Human Abuse Potential of HSK3486 Injection in Nondependent, Recreational Central Nervous System Depressant Users: Trial in Progress

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Background/Introduction: Propofol is an intravenous (IV) anesthetic associated with hypotension, respiratory depression, and injection site pain. HSK3486 is a phenol derivative, non-barbiturate injectable emulsion with fast onset and quick, stable recovery. HSK3486 and propofol have the same mechanism of action and function as direct agonists of the γ-aminobutyric acid receptor subtype A. Prior clinical studies support HSK3486 as an effective, safe anesthetic with substantially less injection site pain than propofol. The phase 1 human abuse potential (HAP) study is planned to address the US Food and Drug Administration requirement that any new chemical entity targeting the central nervous system (CNS) needs to be evaluated for substance abuse potential.

Methods: This single center study (NCT05614544) consists of 2 parts. Part 1 was an open-label, dose-finding study of HSK3486 and propofol conducted in 44 participants (n=24, HSK3486; n=20, propofol) to determine the appropriate doses for use in part 2. Part 2 is a randomized, double-blind, placebo- and active-controlled, 4-period, 4-way crossover study in approximately 42 participants. All participants in the study will be healthy, nondependent, recreational CNS depressant drug users.

Both parts 1 and 2 will consist of an outpatient screening visit, an in-clinic IV naloxone challenge, an in-clinic treatment phase, and follow-up (**Figure 1**). In part 2, participants who successfully complete the qualification phase will be randomized to 1 of 8 treatment sequences according to two 4×4 William squares. The 4 treatments are: HSK3486 dose 1 (highest dose meeting criteria in part 1), HSK3486 dose 2 (second highest dose meeting criteria in part 1), propofol (highest dose meeting criteria in part 1), and placebo (treatment A matched). Each treatment will be separated by approximately 24 hours. Serial pharmacodynamic (PD)/pharmacokinetic (PK) assessments will be performed (**Table 1**). Participants will also undergo safety assessments.

PD/PK endpoints will be analyzed using a mixed-effect model. Stepwise hypothesis testing will be conducted for PD treatment differences. The relationship between PK and PD may be evaluated using correlational analysis or similar methodology. Descriptive statistics or incidence/frequency counts, as applicable, will be used to describe safety parameters.

The primary objective of this study (part 2) is to evaluate the HAP of HSK3486 compared with propofol, with the null hypothesis that HSK3486 has greater abuse potential than propofol (**Table 1**). Secondary objectives are to evaluate the safety and tolerability of HSK3486 alone (part 1) and compared with propofol (part 2). An additional secondary objective (part 2) is to evaluate the PK profile of HSK3486.

Results: Part 1 of the HSK3486 HAP study has been completed. Part 2 is estimated to be completed in September 2023.

Conclusions: This study was designed to evaluate abuse potential, safety, and tolerability of HSK3486 as compared with propofol. Enrollment is ongoing, and the results will inform future HSK3486 clinical development. This study is sponsored by Haisco-USA Pharmaceuticals, Inc.

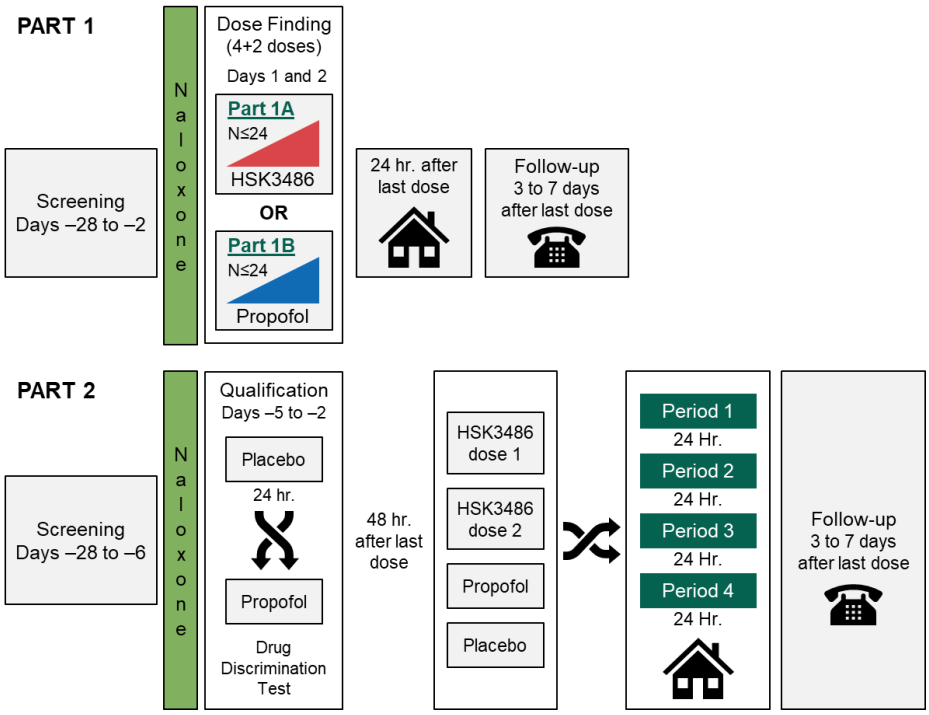

Figure 1. HSK3486 HAP Study Design. Key inclusion criterion: nondependent, nontreatment-seeking recreational CNS depressant user. Key exclusion criteria: drug, alcohol, or opioid dependence; history of mental illness. A naloxone challenge will be administered on the day of admission to ensure that participants are not opioid dependent. Only participants who do not have signs or symptoms of opioid withdrawal (Clinical Opioid Withdrawal Scale score <5) will be eligible for further participation in the study. Doses to be used in part 2 will be determined during dose finding in part 1. Groups of 4 participants will receive 1 dose level. Enrollment will be halted after the doses to be used in part 2 have been determined. The drug discrimination test during the qualification phase will ensure that participants can differentiate between the effects of active control (propofol) and placebo. Participants will receive each of the 4 treatments in a randomized, double-blind, 4-way crossover manner.

PD: parts 1 and 2	
Drug Liking ("at this moment") VAS (E_{max})[a]	
Drug Liking ("at this moment, I feel high") High VAS (E_{max})[b]	
Drowsiness/Alertness VAS (E_{min}, TE_{min}, TA_AUE_{0-1}, and TA_AUE_{0-2})[c]	
Modified Observer's Assessment of Awareness/Sedation scale	
Ability to complete battery of human abuse potential assessment questions for 1 hour	
PD: part 2	**PK: part 2**
Overall Drug Liking VAS (12- and 24-hour score)[b]	C_{max}
Take Drug Again VAS (12- and 24-hour score)[b]	T_{max}
Drug Liking VAS (TE_{max}, TA_AUE, E_{min}, TE_{min}, and percent reduction)	C_{max}/T_{max}
DEQ: Any Drug Effect VAS (E_{max}, TE_{max}, and TA_AUE_{0-1})	AUC
DEQ: Good Drug Effects VAS (E_{max}, TE_{max}, and TA_AUE_{0-1})[c]	k_{el}
DEQ: Bad Drug Effects VAS, Sick-Nausea (E_{max}, TE_{max}, and TA_AUE_{0-1})[c]	$t_{1/2}$
Relaxation/Agitation VAS (E_{max}, TE_{max}, E_{min}, TE_{min}, and TA_AUE_{0-1})	
Drug Similarity ("How similar is the drug you most recently received [drug 1] to drug you just took [drug 2]?") VAS[c]	

Table 1. Summary of PD and PK Parameters. [a] Primary endpoint for the study; with α=.05, a sample size of 27 will provide 98% power to reject the null hypothesis that HSK3486 has greater abuse potential than propofol, in favor of similarity with less than a margin of δ_2=11 in a 1-sided t-test. This assumes a mean (SD) of the difference in Drug Liking E_{max} between HSK3486 and propofol of 0 (15). [b] Secondary endpoints for the statistical hypothesis testing. [c] Secondary endpoints for the descriptive analysis. AUC, area under the plasma concentration-time curve; C_{max}, maximum observed plasma concentration; C_{max}/T_{max}, abuse quotient; DEQ, Drug Effects Questionnaire; E_{max}, maximum effect; E_{min}, minimum effect; k_{el}, terminal elimination rate; $t_{1/2}$, terminal elimination half-life; TA_AUE, time-averaged area under the effect curve; T_{max}, time to attain maximum observed plasma concentration; TE_{max}, time to maximum effect; TE_{min}, time to minimum effect; VAS, visual analog scale.