days (a spermatogenesis cycle):

- 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/barrier as detailed below:
- Agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- Male participants should 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 WOCBP who is not currently pregnant.

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3);

OR

- Is a WOCBP and using a contraceptive method, as described below, during the intervention period and for at least 42 days after the last dose of study intervention, which corresponds to the time needed to eliminate any study intervention(s).
- A WOCBP agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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.

10.4.3. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

   - 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), investigator discretion should be applied to determining study entry.

   Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female.

   - A postmenopausal state is defined as age 60 years or older or 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 hormone replacement therapy (HRT).
   - Females on HRT and whose menopausal status is in doubt will be required to use at least one of the contraception methods below.

10.4.4. Contraception Methods

Female subjects of child-bearing potential must use at least one form of the following contraception methods.

1. Intrauterine device (IUD).
2. Bilateral tubal occlusion.

3. Hormonal contraception.
4. Contraceptive implants.
5. Double-barrier method (any combination of physical and chemical methods).
6. Confirmed infertility of sexual partner.
7. Engaged exclusively in a same-sex relationship.
8. Total abstinence (periodic abstinence is not acceptable).
9. Vasectomized partner.

    - Vasectomized partner 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 method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Collection of Pregnancy Information

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
- An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products);
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done

irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to gabapentin and diazepam or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

- Samples for banking (see Section 8.7.2) will be stored indefinitely or other period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Banked biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

Liver function tests (LFTs) results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

- Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as Adverse Events (AEs)
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) atrioventricular (AV) block of >30 seconds' duration. • Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That May Qualify as Serious Adverse Events (SAEs)

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Viatris study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: Clinical Opioid Withdraw Scale

For each item, circle the number that best describes the patient' s signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if pulse rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:	Date and Time:
Reason for this assessment:	
Resting Pulse Rate: beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 1 20	**GI Upset:** *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 participant report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *if patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection
Runny nose or tearing *Not accounted for by cold-symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment:_____
Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal	

10.9. Appendix 9: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
Abs	absolute
ACLS	advanced cardiac life support
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{inf}	area under the plasma concentration-time profile from time 0 extrapolated to infinity time
AUC_{last}	area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration
AUEC	area under the effect curve
$AUEC_{last}$	area under the effect-time profile from time 0 to the time of the last quantifiable effect
AV	atrioventricular
β-hCG	beta-human chorionic gonadotropin
BBS	biospecimen banking system
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CANTAB	cambridge neuropsychological test automated battery
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
COWS	clinical opiate withdrawal scale
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	clinical study report
CT	clinical trial
CTMS	clinical trial management system
CV	coefficient of variation
CYP	Cytochrome P450
DAI	Drug Administration Instructions
DILI	drug-induced liver injury
DMC	data monitoring committee

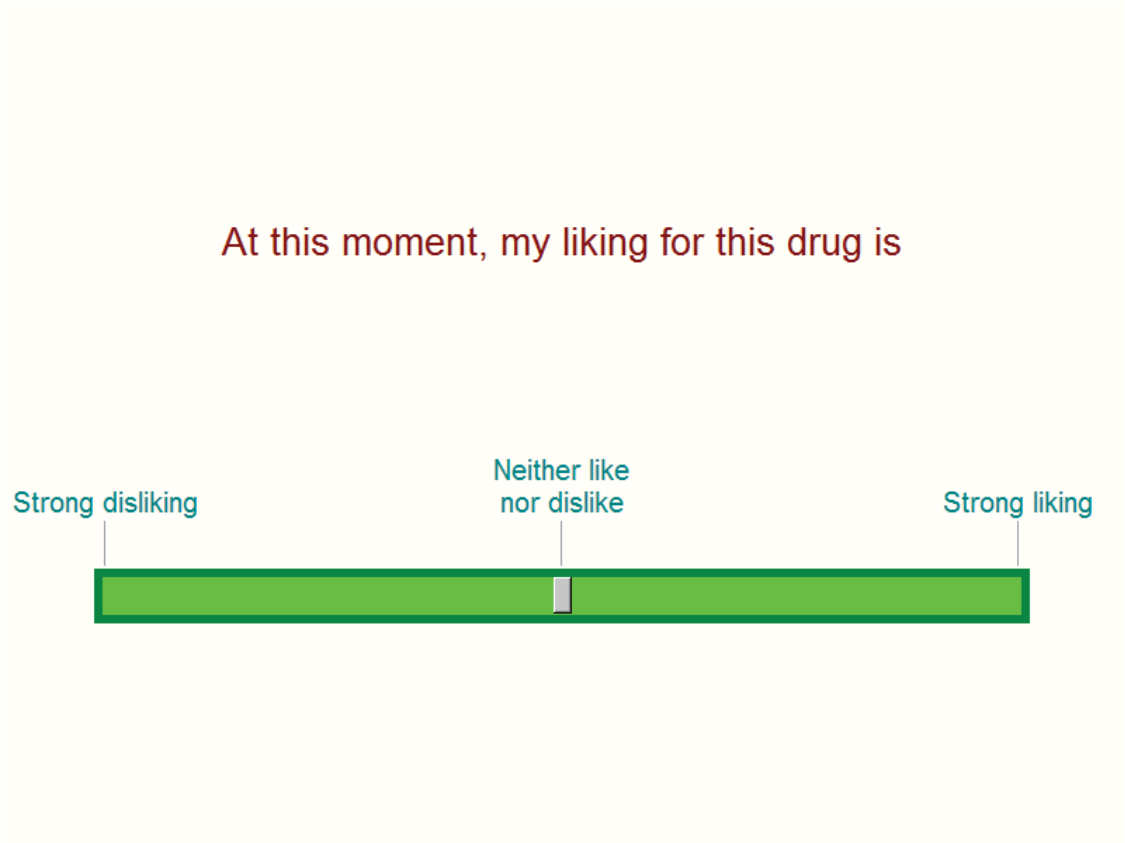
Abbreviation	Term
DNA	deoxyribonucleic acid
DSM- IV	Diagnostic and Statistical Manual of Mental Disorders IV
EC	ethics committee
ECG	electrocardiogram
eCRF	Electronic case report form
EDP	exposure during pregnancy
EMA	European Medicines Agency
E_{max}	maximum effect
ETCO	end-tidal carbon dioxide
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HAV IgM/G	Hepatitis A virus immunoglobulin M/G
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVRS	Interactive Voice Response System
LFT	liver function test
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MHP	mental health professional
msec	millisecond
N/A	not applicable
PCD	primary completion date

Abbreviation	Term
CRU	Clinical Research Unit
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PR	pulse rate
PT	prothrombin time
PVC	premature ventricular complex
Q1	first quartile
Q3	third quartile
QTc	corrected QT
QTcB	corrected QT using Bazett's method
QTcF	corrected QT using Fridericia's method
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SD	standard deviation
SE	standard error
SoA	schedule of activities
SOP	standard operating procedure
SpO_2	peripheral oxygen saturation
SRSD	single reference safety document
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	Terminal elimination half-life
TBili	total bilirubin
TE_{max}	time for E_{max}
T_{max}	time for C_{max}
THC	tetrahydrocannabinol
TID	3 times a day
UDS	urine drug screen
ULN	upper limit of normal
US	United States
USPI	United States Package Insert
VAS	visual analog scale
VT	tidal volume
WBC	white blood cell
WOCBP	woman of childbearing potential

10.10. Appendix 10: VAS Assessment Methods

The overall appearance of all VAS items utilizing the Cambridge Neuropsychological Test Automated Battery (CANTAB) or using comparable software will be similar to screen images shown below. The participants will be trained to use the software at the site.

Image A: screen display of Drug Liking VAS



The questions and anchors on VAS items will be modified appropriately to reflect study specific questions as shown in Images B-D (see Table 7).

Image B: screen display of High VAS

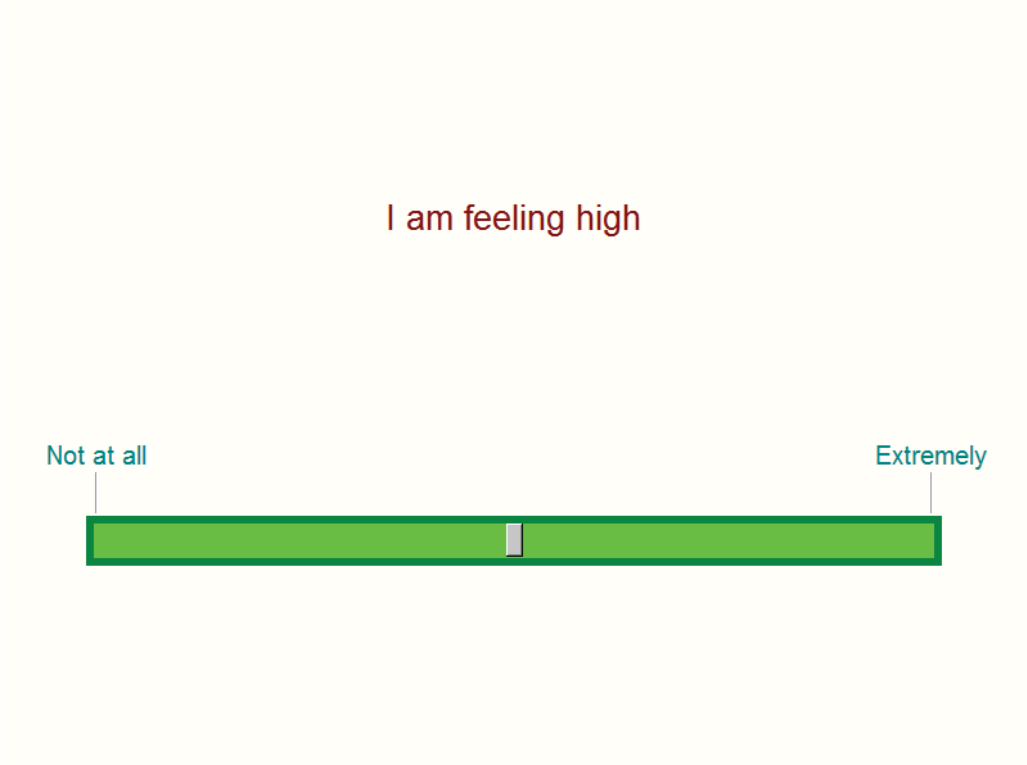


Image C: screen display of Overall Drug Liking VAS

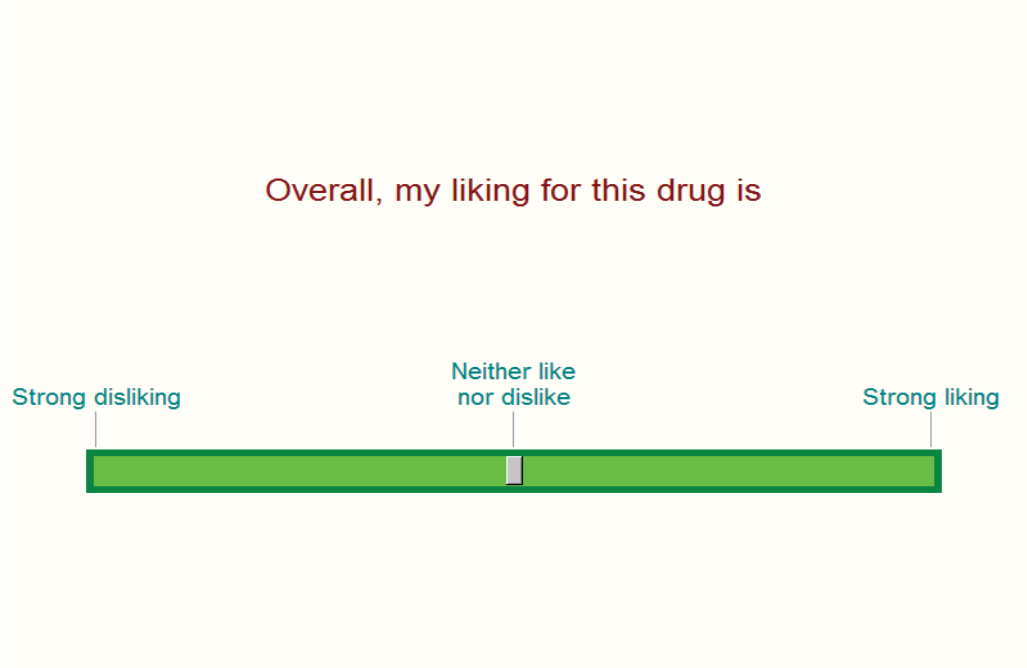


Image D: screen display of Take Drug Again VAS

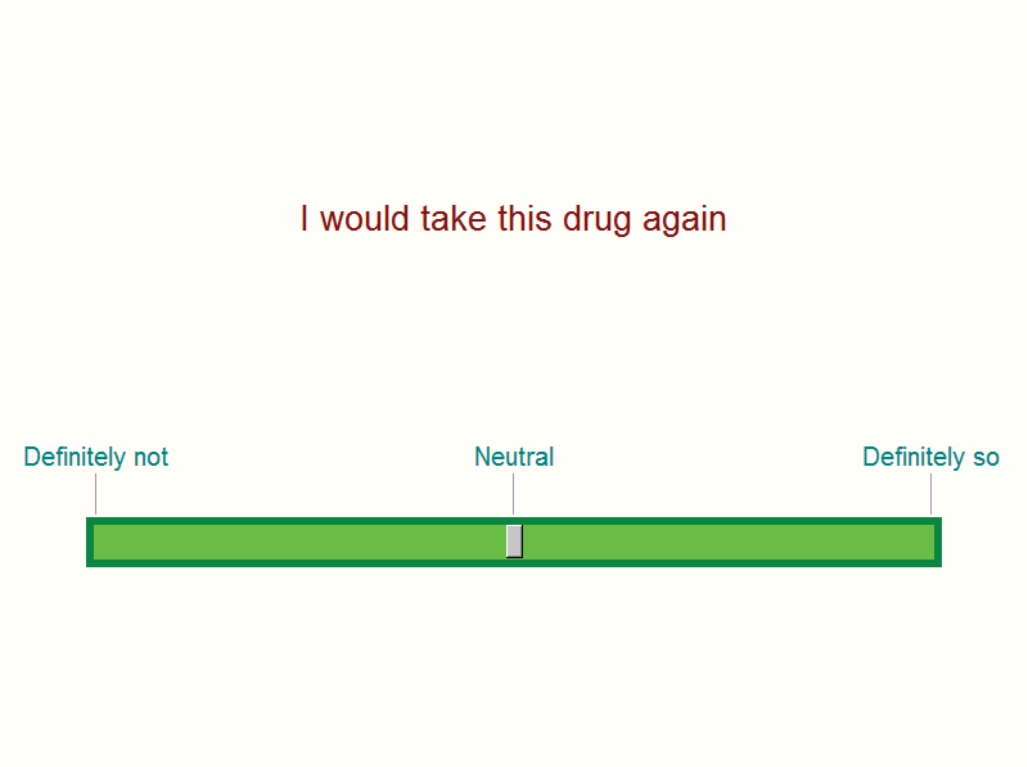


Table 7. Other Subjective Effects Visual Analog Scales

SCALE DESCRIPTION	STATEMENT TEXT	RESPONSE ANCHORS
Good Drug Effects	*I can feel good drug effects*	0: Not at all 100: Extremely
Bad Drug Effects	*I can feel bad drug effects*	
Feeling Sick	*I am feeling sick*	
Nausea	*I am feeling nausea*	
Any Drug Effects	*I can feel any drug effect*	
Sleepy	*I am feeling sleepy*	
Dizzy	*I am feeling dizzy*	

10.11. Alertness/Sedation Assessment

The Modified Observer's Assessment of Alertness/Sedation scale or comparable scale will be used for the assessment of alertness/sedation (see Table 8).

Table 8. Modified Observer's Assessment of Alertness/Sedation Scale

Responsiveness	Numerical score
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze*	1
No response after painful trapezius squeeze	0
*Purposeful response, not withdrawal.	

10.12. Appendix 12: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Viatris.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.12.1. Eligibility

Not applicable

10.12.2. Telehealth Visits

Not applicable

10.12.3. Alternative Facilities for Safety Assessments

Not applicable

10.12.4. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered. For participant discontinuation reporting in the CRF: select the most appropriate status for discontinuation; if the discontinuation is associated with the current COVID-19 pandemic, enter "COVID-19" in the "Specify Status" field.

10.12.5. Home Health Visits

Not applicable

10.12.6. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

10.12.7. Efficacy Assessments

Not applicable

10.12.8. Independent Oversight Committees

Not applicable

10.13. Appendix 13: Summary of Changes

Protocol Title	A phase 4, randomized, double-blind, double-dummy, placebo- and active-controlled, single-dose, five-way crossover study evaluating the Abuse Potential of three Doses of Neurontin® taken orally in healthy, non-drug dependent participants with sedative drug abuse experience
Product	Neurontin® (gabapentin)
Protocol Number	A9451181
Study Type	Phase 4
Version	5.0
Protocol Date	29 Apr 2022
Legal/Filing Sponsor	Viatris Specialty LLC 3711 Collins Ferry Road Morgantown, WV 26505

Table 9. Summary of changes from Protocol dated 14 May 2020 to Protocol 2.0 dated 11 Dec 2020

Section	Old Text (Protocol dated 14 May 2020	New Text (Protocol Version 2.0 dated 11 Dec 2020)	Rationale for amendment
Administrative Changes Sponsor and Sponsor contacts details updated	Missing Sponsor name 'Pfizer'	Added Upjohn US 1 LLC 235 East 42nd Street New York, NY 10017-5703 **Dr. Sandeep Jagtap** Clinical Strategy Lead – CNS Global Clinical Strategy & Innovation **David Gillogly** Head, Global Clinical Operations The sponsor name changed from 'Pfizer' to 'Upjohn' wherever applicable throughout the protocol	The sponsor for this study is changed from 'Pfizer' to 'Upjohn US 1 LLC' Administrative changes are made to include updated Sponsor details and authorized sponsor protocol approvers
Section 1.3 Schedule of Activities (Table:1 footer)	Missing text for bullet h. vital signs will be recorded at pre-do rst naloxone dose) and at 5 n s, 0.25, 0.5, 1, 1.5, and 2 hours follo ng the second dose of naloxone.	Added "vital signs will be recorded at pre-ose (first naloxone dose) and at 5 minutes, .25, 0.5, 1, 1.5, and 2 hours following the econd dose of naloxone. Vital signs will be ecorded at nominal time points ± 5 minutes"	The changes are made to provide clarification
Section 1.3 Schedule of Activities (Table:2-footer)	Missing "12-lead Electrocar gram" measurements at Day -1 (baseline) and Day 4 during Treatment Phase.	dded "12-lead Electrocardiogram" easurements (Conducted after a resting eriod of at least 10 minutes in a supine position) at Day -1 (baseline) and Day 4 during Treatment Phase.	The changes are made to add missing and typographical error

	Missing text for bullet g. Vital signs (including pulse rate, systolic and diastolic blood pressures are measured at the nominal time points after a resting period of at least 5 minutes in a sitting position. Temperature (oral or with a temporal infrared scanner) will be measured on Day -1 of each Treatment Visit only.	Added "Vital signs (including pulse rate, systolic and diastolic blood pressures are measured at the nominal time points after a resting period of at least 5 minutes in a sitting position. Temperature (oral or with a temporal infrared scanner) will be measured on Day -1 of each Treatment Visit only. Vital signs will be recorded at nominal time points ± 5 minutes"	The changes are made to add missing and typographical error
Section 2.1 Study Rationale From (4th paragraph):	Epidemiological studies have shown that gabapentin may have abuse potential, particularly among individuals with a history of opioid abuse. Gabapentin abuse is reported both alone (*ie*, without other drugs), and in conjunction with opioids to enhance the 'high' obtained from opioids.1,4 Further, published data suggest that gabapentin is recorded on death certificates suggesting drug overdose, both as the primary and contributory causes of death, and reported with and without other drugs like opioids, benzodiazepines, and alcohol.1,5-7 This clinical trial will evaluate gabapentin in a cross-over design with comparison to placebo and a positive control, diazepam, regarding abuse-related subjective responses, physiological responses (including an assessment of respiratory depression), and drug pharmacokinetics in a	Epidemiological studies have shown that gabapentin may have abuse potential, particularly among individuals with a history of opioid abuse. Gabapentin abuse is reported both alone (*ie*, without other drugs), and in conjunction with opioids to enhance the 'high' obtained from opioids.1,4 Further, published data suggest that gabapentin is recorded on death certificates suggesting drug overdose, both as the primary and contributory causes of death, and reported with and without other drugs like opioids, benzodiazepines, and alcohol.1,5-7 As a consequence, the FDA has required this post-authorization safety study (PASS) to evaluate gabapentin in a cross-over design with comparison to placebo and a positive control, diazepam, regarding abuse-related subjective responses, physiological responses (including an assessment of respiratory depression), and drug pharmacokinetics in a healthy non-drug	The changes were made for clarification (modifying the last sentence from "This clinical trial will evaluate gabapentin in a cross-over design-----" to "As a consequence, the FDA has required this post-authorization safety study (PASS) to evaluate gabapentin in a cross-over design

	healthy non-drug dependent population with drug abuse experience with sedative drugs.	dependent population with drug abuse experience with sedative drugs.	
Section 5.2 Exclusion Criteria	Participants are heavy smokers (>20 cigarettes per day) and/or use e-cigarettes, pipes, cigars, chewing tobacco, nicotine topical patches, nicotine gum, or nicotine lozenges.	Participants are heavy smokers or users of other types of nicotine products (>20 cigarettes equivalents per day)	Changes are made to provide clarification
Section 5.2 Exclusion Criteria and Section 5.3 Lifestyle Considerations	Section 5.2: Participants are unable to abstain from smoking for at least 1 hour before and at least 8 hours after study drug administration. Section 5.3: Participants will not be permitted to smoke from at least 1 hour before until at least 8 hours after dosing in the Qualification and Treatment Phases.	Section 5.2: Participants are unable to abstain from smoking for at least 2 hours before and at least 8 hours after study drug administration. Section 5.3: Participants will not be permitted to smoke from at least 2 hours before until at least 8 hours after dosing in the Qualification and Treatment Phases.	The changes are made due to a typographical error (e.g. From “at least 1 hour before” To “at least 2 hours before”).
Section 5.3.2 Caffeine, Alcohol, and Tobacco	The use of oral or chewed tobacco and/or nicotine-containing products (including topical patches) is not permitted for the entire study	The use of oral or chewed tobacco and/or nicotine-containing products (including topical patches) is not permitted from at least 2 hours before and at least 8 hours after study drug administration	The changes are made to correct the typographical error
Section 6.3.1 Allocation to Investigational Product	At screening, participants will be assigned a Single Participant Identifier number via an automated Interactive Voice Response System (IVRS) or equivalent system provided by Pfizer. Following screening the participants will be randomized. The randomization number for the	At screening, participants will be assigned a subject screening identification number (SSID) via an automated Interactive Response Technology (IRT) or equivalent system. Following screening the participants will be randomly assigned a qualification randomization number (QRN)via the IRT or	Changes are made to provide clarity for changes in study conduct

	participant will be allocated via the IVRS or equivalent system using a 1:1 randomization within each of the randomization strata. This number will be retained throughout the study and will correspond to a blinded treatment schedule determined by a Pfizer generated randomization code.	equivalent system using a 1:1 randomization. The QRN will be retained throughout the study and will correspond to the blinded qualification phase. After satisfactory completion of the qualification phase, participants will randomly be assigned a study randomization number (SRN) via the IRT or equivalent system using a 1:1 randomization for the treatment phase. The SRN will be retained throughout the study and will correspond to the blinded treatment sequence.	
Section 6.3.2 Breaking the Blind From (the 3rd and 4th paragraphs):	The method for breaking the blind in this study will be manual. A sealed envelope that contains the study intervention assignment(s) for each participant will be provided to the investigator. The sealed envelope will be retained by the investigator (or representative) in a secured area. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment 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	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 treatment 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 or medical monitor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken	The changes are made to transfer responsibility of an IRT to a CRO and provide a flexibility of randomization to the CRO.

	participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the CRF. Once the study is complete, all envelopes (sealed and opened) must be inventoried and retained until authorization for destruction has been provided.	must be recorded in the source documentation and data collection tool (DCT). The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.	
Section 8.2.2 Vital Signs From (3rd paragraphs):	Pulse and respiratory rates, oxygen saturation, diastolic and systolic blood pressure will be monitored continuously post-drug. These measures are done in abuse liability testing to ensure safety.	Pulse and respiratory rates, oxygen saturation, diastolic and systolic blood pressure will be monitored post-drug (see SoA). These measures are done in abuse liability testing to ensure safety.	The changes are made due to a typographical error.
Section 8.2.3.1 Continuous Cardiac Monitoring by Telemetry	All abnormal rhythms will be recorded and reviewed by the study physician for the presence of rhythms of potential clinical concern. The time, duration, and description of the clinically significant event will be recorded in the CRF. In addition, a printed record of the tracing(s) of the clinically significant rhythm(s) will be	Continuous cardiac monitoring will be performed as noted in the SoA. The time, duration, and description of any clinically significant abnormal rhythm will be reported as an adverse event.	The change are made because, as part of standard of care, an ECG will be performed for any clinically significant abnormal rhythm making telemetry record storage and data transfer

	made and retained with other source documents. Telemetry should be collected using a centralized system that also allows for the storage and advanced analysis of all recorded data in order to preserve important events for future evaluations. Holter monitoring should not be used in parallel with continuous telemetry, unless it is the only means of data storage available at the investigator site, or verifiable arrhythmia quantification is required. To establish a baseline, telemetry should be recorded for at least 2 hours before dosing in Period 1 of the Treatment Phase. This may be done immediately prior to dosing or at some 2-hour continuous interval in the 24 hours prior to dosing, as long as the recording is performed when the participant is awake. Telemetry may be stopped within a reasonably short period of time prior to dosing, in order to avoid interference with study operations conducted immediately before dosing. However, it is expected that the telemetry leads will be in place and the system connected prior to dosing.		capability unnecessary.

Section 8.6.2 Visual Analog Scale (VAS)	Missing a text at the end of 1st paragraph for the VAS testing time window as "All VAS testing will be administered at the nominal time points ±5 minutes."	Add a text at the end of 1st paragraph for the VAS testing time window as "All VAS testing will be administered at the nominal time points ±5 minutes."	The change are made to provide clarification.
Section 10.1.5 Dissemination of Clinical Study data	Removed www.pfizer.com Pfizer posts public disclosure synopsis, a clinical study report (CSR) in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.	No information added	This information is removed due to change of study sponsor from Pfizer to Upjohn.
Section 10.1.10 Sponsor's Qualified Medical Personnel	Removed For sites other than a Pfizer CRU, the contact number is not intended for use by the participant directly and if a participant calls that number, he or she will be directed back to the investigator site.	No information added	This statement is removed due to change of study sponsor from Pfizer to Upjohn.

Section 10.13. Appendix 13: Alternative Measures During Public Emergencies	None (No appendix information available in the protocol regarding COVID-19)	10.13. Appendix 13: Alternative Measures During Public Emergencies The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other Public emergencies only upon written notification from Upjohn. Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories). 10.12.1 Eligibility Not applicable 10.12.2 Telehealth Visits Not applicable 10.12.3 Alternative Facilities for Safety Assessments Not applicable 10.12.4 Study Intervention If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered. For	The changes were made to provide sufficient details about the protocol changes and enable an impact assessment of alternative measures due to COVID-19.

		participant discontinuation reporting in the CRF: select the most appropriate status for discontinuation; if the discontinuation is associated with the current COVID-19 pandemic, enter "COVID-19" in the "Specify Status" field. 10.12.5 Home Health Visits Not applicable 10.12.6 Adverse Events and Serious Adverse Events If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided. It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor. 10.12.7 Efficacy Assessments Not applicable 10.12.8 Independent Oversight Committees Not applicable	

Table 10. Summary of changes from Protocol version 2.0 dated 11 Dec 2020 to Protocol version 3.0 dated 26 Feb 2021

Section	Old Text (Protocol Version 2.0 dated 11 Dec 2020)	New Text (Protocol Version 3.0 dated 26 Feb 2021)	Rationale for amendment
Section 1.3, Table 2 schedule of activities for treatment phase	There is 'X' denoting VAS pre-dose assessment for good drug effects, bad drug effects & any drug effects in the treatment phase.	'X' denoting VAS pre-dose assessment for good drug effects, bad drug effects & any drug effects in the treatment phase is deleted.	Correction of inadvertent error
Section 5.2 Exclusion Criteria # 11:	Herbal supplements, herbal medications and hormone replacement therapy must be discontinued at least 28 days prior to the first dose of study medication.	Herbal supplements and herbal medications must be discontinued at least 28 days prior to the first dose of study medication. (hormone replacement therapy is deleted)	Correction of typographical error

Table 11. Summary of changes from Protocol version 3.0 dated 26 Feb 2021 to Protocol version 4.0 dated 04 Aug 2021

Section	Old Text (Protocol Version 3.0 dated 26 Feb 2021)	New Text (Protocol Version 4.0 dated 04 Aug 2021)	Rationale for amendment
Administrative change	Upjohn US 1 LLC	Upjohn US 1 LLC, a Viatris Company	Sponsor name change
Administrative change Sponsor contact details updated	Sandeep Jagtap, MD Clinical Strategy Lead – CNS Viatris, Bangalore Prestige Platina, Block 3, Ka nah Village, Outer Ring Road, Bangalore 60 7, Karnataka, INDIA Sandeep.Jagtap@viatris.com	g, PhD al Development Lead s very Park gate Road wich, Kent, CT13 9ND ited Kingdom .ng@viatris.com	Change to Sponsor personnel
Section 5.1 Inclusion criterion #1	Male and female participants must 18 55 years of age, inclusive, at the ti of screening	Male and female participants must be 18 to 65 years of age, inclusive, at the time of screening	Increase in age range to facilitate subject enrolment
Section 5.1 Inclusion criterion #4	Participants must be recreational sedativ users, defined as those report sedative agent (eg, barbiturat benzodiazepines) for its intox on at least 10 occasions with and at least once in the 8 wee Screening Visit (Visit 1), but signs of dependence and are ing treatment for their sedative u	Participants must be recreational sedative , defined as those reporting using a ive agent (eg, barbiturates, diazepines) for its intoxicating ts on at least 10 lifetime occasions t least once in the 12 weeks before Screening Visit (Visit 1), but who have signs of dependence and are not king treatment for their sedative use	Aligning the definition of an experienced recreational sedative user to other similar Human Abuse Potential studies in recreational sedative users to facilitate subject enrolment

Section 5.2 Exclusion criterion #19	Participants with ANY of the following abnormalities in clinical laboratory tests at screening, as assessed by the study specific laboratory and confirmed by a single repeat test, if deemed necessary: • Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level ⩾ 1.5 × upper limit of normal (ULN) Total bilirubin level ⩾ 1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ⩽ ULN	Participants with ANY of the following abnormalities in clinical laboratory tests at screening, as assessed by the study specific laboratory and confirmed by a single repeat test, if deemed to be clinically significant in the opinion of the investigator: • Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level ⩾1.5 × upper limit of normal (ULN) Total bilirubin level ⩾ 1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ⩽ ULN	Clarification to allow the investigator to apply clinical judgement
Administrative change Appendix 13 Table numbering re-ordered	Table 9. Summary of changes from Protocol version 2.0 dated 11 Dec 2020 to Protocol version 3.0 dated 26 Feb 2021 Table 10. Summary of changes from Protocol dated 14 May 2020 to Protocol 2.0 dated 11 Dec 2020	Table 9. Summary of changes from Protocol dated 14 May 2020 to Protocol 2.0 dated 11 Dec 2020 Table 10. Summary of changes from Protocol version 2.0 dated 11 Dec 2020 to Protocol version 3.0 dated 26 Feb 2021	To enable new amendments to be assigned successively higher table numbers in date order

Table 12. Summary of changes from Protocol version 4.0 dated 04 Aug 2021 to Protocol version 5.0 dated 29 Apr 2022

Section	Old Text (Protocol Version 4.0 dated 04 Aug 2021)	New Text (Protocol Version 5.0 dated 29 Apr 2022)	Rationale for amendment
Administrative change Sponsor details throughout the document	Upjohn US 1 LLC	Viatris Specialty LLC 3711 Collins Ferry Road Morgantown, WV 26505	Sponsor name change
Section 1.2	The Treatment Phase of the study will use a Williams square study design involving approximately 40 participants (4 participates in each sequence) to ensure at least 32 participants complete the treatment phase of the study as shown in Figure 1	The Treatment Phase of the study will use a Williams square study design involving approximately 50 participants (5 participants in each sequence) to ensure at least 32 participants meeting the definition of the Modified Completer Population complete the treatment phase of the study as shown in Figure 1	Increasing the number of subjects enrolled to ensure sufficient subjects meeting the newly-defined Modified Completer Population
Table 2, footnote g	Vital signs (including pulse rate, systolic and diastolic blood pressures are measured at the nominal time points after a resting period of at least 5 minutes in a sitting position. Temperature (oral or with a temporal infrared scanner) will be measured on Day -1 of each Treatment Visit only. Vital signs will be recorded at nominal time points ±5 min	Vital signs (including pulse rate, systolic and diastolic blood pressures are measured at the nominal time points after a resting period of at least 5 minutes in a sitting position. Temperature (oral or with a temporal infrared scanner) will be measured on Day -1 of each Treatment Visit only. Vital signs will be recorded at nominal time points ±5 min for time points up to and including 4 h post-dose, within ±15 minutes for time points from 6-12 h post-dose, and within ±60 minutes for the	Increasing the permitted time windows for vital signs assessments

		remaining time points up to and including 72 h post-dose	
Table 2, footnote p	None (new text added)	Subjects may be discharged after completion of Day 3 assessments and return for Day 4 assessments, at the discretion of the investigator.	Reducing the number of residential nights from 4 to 3 to facilitate subject enrollment
Section 4.1	This will be a randomized, double-blind, double-dummy, placebo- and active controlled, 5 treatment, 10 sequence, 5 period crossover single dose, Williams square design study in healthy adult, non drug dependent male and female participants with drug abuse experience with sedative drugs…This study will randomize approximately 40 participants to ensure at least 32 participants complete the Treatment Phase of the study.	This will be a multi-center, randomized, double-blind, double-dummy, placebo- and active controlled, 5 treatment, 10 sequence, 5 period crossover single dose, Williams square design study in healthy adult, non drug dependent male and female participants with drug abuse experience with sedative drugs…This study will randomize approximately 50 participants to ensure at least 32 participants meeting the definition of the Modified Completer Population complete the Treatment Phase of the study.	Adding "multi-center" in the study description and increasing the number of subjects enrolled to ensure sufficient subjects meeting the newly-defined Modified Completer Population

Section 4.1	• Visits 3 to 7, Treatment Phase:
	  • Each visit will require an inpatient stay at the CRU of 4 nights.
	  • For the entire study, 23 overnight inpatient stays will be required
		• Visits 3 to 7, Treatment Phase:
		  • Each visit will require an inpatient stay at the CRU of 3 or 4 nights. Subjects may be discharged after completion of 48 h postdose assessments and return for 72 h postdose assessments on an ambulatory basis, at the discretion of the investigator.
			Reducing the number of residential nights from 4 to 3, at the investigator's discretion, to facilitate subject enrollment

		• For the entire study, 18 - 23 overnight inpatient stays will be required	
Section 5.2	14. Participants unable to abstain from using THC during the Qualification and Treatment Phases of the study	14. Participants unable to abstain from using THC during the inpatient stays in the Qualification and Treatment Phases of the study	Clarification that subjects must abstain from using THC while resident in the clinic
Section 5.3.4	At time points indicated in the schedule of activities (SoA), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception)	At time points indicated in the schedule of activities (SoA), the investigator or designee will inform the participant of the need to use effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception)	Change to reflect the addition of further forms of acceptable female contraception, in order to facilitate subject enrollment
Section 8.2.2	The same arm (preferably the dominant arm) will be used throughout the study.	The same arm (preferably the dominant arm) should be used throughout the study.	Change from the mandatory requirement to a recommendation
Section 8.5	Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on	Collection of samples up to and including 10 hours after dose administration that are obtained within 5 minutes or 10% of the nominal time (eg, within 6 minutes of a 60 minute sample), whichever is greater, relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the	Redefining the permitted time windows for PK sampling

	the source document and data collection tool (eg, CRF).	source document and data collection tool (eg, CRF).	
Section 8.6.2	All VAS testing will be administered at the nominal time points ±5 minutes.	All VAS testing will be administered at the nominal time points ±5 minutes for time points up to and including 4 h post-dose, within ±15 minutes for time points from 6-12 h post-dose, and within ±60 minutes for the remaining time points up to and including 72 h post-dose.	Increasing the permitted time windows for vital signs assessments
Section 9.1	Study Validation: The sensitivity and integrity of the study will be validated by comparing the mean responses of diazepam, the positive control (C), to the placebo: *H0: $\mu C - \mu P \leqslant \delta 1$ versus Ha: $\mu C - \mu P > \delta 1$ where $\delta 1 > 15$.* Gabapentin versus diazepam: 1. Does gabapentin (T) produce mean responses that show less abuse potential than diazepam? *H0: $\mu C - \mu T \leqslant \delta 2$ versus Ha: $\mu C - \mu T > \delta 2$ where $\delta 2 \geqslant 0$.* Gabapentin versus placebo (Primary):	Study Validation: The sensitivity and integrity of the study will be validated by comparing the mean responses of diazepam, the positive control (C), to the placebo (P): *H0: $\mu C - \mu P \leqslant \delta 1$ versus Ha: $\mu C - \mu P > \delta 1$ where $\delta 1 = 15$.* Gabapentin versus diazepam: 1. Does gabapentin (T) produce mean responses that show less abuse potential than diazepam? *H0: $\mu C - \mu T \leqslant \delta 2$ versus Ha: $\mu C - \mu T > \delta 2$ where $\delta 2 = 0$.* Gabapentin versus placebo (Primary):	Corrections to the three equations

	2. Does gabapentin (T) produce mean responses that show abuse potential similar to placebo? *H0: $\mu T - \mu P \geq \delta 3$ versus Ha: $\mu p - \mu T < \delta 3$ where $\delta 3 > 11$.*	2. Does gabapentin (T) produce mean responses that show abuse potential similar to placebo? *H0: $\mu T - \mu P \geq \delta 3$ versus Ha: $\mu T - \mu P < \delta 3$ where $\delta 3 = 11$.*	
Section 9.2	This study will randomize 40 participants to ensure at least 32 participants complete the Treatment Phase of the study.	This study will randomize approximately 50 participants to ensure at least 32 participants who meet the definition of the Modified Completer Population complete the Treatment Phase of the study. Among the 50 participants, at least 20% will be females to ensure that the findings are valid across different populations.	Increasing the number of subjects enrolled to ensure sufficient subjects meeting the newly-defined Modified Completer Population and to specify the proportion of females
Section 9.3	• The Completer Population will include all randomized participants who complete all 5 periods of the Treatment Phase and who contribute post dose PD data from each period. These participants must have all post dose responses for each treatment group present until median Tmax sampling time after dosing. This population will be analyzed as randomized. • The Evaluable Population will include all randomized participants in the Completer Population who do not have major protocol violations or adverse events that would interfere with drug absorption	• The Completer Population will include all randomized participants who complete all 5 periods of the Treatment Phase and who contribute post dose PD data from each period. These participants must have at least one post dose response on the VAS for Drug Liking within 2 hours of Tmax for each treatment group: ie, at least one VAS response within the interval 0-3h postdose (assuming the Tmax of 20 mg diazepam is 1h) and at least one VAS response within the interval 1-5h postdose (assuming the Tmax of 600/1200/1800 mg gabapentin is 3h).	Modifying the definition of the Completer Population (upon which other analysis sets are defined) to specify the minimum required post-dose responses required within the Tmax time periods specific to the two study drugs, in line with FDA guidance on assessing

	such as vomiting within 4 hours of study drug administration. Major protocol violations, including deviations related to study drug intake are defined as those that could potentially affect the PD conclusions of the study. Prior to unblinding the Treatment Phase data, the sponsor (or designee) will identify protocol violations or adverse events that would disqualify a participant from the evaluable population and determine which participants or participant visits will be excluded. This population will be analyzed as randomized. All PD analyses will be performed using the Modified Completer Population and all available post dose data; these will be the primary PD analyses. Key PD analyses may be repeated on the Evaluable Population using all available post-dose data.	This population will be analyzed as randomized. • The Modified Completer Population will include all randomized participants in the Completer Population, but will exclude any participant who meet either or both of the following criteria for Drug Liking VAS: 1. Emax scores are within a 5 point difference across all five treatments (ie, Maximum Emax score – Minimum Emax score $\leqslant 5$); 2. Emax(P) > 60 AND Emax(P) - Emax(Dia) $\geqslant 5$; where Emax(P) and Emax(Dia) are the VAS Emax scores for placebo and diazepam 20 mg, respectively. This population will be analyzed as randomized. • The Evaluable Population will include all randomized participants in the Modified Completer Population who do not have major protocol violations or adverse events that would interfere with drug absorption such as vomiting within 4 hours of study drug administration. Major protocol violations, including	abuse potential of drugs Also, addition of the Modified Completer Population as the primary analysis population, and clarification that the Evaluation Population will be the subset of the Modified Completer Population who do not have major protocol deviations

		deviations related to study drug intake are defined as those that could potentially affect the PD conclusions of the study. Prior to unblinding the Treatment Phase data, the sponsor (or designee) will identify protocol violations or adverse events that would disqualify a participant from the evaluable population and determine which participants or participant visits will be excluded. This population will be analyzed as randomized. All PD analyses will be performed using the Modified Completer Population and all available post dose data; these will be the primary PD analyses. Key PD analyses may be repeated on the Evaluable Population using all available post-dose data.	
Section 9.6	Maximum (peak) effect (Emax); calculated as maximum change from pre-dose response if pre-dose assessment is performed;	Maximum (peak) effect (Emax); calculated as maximum change from pre-dose response if pre-dose assessment is performed; the neutral VAS point (50 for Drug liking, 0 for High) will be used as pre-dose response when VAS not performed or missing.	Clarification of how missing pre-dose VAS values will be handled
Section 9.8	• A linear mixed-effects model that includes period, sequence, and treatment	• A linear mixed-effects model that includes site, period, sequence, and treatment as fixed effects, and the	Addition of "site" as a fixed effect in response to the

	as fixed effects, and the participant as a random effect will be used	participant as a random effect will be used	addition of a new investigator site
Section 9.8.1	The changes from baseline will be analyzed with an analysis of variance (ANOVA) model consisting of: Sequence, Period, Treatment, Time, Period*Time and Treatment*Time terms as fixed effects, and a participant (Sequence) term as a random effect for. To accommodate the repeated measures aspect of the design, a compound symmetric covariance matrix will be employed, with the participant set to Period*Participant (Sequence).	The changes from baseline will be analyzed with an analysis of variance (ANOVA) model consisting of: Site, Sequence, Site*Sequence, Period, Treatment, Time, Period*Time, Site*Treatment and Treatment*Time terms as fixed effects, and a participant (Site*Sequence) term as a random effect for testing Site, Sequence, and Site*sequence effect. Site*Treatment interaction will be evaluated and this interaction term will be dropped from the final model if it is not significant. To accommodate the repeated measures aspect of the design, a compound symmetric covariance matrix will be employed, with the participant set to Period*Participant (Sequence).	Addition of "site" as a fixed effect in response to the addition of a new investigator site
Section 9.8.3	Samples from gabapentin treatment will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures	Samples from gabapentin treatment will be analyzed using a validated analytical method in compliance with Viatris standard operating procedures	Updating the applicable standard operating procedures of the new Sponsor
Section 10.1.5	Data Sharing Upjohn will make available data from these trials 24 months after study completion.	Data Sharing Viatris will make available data from these trials 12 months after study completion.	Updating the time period for making trial data available to reflect the change of Sponsor

Section 10.4.2	Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described below, during the intervention period and for at least 42 days after the last dose of study intervention, which corresponds to the time needed to eliminate any study intervention(s).	Is a WOCBP and using a contraceptive method, as described below, during the intervention period and for at least 42 days after the last dose of study intervention, which corresponds to the time needed to eliminate any study intervention(s).	Change to reflect the addition of further forms of acceptable female contraception, in order to facilitate subject enrollment
Section 10.4.3	2. Postmenopausal female. • Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods.	2. Postmenopausal female. • Females on HRT and whose menopausal status is in doubt will be required to use at least one of the contraception methods below.	Change to reflect the addition of further forms of acceptable female contraception, in order to facilitate subject enrollment
Section 10.4.4	Highly Effective Methods That Have Low User Dependency. 1. Intrauterine device (IUD). 2. Bilateral tubal occlusion. 3. Vasectomized partner. • Vasectomized partner 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. The	Female subjects of child-bearing potential must use at least one form of the following contraception methods. 1. Intrauterine device (IUD). 2. Bilateral tubal occlusion. 3. Hormonal contraception. 4. Contraceptive implants. 5. Double-barrier method (any combination of physical and chemical methods). 6. Confirmed infertility of sexual partner.	Change to add further forms of acceptable female contraception, in order to facilitate subject enrollment

	spermatogenesis cycle is approximately 90 days.	7. Engaged exclusively in a same-sex relationship. 8. Total abstinence (periodic abstinence is not acceptable). 9. Vasectomized partner. • Vasectomized partner 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 method of contraception should be used. The spermatogenesis cycle is approximately 90 days.	

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