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A Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Interactions Between Alcohol and Sunobinop in Healthy Participants

Stephen C. Harris, MD,[1] Manjunath S. Shet, PhD,[1] Alessandra Cipriano, MS,[1] Garth T. Whiteside, PhD,[1] Ellie He, PhD,[1] Mingyan Zhou, PhD,[1] Ram P. Kapil, PhD,[1] and Glen Apseloff, MD[2]

Background: Sunobinop is a potent, selective partial agonist at nociception/orphanin-FQ receptors with therapeutic potential in a variety of clinical disorders. This study assessed safety, tolerability, pharmacodynamics, and pharmacokinetic interactions of sunobinop and alcohol in healthy adults.

Methods: This was a single-center, randomized, blinded, crossover study in 48 participants. Single doses of placebo, sunobinop 2 mg (therapeutic), and 6 mg (supratherapeutic), were administered in the morning with alcohol or placebo. Pharmacokinetic and pharmacodynamic profiles were compared.

Results: Coadministration with alcohol did not alter the pharmacokinetics of alcohol or of sunobinop at either dose. A dose-effect relationship in the magnitude/duration of impairment in psychomotor/cognitive parameters was observed, with transient additive effects at 2 mg and greater-than-additive effects at 6 mg that resolved by 5 hours post administration. The most common treatment-emergent adverse event was somnolence, which was mild to moderate.

Conclusions: A single oral dose of sunobinop was safe and tolerated alone and in combination with alcohol. No pharmacokinetic interaction between sunobinop and alcohol was observed. An additive or greater-than-additive effect was observed for psychomotor/cognitive measures consistent with sunobinop's sleep-promoting effect, and would peak and resolve during a typical night's sleep.

Key Words: sunobinop, alcohol interaction, pharmacodynamics, pharmacokinetics

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From the [1]Imbrium Therapeutics, Stamford, CT; and [2]Ohio Clinical Trials, Inc., Columbus, OH.

Mingyan Zhou and Ram P. Kapil are co-authors.

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Address correspondence to: Stephen C. Harris, MD, Imbrium Therapeutics, 201 Tresser Boulevard, Stamford, CT 06901 (e-mail: stephen.harris@imbriumthera.com).

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Sunobinop (V117957; Imbrium Therapeutics/Purdue Pharma) is an investigational drug that functions as a potent and selective partial agonist at the nociceptin/orphanin-FQ peptide (NOP) receptor.[1] NOP is widely expressed in the central and peripheral nervous systems, and the endogenous ligand functions as an inhibitory neurotransmitter. The NOP system has been implicated in a wide range of biological processes, including pain sensitivity, addiction, anxiety/depression, sleep, bladder function, cardiovascular control, and immunity.[2,3] While the broad therapeutic potential of NOP receptor agonists has been recognized for almost 2 decades;[2] a NOP-targeted compound has not yet been successfully developed. Sunobinop has a high affinity for human NOP receptors and a low affinity for mu and kappa-opioid receptors without agonist activity; it is also a weak agonist for delta receptors.[1] Safety and tolerability and pharmacokinetics of sunobinop have been previously evaluated in phase 1 pharmacokinetic (PK) studies in healthy participants and in patients.[3,4] The initial PK studies in healthy participants demonstrated that sunobinop administered orally at doses ranging from 0.6 to 30 mg exhibited less than dose-proportional systemic exposure at doses > 3 mg. The median time to peak concentration (T_{max}) was 1.5 hours, and mean half-life was 2.4 to 2.7 hours. Systemically available sunobinop underwent minimal to no hepatic metabolism and was eliminated unchanged through urine within 8 hours of oral administration with no appreciable accumulation after 14 days of once-daily dosing.

Sunobinop has therapeutic potential in a variety of clinical disorders and has been studied in insomnia, overactive bladder, interstitial cystitis, as well as alcohol use disorder (AUD).[4–8] In a randomized, double-blind, repeat-dose, crossover study in patients with insomnia disorder, sunobinop administered at bedtime showed increased sleep efficiency and improved sleep maintenance with limited residual next-day effects at clinically relevant doses (< 3 mg).[4] No clinically meaningful changes in clinical laboratory tests, vital signs, including SpO_2, or 12-lead electrocardiograms (ECGs) were observed. Furthermore, a phase 2, randomized, double-blind, multicenter, placebo-controlled, parallel-group study in 114 patients diagnosed with AUD who are in recovery and have comorbid insomnia demonstrated that sunobinop administered at bedtime improved sleep maintenance, particularly in the second half of the night, as well as sleep efficiency and total sleep time.[5] Treatment with sunobinop did not worsen alcohol craving in this population.

Given the efficacy of sunobinop in sleep disorders and its potential utility in treating participants with AUD, understanding the impact of concomitant alcohol administration is clinically important. The aim of this study was to assess the safety, tolerability, pharmacodynamics (PD), and PK interactions between sunobinop and alcohol.

METHODS

This study was a single-center, single-dose, randomized, blinded crossover study. The protocol (#OAG1010) and informed consent form were reviewed and approved by IntegReview Institutional Review Board, Austin, TX, before any participants were screened. All participants provided informed consent before any study procedures. The study was conducted with standard operating procedures designed to ensure adherence to Good Clinical Practice guidelines and the principles of the Declaration of Helsinki.

Participants included in the study were 48 healthy men and women of non-childbearing potential between the ages of 21 and 55 years inclusive, with a body weight between 50 and 100 kg inclusive, and a body mass index between 18 and 30 kg/m^2 inclusive. Participants were required to have a current alcohol consumption of at least 2 standard drinks per week but no more than 2 standard drinks per day on average.

Participants were excluded from the study if they had any clinically significant abnormalities on physical examination, vital signs, ECG, or clinical laboratory values, or if they had a history of any clinically significant illness that might jeopardize their safety. Participants with a history of frequent nausea or emesis, or frequent smoking or use of nicotine products (> 1/2 pack/d) were excluded, as were participants with a known or expected aldehyde dehydrogenase deficiency, who were pregnant or lactating, or who had a current or recent history (within 5 y) of drug or alcohol abuse. Participants who refused to abstain from alcohol consumption (except as required per protocol) for 48 hours before initial study drug administration and continuing through 48 hours after each study treatment were excluded.

The study duration was up to 57 days, including screening, check-in, treatment, and posttreatment follow-up periods, as shown in Figure 1.

Screening Period

A screening visit was conducted no more than 28 days before check-in. Screening included informed consent, medical history, demographic characteristics, physical examination, Columbia-Suicide Severity Rating Scale (C-SSRS), vital signs, including orthostatic measurements, alcohol breath test, pulse oximetry (SpO_2), oral temperature, ECG, and alcohol consumption history. Laboratory assessments at screening included clinical laboratory tests, drug/alcohol/cotinine (nicotine metabolite) screens, serum pregnancy test for women, serum follicle-stimulating hormone test (for postmenopausal women only), and serology testing.

Check-in Period

Participants were confined to the clinical site from the day before first dose until the end of the study. During check-in, all participants received repeat screening, including clinical laboratory tests and drug/alcohol/cotinine screens, demographic characteristics, vital signs, oral temperature, ECG, and an optional targeted physical examination if deemed necessary by the investigator. In addition, women received a urine pregnancy test.

Treatment Period

Participants were randomly assigned to 1 of 6 treatment sequences. Treatment consisted of 1 administration of each of the following treatments, double-blinded, with each participant receiving all treatments according to their randomly assigned sequence:

- Sunobinop 2 mg with alcohol 0.7 g/kg.
- Sunobinop 6 mg with alcohol 0.7 g/kg.
- Sunobinop 2 mg with placebo for alcohol.
- Sunobinop 6 mg with placebo for alcohol.
- Placebo for sunobinop with alcohol 0.7 g/kg.
- Placebo for sunobinop with placebo for alcohol.

Study treatments were administered orally in the morning following an overnight fast, which was continued for 4 hours post dosing. Alcohol (100-proof Absolut vodka) was served in a chilled solution that was prepared at a dose of 0.7 g/kg, based on the participant's body weight on day 1. The alcohol dose was chosen to result in a blood-alcohol concentration of ~0.08%, which corresponds to the National Institute on Alcohol Abuse and Alcoholism definition of binge drinking.[9] The alcohol was diluted with Sprite to bring the total volume to 240 mL, then divided into three 80-mL servings. Before dosing, participants were required to rinse their mouths with 20 mL of Original Listerine mouthwash (a high-alcohol-content mouthwash) for 30 seconds at each administration to mask the subsequent taste of the alcohol plus Sprite versus Sprite alone. Ten minutes before dosing, participants were given the first 80 mL serving of alcohol or placebo. Sunobinop/

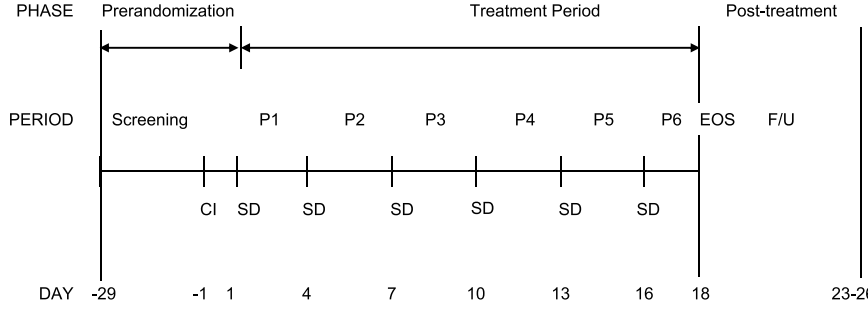

FIGURE 1. Study design. F/U indicates follow-up visit; P, period; SD, study drug.

placebo was administered at time 0, at which time participants were given the second 80 mL serving of alcohol or placebo. The third 80 mL serving was provided 10 minutes after dosing. Immediately following each 80 mL dose, the container was rinsed with 20 mL of water, which the participant was also required to consume. The washout interval between treatments was at least 72 hours.

Endpoints

PK endpoints included analyses of PK profiles of sunobinop following combined administration with alcohol compared with sunobinop alone, as well as of alcohol following combined administration of sunobinop and alcohol compared with alcohol alone. The concentrations of sunobinop and alcohol were determined in plasma samples (collected 20 min before dosing and following dosing at 0.25, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, and 48 h). Urine samples were analyzed for sunobinop only (collected after dosing at 0 to 2, 2 to 4, 4 to 8, 8 to 16, 16 to 24, and 24 to 48 h). The concentrations of sunobinop and alcohol in plasma and urine (only sunobinop) were determined using validated liquid chromatography/tandem mass spectrometry methods.

The primary PD endpoints were the effects of combined administration of sunobinop and alcohol on change from baseline in body sway, digit vigilance test (DVT), and numeric working memory (NWM) as compared with sunobinop alone or alcohol alone (Tables S1, S3–S5, Supplemental Digital Content 1, http://links.lww.com/JCP/B17). The secondary PD endpoints were the effect of combined administration of sunobinop and alcohol on change from baseline on choice reaction time (CRT), digit symbol substitution test (DSST), immediate word recall (IWR), delayed word recall (DWR), and Bond and Lader Visual Analog Scale (VAS) as compared with sunobinop alone or alcohol alone (Tables S6–S10, Supplemental Digital Content 1, http://links.lww.com/JCP/B17). All PD assessments were administered through Signant SmartSignals (formerly Bracket CDR System).

The primary safety endpoint was the effect of combined administration of sunobinop and alcohol on changes from baseline in adverse events (AEs), ECGs, clinical laboratory values, and SpO_2 as compared with sunobinop alone or alcohol alone.

Statistical Methods

Continuous demographic and baseline variables were summarized using n, mean, and SD. For categorical variables, the number and percentage of participants were calculated.

The randomized safety population consisted of participants who were randomized and received ≥1 dose of the study drug. The full analysis population (FAP) for PK analyses consisted of participants who were randomized, received ≥1 dose of the study drug, and had ≥1 valid PK metric. The FAP for PD analyses consisted of participants who were randomized, received ≥1 dose of the study drug, and had ≥1 valid PD metric.

PK metrics were summarized with descriptive statistics that were tabulated by treatment for all sunobinop and alcohol plasma and urine sunobinop concentrations. All plasma or urine concentration values below the limit of quantification (BLQ) were listed as BLQ and set to 0. For the area under the curve from time 0 to the last measurable concentration (AUC_t), the area under the curve from time 0 to infinity (AUC_{inf}), and the maximum plasma concentration (C_{max}), a mixed-model analysis of variance was used to compare logarithmic-transformed values from the test and reference treatments, with treatment, period, and sequence as fixed effects, and participant within sequence as a random effect. The 90% CIs were estimated for the ratio of exponentiated least squares mean (LSM). To compare the time to C_{max} between treatments, the Wilcoxon signed-rank test was performed.

PD data at each time point were summarized by descriptive statistics. The analysis of the change from baseline in PD parameters was performed using a mixed model for repeated measures with sequence, treatment, period, time point, and treatment x time point as the repeated measures. The LSM treatment differences and 95% CIs were calculated for each time point. In addition, the additive effects of sunobinop with alcohol were evaluated, and LSM with corresponding 95% CIs were calculated. *P*-values were adjusted using the Hochberg step-up procedure for each parameter by time point to reduce the likelihood of finding false significance due to multiple comparisons, and the threshold for statistical significance was $P < 0.05$. Safety data were analyzed using the randomized safety population. AEs were coded to MedDRA Version 21.0 terms and summarized by treatment. AEs were assessed by the investigator as mild (a symptom or event that was easily tolerated), moderate (discomfort that interfered with usual activity and possibly warranted intervention), or severe (incapacitation or inability to do usual activities or significantly affected clinical status that warranted intervention). Treatment-emergent AEs (TEAEs) were assigned to the study drug according to their onset dates. AEs that started after a participant's last dose but within 7 days of dosing were considered TEAEs and were assigned to the last dose administered. AEs that started more than 7 days after the last dose of study drug were considered non-TEAEs. Summary statistics for screening, baseline, each scheduled time point, end of study (EOS), and values for change from baseline to EOS were produced for each continuous safety parameter.

RESULTS

Demographics and Baseline Characteristics

A total of 89 participants were screened for inclusion in the study. There were 41 screen failures resulting in a randomized safety population of 48 participants. The majority, 63%, of screen failures were due to participants not meeting inclusion or exclusion criteria. The remaining screen failures were related to participant choice or administrative reasons, 20% and 17%, respectively. Of the 48 participants in the randomized population, 46 completed the study, and 2 participants discontinued the study due to choice. Patient demographics and baseline characteristics are shown in Table 1. Study participant ages ranged from 23 to 54 years, with a median age of 39.5 years. The population primarily consisted of men (92%) and was mainly black/African American (50%) or white (42%).

Pharmacokinetic Parameters of Alcohol

Mean plasma concentrations of alcohol versus time are shown in Figure 2A, B. Following either a single oral dose of alcohol alone or sunobinop (2 or 6 mg) with alcohol, mean alcohol concentration time profiles showed a rapid absorption phase, with peak concentrations occurring

TABLE 1. Summary Demographic and Baseline Characteristics

	Treatment Sequence*						
Variable	ABFCED (N = 8)	BCADFE (N = 8)	CDBEAF (N = 8)	DECFBA (N = 8)	EFDACB (N = 8)	FAEBDC (N = 8)	Overall (N = 48)
Age, years							
Mean	37.3	38.9	34.3	39.5	42.9	41.9	39.1
Range	27-43	23-49	25-44	30-51	36-54	26-54	23-54
Age group (y), n (%)							
21-39	4 (50)	3 (38)	6 (75)	5 (63)	3 (38)	3 (38)	24 (50)
40-55	4 (50)	5 (63)	2 (25)	3 (38)	5 (63)	5 (63)	24 (50)
Sex, n (%)							
Male	8 (100)	7 (88)	8 (100)	7 (88)	7 (88)	7 (88)	44 (92)
Female	0	1 (13)	0	1 (13)	1 (13)	1 (13)	4 (8)
Race, n (%)							
White	1 (13)	2 (25)	4 (50)	7 (88)	2 (25)	4 (50)	20 (42)
Black/African American	4 (50)	6 (75)	4 (50)	1 (13)	6 (75)	3 (38)	24 (50)
Asian	1 (13)	0	0	0	0	1 (13)	2 (4)
Other	2 (25)	0	0	0	0	0	2 (4)
Ethnicity, n (%)							
Hispanic or Latino	0	0	1 (13)	3 (38)	1 (13)	0	5 (10)
Not Hispanic or Latino	8 (100)	8 (100)	7 (88)	5 (63)	7 (88)	8 (100)	43 (90)
Screening height (cm)							
Mean	175	179	177	171	175	173	175
Range	164-182	171-185	168-186	160-180	163-188	157-192	157-192
Screening weight (kg)							
Mean	82.6	85.2	78.7	76.0	79.5	75.6	79.6
Range	64.6-92.2	74.9-94.5	67.6-84.0	64.7-88.9	65.5-94.5	60.5-96.5	60.5-96.5
Body mass index (kg/m^2)							
Mean	27	27	25	26	26	25	26
Range	22-29	23-29	22-30	24-29	23-29	21-30	21-30

*Treatment A = sunobinop 2 mg with alcohol; B = sunobinop 6 mg with alcohol; C = sunobinop 2 mg alone; D = sunobinop 6 mg alone; E = alcohol alone; F = placebo.

in < 1.5 hours. Mean alcohol concentrations declined in a biphasic manner, with alcohol detectable up to 8 hours in most cases. In addition, the systemic exposures of alcohol, as estimated with C_{max}, AUC_t, and AUC_{inf}, were comparable across all treatments. Mean C_{max} ranged from 0.964 to 0.991 ng/mL; mean AUCs (AUC_t and AUC_{inf}) ranged from 3.80 to 4.31 ng·h/mL.

Pharmacokinetic Parameters of Sunobinop

Sunobinop plasma concentrations versus time are shown in Figure 3A, B. Sunobinop 2 mg alone and sunobinop 6 mg alone reached peak plasma concentrations approximately 1.5 to 2 hours after oral administration and increased with increasing dose. Mean concentrations of sunobinop declined in a biphasic manner and were detectable up to 48 hours post dose. PK profiles of sunobinop 2 mg and 6 mg were superimposable in the presence of alcohol.

A summary of plasma sunobinop PK metrics is shown in Table 2. The respective systemic exposures for sunobinop were comparable in the presence and absence of alcohol following administration of the 2 mg and 6 mg doses. Both C_{max} and AUC increased with increasing dose from 2 to 6 mg. Mean C_{max} ranged from 28.2 to 31.0 ng/mL, and mean AUCs ranged from 130.0 to 136.0 ng·h/mL for sunobinop 2 mg. Mean C_{max} ranged from 78.3 to 85.0 ng/mL, and mean AUCs ranged from 402.0 to 415.0 ng·h/mL. The mean half-life of sunobinop ranged from 3.95 to 4.50 hours across all treatments. The mean CL/F (apparent total clearance of the drug) and Vd/F (apparent total volume of distribution after non-intravenous administration) values were comparable across all treatments. In addition, most unchanged sunobinop was excreted through the urine in the first 0 to 8 hours across all treatments. Approximately 80% of sunobinop was excreted unchanged, with mean sunobinop renal clearance ranging from 11.9 to 12.7 L/h across all treatments (Table S2, Supplemental Digital Content 1, http://links.lww.com/JCP/B17).

Pharmacodynamic Parameters

Results are discussed separately for the therapeutic and supra-therapeutic dose levels of sunobinop 2 and 6 mg, respectively (both doses are presented together in Figures 4, 5A, B, 6A, B). Effect size is shown as LSM treatment difference (LSMD) (corresponding 95% CIs).

Pharmacodynamic Parameters of Sunobinop 2 mg

Change from baseline in body sway is shown in Figure 4 and for selected time points in Table 3. Body sway increased after sunobinop 2 mg dosing with and without alcohol and returned to baseline values by 12 hours post dose. The increase at 2 mg alone was statistically significantly different from placebo only at 3 and 4 hours post dose [adjusted $P = 0.019$, LSMD: 18.5 (5.2, 31.8), LSMD: 18.0 (4.6, 31.4), and adjusted $P < 0.033$,

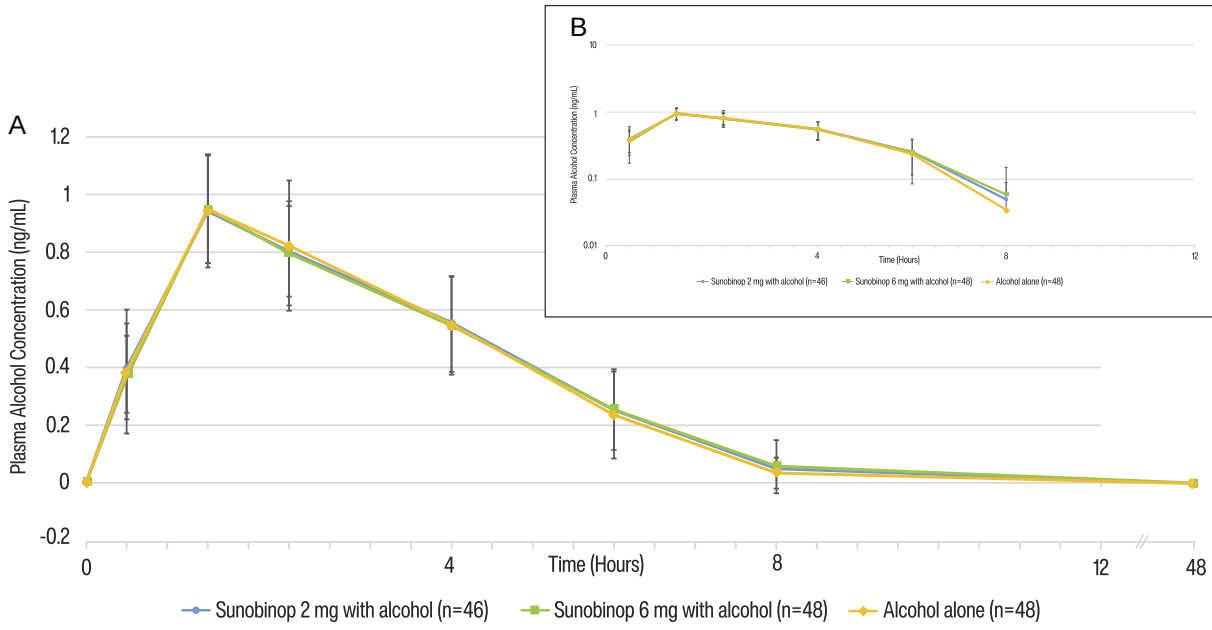

FIGURE 2. Mean plasma concentrations of alcohol vs time.

respectively], while 2 mg was statistically significantly different. Sunobinop 2 mg plus alcohol at 1 to 4 hours post dose [adjusted *P*-value range, < 0.001 to 0.036, LSMD 24.3 (11.0, 37.6), 34.6 (21.2, 47.9), 18.9 (5.6, 32.2), and 17.1 (3.8, 30.4), respectively]. Greater-than-additive effects were not observed at any time point.

Change from baseline in the DVT is shown in Figure 5A, B, and for selected time points in Table 3. Mean reaction time (Figure 5A) increased after sunobinop 2 mg dosing with and without alcohol and returned to baseline values by 12 hours post dose. The increase at 2 mg alone was statistically significantly different from placebo from 2 to 8 hours post dose [adjusted *P*-value range, < 0.001 to 0.002, LSMD: 37.2 (18.1, 56.4), 47.4 (28.2, 66.5), 51.2 (32.0, 70.4), 45.3 (26.1, 64.4), 52.8 (33.6, 74.9) and 35.4, (16.3, 54.6), respectively]. Sunobinop 2 mg alone was

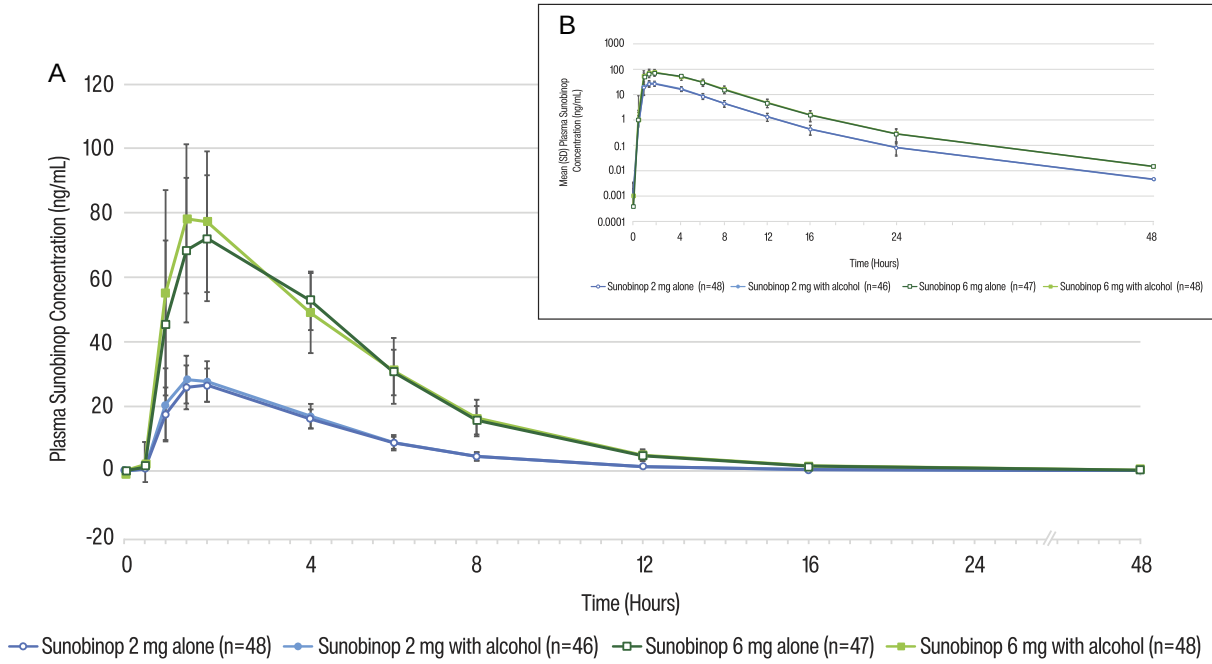

FIGURE 3. Mean plasma concentrations of sunobinop vs time.

TABLE 2. Summary of Plasma Sunobinop PK Metrics

Metric	Sunobinop 2 mg Alone (N = 48)	Sunobinop 2 mg With Alcohol (N = 46)	Sunobinop 6 mg Alone (N = 47)	Sunobinop 6 mg With Alcohol (N = 48)
C_{max} (ng/mL)				
Mean	28.2	31.0	78.3	84.9
CV (%)	16.6	19.9	14.4	23.2
Range	19.0-41.5	16.2-42.9	58.6-109.0	29.1-133.0
T_{max} (h)				
Mean	1.74	1.76	1.88	1.82
CV (%)	25.1	39.6	34.1	55.9
Range	1.00-4.00	1.00-4.00	1.00-4.00	1.00-6.00
AUC_t (ng·h/mL)				
Mean	130.0	136.0	402.0	415.0
CV (%)	15.0	16.4	13.1	19.2
Range	93.7-172.0	64.8-186.2	283.0-533.0	139.0-566.0
AUC_{inf} (ng·h/mL)				
Mean	130.0	136.0	402.0	415.0
CV (%)	15.0	16.4	13.1	19.2
Range	93.9-172.0	64.9-186.0	283.0-533.0	140.0-566.0
$t_{1/2}$ (h)				
Mean	4.01	3.95	4.50	4.48
CV (%)	32.5	31.2	7.83	7.89
Range	2.40-6.39	2.39-6.44	3.88-5.25	3.63-5.48
CL/F (L/h)				
Mean	15.7	15.1	15.2	15.3
CV (%)	14.9	21.4	14.2	33.3
Range	11.6-21.3	10.7-30.8	11.3-21.2	10.6-43.0
V_d/F (L)				
Mean	90.7	84.5	98.8	100
CV (%)	36.4	31.7	16.9	40.0
Range	45.2-164.0	43.7-157.0	70.6-147.0	68.2-323.0

CV indicates coefficient of variation; $t_{1/2}$, half-life.

statistically significantly different from 2 mg plus alcohol at 0.5, 1, 2 and 4 hours post dose [not at 3 hours post dose; adjusted *P*-value, <0.001 to 0.004, LSMD: 48.5 (29.1, 67.8), 46.9 (27.6, 66.1), 44.6 (25.3, 63.8) and 32.1 (12.9, 51.4), respectively]. Greater-than-additive effects were not observed. Accuracy (Figure 5B) decreased after sunobinop 2 mg dosing with and without alcohol, returning to baseline values by 12 hours post dose. The decrease for 2 mg alone was statistically significantly different from placebo at 3, 5, and 6 hours post dose [adjusted $P < 0.001$, 0.016, and 0.002, LSMD: −11.2 (−17.0, −5.3), −8.8 (−14.7, −2.9), and −10.8 (−16.7, −4.9), respectively]. Sunobinop 2 mg was statistically significantly different from 2 mg plus alcohol only at 5 and 6 hours post dose [adjusted $P < 0.001$ and $P = 0.002$, LSMD: −11.8 (−17.7, −5.9) and −10.9 (−16.8, −5.0), respectively]. Greater than additive effects on accuracy were observed only at 5 and 6 hours post dose for sunobinop 2 mg with alcohol [$P = 0.023$ and $P = 0.027$, LSMD: −11.7 (−20.0, −3.4) and −11.5 (−19.9, −3.2), respectively].

Change from baseline in NWM time is shown in Figure 6A, B, and for selected time points in Table 3. Mean reaction time (Figure 6A) increased after dosing and returned to baseline by 12 hours post dose in participants receiving sunobinop 2 mg with and without alcohol. The increase at 2 mg alone was not statistically significantly different from placebo at any time point; also, 2 mg alone was not statistically significantly different from 2 mg plus alcohol at any time point post dose. A greater-than-additive effect was not observed at any time point post dose. The sensitivity index (Figure 6B) decreased after dosing, returning to baseline by 12 hours post dose following sunobinop 2 mg with and without alcohol. The decrease at 2 mg alone was statistically significantly different from placebo at 3 and 6 hours post dose [adjusted *P*-value = 0.018 and <0.001, LSMD: −0.02 (−0.20, −0.04) and LSMD: −0.16 (−0.24, -0.08), respectively], while 2 mg was statistically significantly different from 2 mg plus alcohol from 2 to 5 hours post dose [adjusted *P*-value range, 0.008 to 0.048, LSMD: −0.13 (−0.21, −0.05), −0.10 (−0.18, −0.02), −0.12 (−0.20, −0.04), and −0.11 (−0.19, −0.03), respectively]. Greater-than-additive effects were not observed for sunobinop 2 mg with alcohol.

Change from baseline in CRT-mean reaction time is shown in Figure S1 (Supplemental Digital Content 1, http://links.lww.com/JCP/B17). Mean reaction time increased after sunobinop 2 mg with and without alcohol dosing and returned to baseline by 12 hours post dose. The increase at 2 mg alone was not statistically significantly

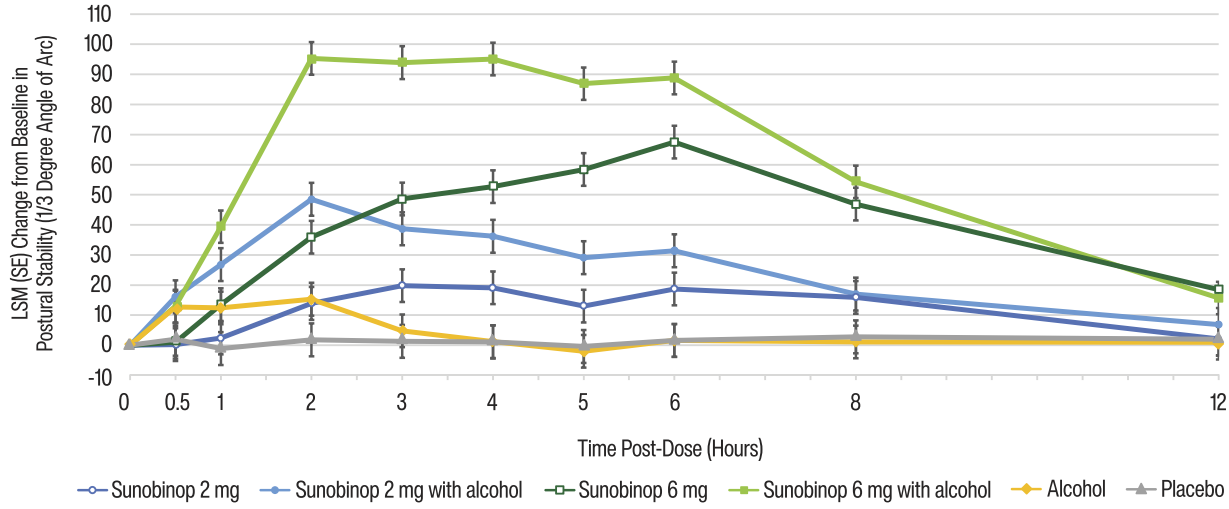

FIGURE 4. Change from baseline in body sway following sunobinop 2 mg with and without alcohol.

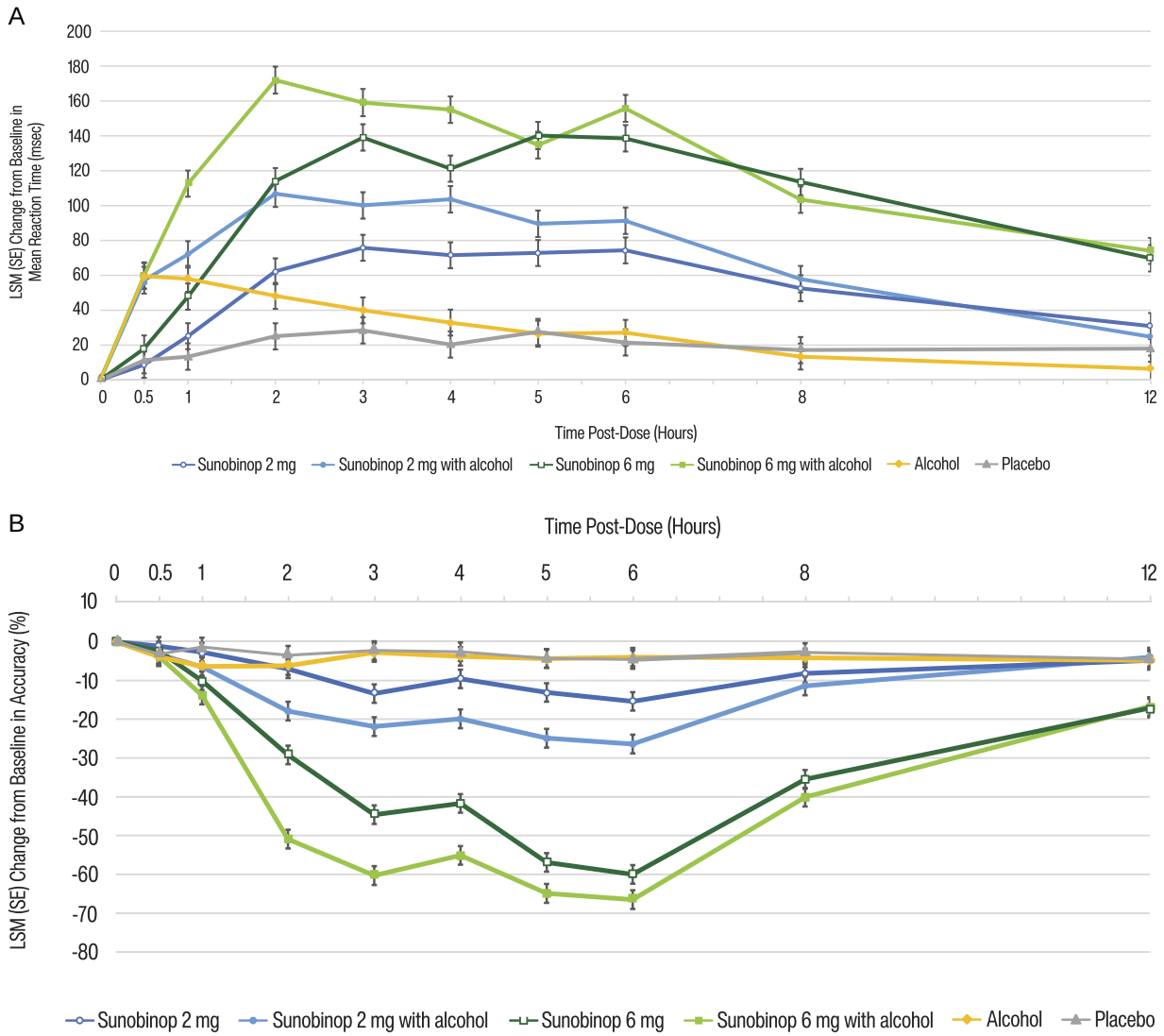

FIGURE 5. Change from baseline in digit vigilance test following sunobinop 2 mg with and without alcohol. A, Mean reaction time. B, Accuracy.

different from placebo at any time point post dose, while 2 mg was statistically significantly different from 2 mg plus alcohol only at 3 and 5 hours post dose [adjusted $P = 0.029$ and 0.007, LSMD: 528.5 (161.6, 895.4) and 582.4 (219.4, 945.5), respectively]. Greater-than-additive effects were not observed for sunobinop 2 mg with alcohol.

Change from baseline in DSST-total number correct is shown in Figure S2 (Supplemental Digital Content 1, http://links.lww.com/JCP/B17). The total number of correct answers decreased after dosing in participants receiving sunobinop 2 mg with and without alcohol, returning to baseline by 12 hours post dose. The decrease at 2 mg alone was statistically significantly different from placebo only at 3 and 4 hours post dose [adjusted $P < 0.001$, LSMD: -10.9 (−14.9, −6.9) and −9.8 (−13.8, −5.8), respectively] and at 6 and 8 hours post dose [adjusted $P = 0.001$ and < 0.001, LSMD: −7.6 (−11.6, −3.6) and −10.5 (−14.5, −6.4), respectively]. Sunobinop 2 mg was statistically significantly different from 2 mg plus alcohol from 0.5 to 2 hours post dose [adjusted P-value range, < 0.001 to 0.005, LSMD: −7.1 (−11.2, −3.1), −8.1 (−12.1, −4.0) and -7.0 (−11.0, −3.0), respectively] and at 4 and 6 hours post dose [adjusted $P = 0.021$ and 0.002, LSMD: −5.9 (−9.9, −1.9) and −7.1 (−11.2, −3.1), respectively]. Greater-than-additive effects were observed only at 6 hours post dose for sunobinop 2 mg with alcohol [adjusted $P = 0.002$, LSMD: −10.2 (−15.9, −4.5)].

Change from baseline in IWR is shown in Figures S3a and S3b (Supplemental Digital Content 1, http://links.lww.com/JCP/B17). The number of words recalled and accuracy decreased after dosing for all treatments, including placebo. Recall and accuracy values were similar to baseline by 12 hours post dose following sunobinop 2 mg with and without alcohol dosing. The decrease at 2 mg alone was not statistically significantly different from placebo at any time point post dose, while 2 mg was statistically significantly

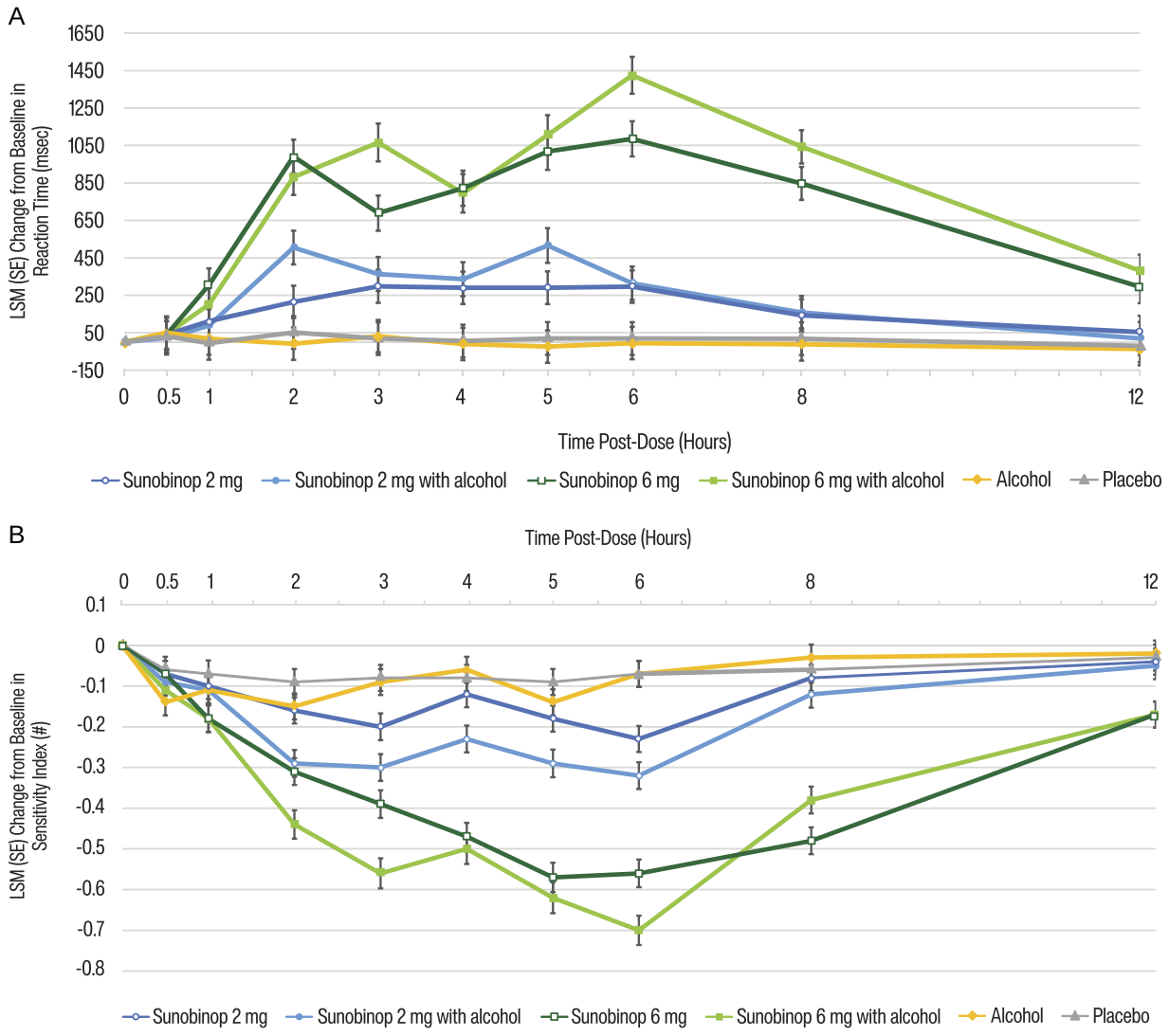

FIGURE 6. Change from baseline in numeric working memory following sunobinop 2 mg with and without alcohol. A, Mean reaction time. B, Sensitivity Index.

different from 2 mg plus alcohol only at 0.5 hours post dose for both recall and accuracy [adjusted $P = 0.004$ and 0.010; LSMD: −1.3 (−2.1, −0.6) and -8.3 (−13.3, −3.3), respectively]. An additive effect for number of words recalled, and accuracy was not observed for sunobinop 2 mg with alcohol.

Change from baseline in DWR is shown in Figures S4a and 4b (Supplemental Digital Content 1, http://links.lww.com/JCP/B17). Similar to IWR, the number of words recalled and accuracy decreased after dosing with all treatments, including placebo. The number of words recalled, and accuracy returned to similar values to baseline following sunobinop 2 mg with and without alcohol 12 hours post dose. The decrease at 2 mg alone was statistically significantly different from placebo for recall only at 2 and 3 hours post dose [adjusted $P = 0.048$ and 0.020, LSMD: −1.0 (−1.7, −0.2) and −1.1 (−1.9, −0.4), respectively] and for accuracy only at 3 hours post dose [adjusted $P = 0.022$, LSMD: −7.5 (−12.5, −2.5)]. Sunobinop 2 mg was statistically significantly different from 2 mg plus alcohol for both recall and accuracy only at 0.5 hours post dose [adjusted $P = 0.002$ and 0.005, LSMD −1.4 (−2.1, −0.6) and −8.7 (−13.7, −3.6), respectively]. Greater-than-additive effects in the number of words recalled were not observed for sunobinop 2 mg with alcohol.

Change from baseline in the Bond and Lader VAS is shown in Figure S5 (Supplemental Digital Content 1, http://links.lww.com/JCP/B17). Drowsiness increased after sunobinop 2 mg with and without alcohol and did not return to baseline values at 12 hours (nor did placebo). The increase at 2 mg alone was statistically significantly different from placebo from 2 to 8 hours post dose [adjusted P-value range, < 0.001 to 0.010, LSMD: 13.9 (5.4, 22.4), 16.6 (8.1, 25.1), 18.6 (10.1, 27.1), 19.2 (10.7, 27.7), 19.4 with (10.9, 27.9) and 18.1 (9.6, 26.6)], while 2 mg was not statistically significantly different from 2 mg plus alcohol at any time point. As such, an additive effect was not observed at any time point for sunobinop 2 mg with alcohol.

TABLE 3. Summary of Change From Baseline in Body Sway, Digit Vigilance Test, and Numeric Working Memory at Selective Time Points

		Study Treatment						
		Placebo (N = 47)	Alcohol Alone (N = 48)	Sunobinop 2 mg Alone (N = 48)	Sunobinop 2 mg with Alcohol (N = 46)		Sunobinop 6 mg Alone (N = 47)	Sunobinop 6 mg With Alcohol (N = 48)	
Parameter	Time Post Dose (h)*	LS Mean (SE)	LS Mean (SE)	LS Mean (SE)	LS Mean (SE)	Adjusted *P* for Greater-Than-Additive Effect†	LS Mean (SE)	LS Mean (SE)	Adjusted *P* for Greater- Than-Additive Effect‡
Summary of change from baseline in body sway (n = 46-48)									
Postural stability (1/3-degree angle of arc)	2	1.8 (5.47)	15.3 (5.47)	13.9 (5.47)	48.5 (5.47)	NS	35.9 (5.43)	95.3 (5.43)	$P < 0.001$
	8	2.8 (5.47)	1.1 (5.43)	15.9 (5.43)	17.0 (5.47)	NS	46.9 (5.43)	64.3 (5.38)	NS
	12	2.0 (5.47)	0.7 (5.43)	2.1 (5.43)	6.9 (5.47)	NS	18.5 (5.43)	15.7 (5.38)	NS
Summary of change from baseline in digit vigilance test (n = 44-48)									
Mean reaction time (msec)	2	25.0 (7.53)	48.2 (7.46)	62.3 (7.46)	106.8 (7.60)	NS	114.0 (7.53)	172.0 (7.75)	$P = 0.035$
	8	17.1 (7.53)	13.4 (7.46)	52.6 (7.46)	57.8 (7.60)	NS	113.5 (7.60)	103.4 (7.60)	NS
	12	18.0 (7.53)	6.4 (7.53)	30.9 (7.46)	24.8 (7.60)	NS	69.8 (7.60)	74.0 (7.46)	NS
Accuracy (%)	2	−3.5 (2.40)	−6.2 (2.38)	−7.0 (2.38)	−17.9 (2.42)	NS	−29.2 (2.40)	−50.9 (2.42)	$P < 0.001$
	8	−2.8 (2.40)	−4.2 (2.38)	−8.2 (2.38)	−11.4 (2.42)	NS	−35.5 (2.42)	−40.1 (2.40)	NS
	12	−4.5 (2.40)	−4.8 (2.40)	−4.8 (2.42)	−4.0 (2.42)	NS	−17.1 (2.42)	−16.7 (2.38)	NS
Summary of change from baseline in numeric working memory (n = 44-48)									
Mean reaction time (msec)	2	51.3 (87.43)	−8.7 (86.60)	214.5 (86.60)	504.7 (90.06)	NS	991.8 (89.15)	880.7§ (95.13)	NS
	8	18.0 (87.43)	−12.8 (86.60)	142.4 (86.60)	158.1 (88.27)	NS	847.3 (88.37)	1042.7 (89.14)	NS
	12	−20.3 (87.43)	−37.0 (87.42)	54.0 (96.60)	19.3 (88.27)	NS	295.2 (87.42)	380.3 (86.60)	NS
Sensitivity index (%)	2	−0.09 (0.032)	−0.15 (0.032)	−0.16 (0.032)	−0.29 (0.033)	NS	−0.31 (0.033)	−0.44‡ (0.035)	NS
	8	−0.06 (0.032)	−0.03 (0.032)	−0.08 (0.032)	−0.12 (0.033)	NS	−0.48 (0.033)	−0.38 (0.033)	NS
	12	−0.03 (0.032)	−0.02 (0.032)	−0.04 (0.032)	−0.05 (0.033)	NS	−0.17 (0.032)	−0.17 (0.032)	NS

*Selected time points to represent ~Cmax (2 h), sleep proxy (8 h), and last time point (12 h).
†(Sunobinop 2 mg with alcohol - alcohol alone) – (Sunobinop 2 mg alone – placebo).
‡(Sunobinop 6 mg with alcohol - alcohol alone) – (Sunobinop 6 mg alone – placebo).
§n = 39.
LS indicates least squares; N, number of participants in the population; n, number of participants with non-missing values; NS, not significant.

Pharmacodynamic Parameters of Sunobinop 6 mg

Sunobinop 6 mg with and without alcohol affected all PD measures (Table 3), and most PD effects could still be observed at 8 to 12 hours post dose as compared with placebo. Greater-than-additive effects were observed following dosing with sunobinop 6 mg with alcohol on body sway from 2 to 5 hours [*P*-value range, <0.001 to 0.008, LSMD: 45.9 (27.1, 64.8), 41.8 (23.0, 60.6), 42.3 (23.5, 61.1) and 30.0 (11.3, 48.7), respectively; Figure 4], on mean reaction time only at 2 hours [$P = 0.035$, LSMD: 34.8 (7.4, 62.2)] and accuracy from 2 to 4 hours [*P*-value range, <0.001 to 0.017, LSMD: −19.1 (−27.4, −10.7), −15.1 (−23.5, −6.8) and −12.2 (−20.5, −3.9), respectively] as measured by the DVT (Figure 5A, B), and on sensitivity index only at 3 hours [$P = 0.031$, LSMD −0.16 (−0.28, −0.04)] as measured by NWM (Figure 6A, B). Similarly, sunobinop 6 mg with alcohol had a greater- than-additive effect on mean reaction time as measured by CRT only at 5 hours post dose [$P = 0.003$, LSMD: 922.9 (393.3, 1452.5); Figure S1, Supplemental Digital Content 1, http://links.lww.com/JCP/B17] but did not have a greater-than-additive effect recall and accuracy on IWR at any time point post dose (Figures S3a and 3b, Supplemental Digital Content 1, http://links.lww.com/JCP/B17). Additive effects on the total number correct on the DSST (Figure S2, Digital Content 1, http://links.lww.com/JCP/B17) and on DWR were not observed (Figures 4a and 4b, Supplemental Digital Content 1, http://links.lww.com/JCP/B17).

Safety

A summary of TEAEs reported by ≥2 participants for any treatment is shown in Table 4. All 48 participants experienced ≥1 TEAE. TEAEs that were experienced by ≥2 participants with any treatment were somnolence, ataxia, headache, nausea, vomiting, dizziness, and vertigo. Somnolence was the most frequent TEAE and was reported by all 48 participants. The percentage of participants who experienced ≥1 TEAE was 67% following sunobinop 2 mg, 80% following sunobinop 2 mg with alcohol, 96% following sunobinop 6 mg, and 90% following sunobinop 6 mg with alcohol, trending higher in treatments that included sunobinop versus alcohol alone (40%) and placebo (28%), and appeared dose-dependent. The majority of TEAEs were mild to moderate in severity (88%), and all TEAEs resolved by the end of the study. No deaths or serious AEs occurred during the study, and no participants discontinued the study due to an AE. No changes in clinical laboratory values, vital signs, SpO_2, ECG, and C-SSRS results were reported during the study.

DISCUSSION

In this single-center, single-dose, randomized, blinded, crossover study, sunobinop was safe and well-tolerated at a potentially useful therapeutic dose. Coadministration of sunobinop with alcohol tended to increase the frequency and/or intensity of characteristic sunobinop TEAEs. Headache was the only new adverse event noted when sunobinop was coadministered with alcohol. The majority of TEAEs

TABLE 4. Summary of Treatment-Emergent Adverse Events

MedDRA SOC Preferred Term Severity*	Placebo (N = 47)	Alcohol Alone (N = 48)	Sunobinop 2 mg Alone (N = 48)	Sunobinop 2 mg With Alcohol (N = 46)	Sunobinop 6 mg Alone (N = 47)	Sunobinop 6 mg With Alcohol (N = 48)	Overall (N = 48)
Any TEAE							
Mild	12 (26)	11 (23)	25 (52)	19 (41)	18 (38)	10 (21)	7 (15)
Moderate	1 (2)	8 (17)	7 (15)	18 (39)	25 (53)	28 (58)	35 (73)
Severe	0	0	0	0	2 (4)	5 (10)	6 (13)
Nervous system disorders							
Somnolence							
Mild	9 (19)	8 (17)	23 (48)	16 (35)	18 (38)	11 (23)	7 (15)
Moderate	1 (2)	5 (10)	7 (15)	18 (39)	25 (53)	27 (56)	35 (73)
Severe	0	0	0	0	2 (4)	5 (10)	6 (13)
Ataxia							
Mild	0	0	1 (2)	2 (4)	1 (2)	6 (13)	6 (13)
Moderate	0	0	0	1 (2)	2 (4)	3 (6)	6 (13)
Headache							
Mild	2 (4)	4 (8)	0	5 (11)	0	0	10 (21)
Dizziness							
Mild	0	0	0	2 (4)	1 (2)	1 (2)	2 (4)
Moderate	0	0	0	0	0	1 (2)	1 (2)
Gastrointestinal disorders							
Nausea							
Mild	1 (2)	5 (10)	0	2 (4)	1 (2)	3 (6)	7 (15)
Vomiting							
Moderate	0	4 (8)	0	1 (2)	0	2 (4)	4 (8)
Ear and labyrinth disorders							
Vertigo							
Mild	0	2 (4)	0	0	0	0	2 (4)
Moderate	0	0	0	0	0	1 (2)	1 (2)

Date are reported as n (%).

*If a participant reports >1 occurrence of the same preferred term, the maximum severity is included in this table. Missing severities are treated as severe. Severity is taken from the severity reported on the CRF by the investigator.

N indicates number of participants who received the specified treatment in the randomized safety population; n, number of participants with at least 1 occurrence of an adverse event; SOC, system organ class.

were mild to moderate in severity, no deaths or serious AEs occurred during the study, and there were no discontinuations due to AEs. Furthermore, sunobinop 6 mg, considered a supratherapeutic dose, accounted for all of the severe TEAEs [consisting of 7 reports of somnolence among 6 participants (13%)]. In addition, no clinically significant changes were observed in clinical laboratory values, vital signs, SpO_2, ECG, and C-SSRS results. Somnolence was the most frequently reported TEAE and accounted for the majority of mild and moderate TEAEs. It is important to note that intended clinical use of sunobinop will include bedtime administration, suggesting that somnolence will primarily occur during the overnight period.

A sunobinop dose-effect relationship in the magnitude and duration of impairment was observed for most psychomotor/cognitive performance parameters, with effects resolved or partially resolved by 12 hours post administration. Administration of 2 mg of sunobinop alone did not affect some psychomotor/cognitive performance parameters as compared with placebo; for the remainder, the effect was statistically significantly different from placebo within an 8-hour window. Additive or greater than additive effects of sunobinop with alcohol treatments were observed for most psychomotor/cognitive performance parameters up to 6 hours post dose, as expected. Finally, no notable PK interactions between sunobinop and alcohol were observed, which were consistent with minimal hepatic metabolism of sunobinop.

Similar studies with other CNS active sleep promoting medications have been conducted. Suvorexant, a dual orexin receptor antagonist, is approved by the FDA for the treatment of insomnia.[10] The psychomotor effects, pharmacokinetics, and safety of suvorexant with and without alcohol were investigated in a double-blind crossover study among 31 healthy adults.[10] Participants were randomized to receive placebo or suvorexant (40 mg) plus placebo solution or alcohol (0.7 g/kg) through single morning doses in each of 4 treatments. This study found that suvorexant without alcohol did not significantly affect DVT reaction time; however, it did affect some PD tests. Suvorexant in combination with alcohol increased reaction time when compared with suvorexant alone and alcohol alone. In addition, additive negative effects were observed on tests of vigilance, working/episodic memory, postural stability, and alertness. No notable effects of suvorexant with alcohol or suvorexant alone were observed by hour 9. No meaningful changes in PK parameters were observed with coadministration of suvorexant and alcohol.

Lemborexant is a dual orexin receptor antagonist approved in the United States for the treatment of insomnia and is being investigated for the treatment of AUD.[11,12] The potential PK/PD interaction between lemborexant (10 mg) and alcohol (0.7 g/kg) was examined in a double-blind, placebo-controlled, 4-period, crossover study among 32 healthy adults.[12] Results from this study showed a 35% increase in lemborexant C_{max} and a 70% increase in overall lemborexant exposure based on $AUC_{0\text{-}72}$ when administered with alcohol. Mean blood alcohol concentrations measured 0.5 and 2 hours post administration were similar for alcohol alone and when administered with lemborexant. When lemborexant was administered with alcohol, body sway was significantly increased at 2 hours post dose when compared with lemborexant alone. Effects on body sway were similar at 12 hours. Across cognitive performance measures for memory and attention, the combination had significant impacts on power and continuity of attention, as well as quality and speed of memory at 2 and up to 6 hours post administration, with resolution by 6 to 9 hours. The authors noted that it was not unexpected to see these findings given lemborexant's sleep effects, and that time to resolution corresponds to the expected time for awakening following a bedtime administration.

Trazodone is a triazolopyridine antidepressant with significant anxiolytic and sedative activity resulting from the blockade of α1 adrenergic and $5\text{-}HT_2$ receptors.[13] Trazodone is indicated for the treatment of major depressive disorders and is frequently used off-label to treat insomnia.[13] Initial clinical trials demonstrated that use of trazodone in combination with ethanol showed little additional impairment of assessed skills over trazodone or alcohol alone, with the exception of manual dexterity, but researchers concluded the result reflected the profound effects of trazodone alone and suggested the combination was unsafe.[14] Furthermore, while research on trazodone use in combination with alcohol use is limited, some findings indicate that trazodone may impede recovery in individuals with AUD, possibly leading to increased alcohol consumption once trazodone is discontinued.[15]

Study Limitations

The main limitation of this study was the small sample size consisting of healthy adult participants with a high proportion of males and with only a single coadministration of sunobinop and alcohol during the day. Due to this limitation, these findings may not be generalizable to patients taking sunobinop nightly along with different patterns of alcohol consumption.

In addition, data from a multiple ascending dose study of sunobinop suggest that multiple daily dosing did not affect the PK of sunobinop.[3] Furthermore, sunobinop is not hepatically metabolized;[3] subsequently, even in patients with decreased liver function resulting from chronic alcohol use, it is unlikely PK findings would be affected. We have no clinical evidence of gender differences in sunobinop drug disposition, pharmacodynamics, or frequency of AEs.The administration of sunobinop in this study does not reflect the intended clinical us,e as it was dosed in the morning after a light breakfast and not at bedtime. Finally, it is difficult to compare these results with other studies due to the study differences, including the use of different PD measures.

CONCLUSIONS

A single oral dose of sunobinop at a therapeutic level was safe and tolerated when administered alone or in combination with alcohol in healthy participants in this study. In addition, concomitant administration of sunobinop with alcohol did not affect either the PK profiles of either alcohol or sunobinop, consistent with sunobinop's lack of hepatic metabolism. An expected transient additive or greater-than-additive effect of sunobinop (2 mg) with alcohol was observed for psychomotor/cognitive performance parameters. At the sunobinop 2 mg dose with alcohol across all parameters, only DSST (total number correct) and DVT (accuracy) were affected in a greater-than-additive manner at limited time points (5/6 and 6 h, respectively). Even at a supratherapeutic dose level of 6 mg, the greater than additive effects were only observed within a 2 to 5 hour period post administration. Given sunobinop's

sleep-promoting pharmacological effect, it is not unexpected that sunobinop alone or in combination with alcohol would result in changes from baseline in psychomotor/cognitive measures. Consequently, with intended bedtime administration, these effects would be anticipated to peak and have resolved within a typical night's sleep.

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AUTHOR DISCLOSURE INFORMATION

S.C.H., M.S.S., A.C., G.T.W., E.H., M.Z., and R.P.K. were employees of Imbrium Therapeutics, a subsidiary of Purdue Pharma LP, at the time of the study. G.A. was an employee of Ohio Clinical Trials, Inc. at the time of the study.

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DATA AVAILABILITY

The data sets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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