ANESTHESIOLOGY

Comparison of the Efficacy of HSK3486 and Propofol for Induction of General Anesthesia in Adults: A Multicenter, Randomized, Double-blind, Controlled, Phase 3 Noninferiority Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- HSK3486 (ciprofol) is a propofol analog that has been reported to be an effective hypnotic, with a safety profile similar to that of propofol but with less injection-site pain and fewer respiratory-related adverse events

What This Article Tells Us That Is New

- The noninferiority of HSK3486 compared with propofol for successful induction of general anesthesia (Modified Observer's Assessment of Alertness/Sedation Score of 1 or less) was assessed in a randomized, double-blind, controlled, phase 3 clinical trial of 251 adults undergoing elective surgery
- Induction success rate was 97.0% for patients administered HSK3486 and 97.6% for those administered propofol; because the lower bound of the 95% CI for the difference in success rate did not cross the noninferiority boundary of –8%, HSK3486 was deemed noninferior to propofol for successful induction of anesthesia
- The incidence of injection-site pain was 18.0% in patients who received HSK3486 and 77.1% in those who received propofol
- The incidence of treatment-emergent adverse events related to study drug was 17.9% for patients administered HSK3486 and 14.5% for those administered propofol when injection-site pain was excluded

ABSTRACT

Background: Propofol is an intravenous anesthetic associated with hypotension, respiratory depression, and injection-site pain. HSK3486 injectable emulsion (ciprofol) is a 2,6-disubstituted phenol derivative with fast onset and quick, stable recovery. Previous studies support HSK3486 as an effective, safe anesthetic with substantially less injection-site pain than propofol. The primary objective of this study was to investigate the noninferiority of HSK3486 compared with propofol in successful general anesthesia induction.

Methods: Two hundred fifty-five participants were enrolled in HSK3486-304, a multicenter, randomized (2:1), double-blind, propofol-controlled, phase 3 study evaluating HSK3486 for general anesthesia induction in adults undergoing elective surgery with tracheal intubation. The primary endpoint was successful anesthesia induction, defined as 1 or less on the Modified Observer's Assessment of Alertness/Sedation scale. Key secondary endpoints were proportion of participants with injection-site pain on the Numerical Rating Scale of 1 or greater and a composite endpoint, including the proportion of participants successfully induced while maintaining the desired anesthetic depth and without substantial cardiac and respiratory events. Safety endpoints included adverse events, abnormal vital signs, and injection-site pain.

Results: Two hundred fifty-one participants (HSK3486, n = 168; propofol, n = 83) were included in the analyses. General anesthesia was successfully induced in 97.0% *versus* 97.6% of participants with HSK3486 and propofol, respectively. The difference in success rate was –0.57% (95% CI, –5.4 to 4.2%); the noninferiority boundary of –8% was not crossed. Thirty participants (18.0%) had injection-site pain with HSK3486 *versus* 64 (77.1%) with propofol ($P < 0.0001$). Eighty-one participants (48.2%) with HSK3486 *versus* 42 (50.6%) with propofol ($P = 0.8780$) satisfied the composite endpoint. When injection-site pain was excluded, the incidence of treatment-emergent adverse events related to study drug was 17.9% for HSK3486 and 14.5% for propofol.

Conclusions: The study met its primary objective and endpoint, demonstrating noninferiority of HSK3486 compared with propofol in successful anesthetic induction. Substantially less injection-site pain was associated with HSK3486 than with propofol.

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This article is featured in "This Month in ANESTHESIOLOGY," page A1. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). Part of the work presented in this article has been presented at the Annual Meeting of the International Society for Anesthetic Pharmacology in New Orleans, Louisiana, October 6, 2022; and at the American Society of Anesthesiologists Anesthesiology 2023 Annual Meeting in San Francisco, California, October 13 to 17, 2023.

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Propofol is used as an intravenous agent for induction and maintenance of general anesthesia during surgery and nonoperative procedures due to its quick onset and fast recovery.[1,2] However, propofol has disadvantages, including a narrow therapeutic window,[3] injection-site pain,[4] and respiratory depression,[3] as well as a decrease in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure.[5–7] Thus, a need exists for anesthetic agents with improved pharmacokinetic and pharmacodynamic profiles, less cardiopulmonary instability, and reduced pain on injection in order to improve patient care and safety without compromising efficacy during induction of anesthesia.[8,9]

HSK3486 (ciprofol) is a short-acting, 2,6-disubstituted phenol derivative propofol analog (fig. 1) and a potentiator of the γ-aminobutyric acid type A receptor. Due to the addition of a cyclopropylethyl group to the side chain of the core phenol structure, HSK3486 has a higher affinity than propofol for the γ-aminobutyric acid type A receptor.[10–12] HSK3486 has shown promise for use during intravenous induction of general anesthesia, with multiple preclinical and clinical studies indicating that HSK3486 exhibits rapid onset, similar sedative or anesthetic effects as propofol at a significantly lower dose due to a potency five times that of propofol, less injection-site pain than propofol, and only minor residual side effects after the administration of a single therapeutic dose.[9,11–15] A phase 1 clinical trial evaluating dose escalation of HSK3486 for the induction of general anesthesia demonstrated that it was well-tolerated at doses of 0.4 to 0.9 mg/kg, exhibited a similar rapid onset *versus* propofol, provided rapid recovery of consciousness, and was associated with similar mild to moderate adverse events, including abnormal limb movements, sinus bradycardia, prolonged QTcF interval, and hypotension.[7]

Recent multicenter phase 2 and 3 studies conducted in China evaluating the safety and efficacy of HSK3486 for induction and maintenance of general anesthesia during elective surgery, gastroscopy, colonoscopy, and bronchoscopy procedures demonstrated that HSK3486 is an effective anesthetic, with a safety profile comparable to that of propofol, along with substantially less injection-site pain and fewer respiratory-related adverse events.[13,14,16] Moreover, a phase 3 clinical study demonstrated that HSK3486 was safe and efficacious and had similar pharmacokinetic characteristics in participants 65 yr or older (0.3 mg/kg) and in a younger population (0.4 mg/kg), indicating that HSK3486 is well-tolerated by a range of age groups.[17]

The primary objective of the current trial, HSK3486-304, was to demonstrate the noninferiority of HSK3486 compared with propofol in successful induction of general anesthesia in adults undergoing elective surgery. Key secondary objectives were to confirm less injection-site pain for HSK3486 compared with propofol and to assess comparative anesthetic effects for HSK3486 and propofol. Exploratory subgroup analyses of American Society of Anesthesiologists (Schaumburg, Illinois) Physical Status (ASA-PS) I to II *versus* III to IV, age less than 65 *versus* 65 yr or greater, and body mass index (BMI) less than 35 *versus* 35 kg/m^2 or greater were also performed.

Materials and Methods

HSK3486-304 was a randomized, double-blind, propofol-controlled, phase 3 clinical trial (ClinicalTrials.gov Identifier, NCT04711837; date of registration, January 15, 2021; see Supplemental Digital Content, S4: Site Information, https://links.lww.com/ALN/D421, for site principal investigators), conducted across 10 study centers in the United States between February 2021 and April 2022 in accordance with the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, and International Council for Harmonisation E6 Good Clinical Practice. Written informed consent was obtained from all participants before enrollment. Approval was obtained from an institutional review board (Ohio State University Research Foundation, Columbus, Ohio, or Western Institutional Review Board, Puyallup, Washington) for each study center.

Participants 18 yr or older and undergoing elective surgery were randomized 2:1 to either HSK3486 or propofol (Diprivan; Fresenius Kabi, USA) for induction of anesthesia (Supplemental Digital Content, eFigure 1[A-B], https://links.lww.com/ALN/D421, HSK3486 study design and methodologies). Participants were eligible if their surgery was anticipated to last 1 h or more and to require tracheal intubation and maintenance of anesthesia using inhaled agents. Participants were randomly allocated to receive HSK3486 0.4/0.2 mg/kg (*i.e.*, 0.4 mg/kg intravenous slow injection greater than 30 ± 5 s, followed by a 0.2 mg/kg top-up dose if needed) or propofol 2.0/1.0 mg/kg (*i.e.*, 2.0 mg/kg intravenous slow injection greater than 30 ± 5 s, followed by a 1.0 mg/kg top-up dose if needed). Investigators were guided to administer study drug on the back of the hand. For participants with BMI 40 kg/m^2 or

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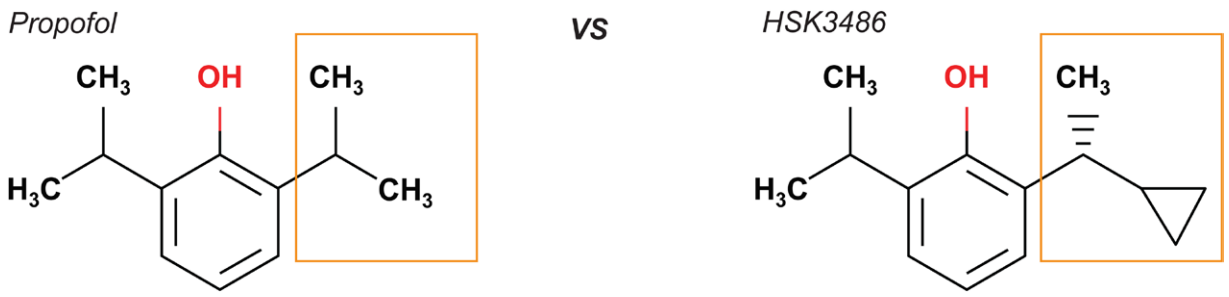


Fig. 1. Structural comparison between propofol and HSK3486. Propofol and HSK3486 are phenols and have a benzene ring and hydroxy group. HSK3486 ([R]-2-[1-cyclopropylethyl]-6-isopropylphenol) preserves the main structure of propofol and substitutes an isopropyl group with a 1-cyclopropylethyl group.

less, total body weight was used to determine dose. Lean body weight calculated with the James formula was used to determine dose for participants with BMI greater than 40 kg/m^2 and rescue dose.

All participants received intravenous fentanyl (1 μg/kg IV rounded up to the nearest 25 μg; maximum, 100 μg) within 5 min before study drug administration. Intravenous rocuronium bromide (0.6 mg/kg) was administered as a neuromuscular blockade to perform tracheal intubation after Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score of 1 or less was achieved. Sevoflurane was used for maintenance of general anesthesia and initiated within 60 s after tracheal intubation. Additional intravenous fentanyl was allowed for intraoperative analgesia only after initiation of sevoflurane. To avoid confounding the injection-site pain evaluation, lidocaine was not given before or during study drug administration. See Supplemental Digital Content, Section S3, https://links.lww.com/ALN/D421, for additional information about the anesthetic regimen used.

Additional inclusion criteria included ASA-PS of I to IV and BMI of 18 kg/m^2 or greater with no upper limit. Exclusion criteria included a history of adverse reactions to sedation or general anesthesia, allergies to opioids or their antidotes or propofol and its constituents, use of medications known to interact synergistically with propofol or HSK3486, cardiovascular or respiratory disorders, or previous failure of a difficult airway for tracheal intubation. A complete list of inclusion and exclusion criteria is provided in Supplemental Digital Content, Section S3 (https://links.lww.com/ALN/D421).

Induction success was defined by MOAA/S score and was evaluated by an investigator blinded to the study drug every 30 s after administration of HSK3486 or propofol until a score of 1 or less was reached. See Supplemental Digital Content, Section S3, https://links.lww.com/ALN/D421, for additional details on blinding. A top-up dose (50% of initial dose) was administered if MOAA/S score was greater than 1 at 1 min (+10 s) after study drug administration. If MOAA/S score was greater than 1 at 2 min (+30 s) after administration of the top-up dose, the rescue drug, propofol, was given. Injection-site pain was evaluated verbally by the Numerical Rating Scale (NRS) during initial administration of HSK3486 or propofol and before the participant losing consciousness. The second injection-site pain evaluation occurred after transfer to the postanesthesia care unit (PACU).

The primary efficacy endpoint was success rate of general anesthesia induction, defined as MOAA/S score of 1 or less after administration of HSK3486 or propofol, 1 or fewer top-up doses, and no use of rescue drug. Key secondary efficacy endpoints included proportion of participants with any injection-site pain (defined as NRS score of 1 or greater) at study drug administration and a composite endpoint of the proportion of participants with successful induction who maintained desired depth of anesthesia with an inhaled anesthetic. The desired depth of anesthesia was specified to be without substantial cardiac and respiratory events for 15 min after administration of the study drug, which was defined by meeting all of the following criteria: no coughing, laryngospasm, or bronchospasm; no blood pressure increase greater than 20% from baseline on two consecutive readings; and Bispectral Index (BIS) score of 60 or less. Furthermore, participants must not exhibit a decrease in blood pressure requiring intervention, or significant respiratory depression or apnea requiring intervention before administration of rocuronium bromide for tracheal intubation.

Baseline vital signs values were the average of two consecutive measurements 2 min or more apart. Respiratory depression was defined as apnea (absence of thoracic movement lasting more than 30 s) or hypoxia (oxygen saturation measured by pulse oximetry less than 90% lasting more than 30 s). Cardiac depression was defined as SBP less than 90 mmHg lasting more than 2 min and requiring medical intervention or life-threatening hypotension requiring immediate intervention.

Additional secondary endpoints included time to successful induction of general anesthesia (defined as time from end of first administration of study drug to time when MOAA/S score was 1 or less), time from end of first

administration of study drug to disappearance of eyelash reflex, and any use of top-up or rescue drug.

Adverse events were evaluated for frequency, severity, and association with study drug. Relationships between adverse events and study drugs were assessed by the investigator using a four-category system: definitely related, likely related, unlikely related, or not related. Adverse events of special interest included hypoxemia (oxygen saturation measured by pulse oximetry less than 90% lasting more than 30 s), bradycardia (heart rate [HR] less than 45 beats/min lasting more than 30 s), and hypotension (SBP less than 90 mmHg lasting more than 2 min). Adverse events of special interest were evaluated from time of initial administration of HSK3486 or propofol until the participant left the operating room. Investigators and site personnel also monitored and reported abuse-related adverse events. See Supplemental Digital Content, Section S3, https://links.lww.com/ALN/D421, for additional adverse event information.

Statistical Analyses

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, USA). The study was designed as a noninferiority study, with a noninferiority margin of −8% for induction success. The noninferiority margin was based on the expectation that propofol and HSK3486 would perform similarly as historical evidence and was considered clinically relevant and meaningful for general anesthesia induction in adults.

For the primary efficacy endpoint, a sample size of 215 participants was expected to provide 90% or greater power to detect a difference in the success rate of general anesthesia induction between participants administered HSK3486 or propofol, assuming a type I error rate of 0.025 (one-sided). For the secondary endpoint of injection-site pain, a sample size of 176 participants would give 90% power to detect a difference between participants administered HSK3486 or propofol, assuming $\alpha = 0.05$ (two-sided). For the secondary composite endpoint, a sample size of 255 participants would provide 80% power to detect a difference between study drugs in the proportion of participants with successful induction who maintained desired depth of anesthesia, assuming $\alpha = 0.05$ (two-sided).

The statistical hypothesis of noninferiority to be tested was $H0$: $pt - pc \leq \delta$ against $H1$: $pt - pc > \delta$, where pt and pc are the anesthesia success rates for HSK3486 and propofol, respectively, and δ is the noninferiority margin (−8%). The hypothesis was tested at the one-sided $\alpha = 0.025$ level. Induction success rate in both groups, the rate difference, and its 95% CI were estimated by the Farrington–Manning method. The participants who were not evaluable for anesthesia success were counted as having treatment failure.

Subgroup analyses of ASA-PS (I to II, III to IV), age group (less than 65 and 65 yr or older), and BMI (less than 35 and 35 kg/m^2 or more) were exploratory and conducted using the same methodology and noninferiority margin as the primary endpoint.

The proportion of participants with successful induction who maintained desired depth of anesthesia was calculated for both groups, as was the difference in proportions between the groups and 95% CI. The P value for comparison between groups ($\alpha = 0.015$) was calculated using the Cochran–Mantel–Haenszel chi-square test using stratification factors from study randomization. The Cochran–Mantel–Haenszel test, stratified by ASA-PS (I to II, III to IV), age group (less than 65 and 65 yr or older), and BMI (less than 35 and 35 kg/m^2 or more), was used to calculate the P value for noninferiority of HSK3486 over propofol and also for the statistical analysis of pain frequencies. The proportion of participants with any injection-site pain (NRS of 1 or greater) during the study drug administration for each group, the difference and comparison between the two groups ($\alpha = 0.035$ level), and the 95% CI were calculated.

Time to successful induction and time to loss of eyelash reflex were summarized by group using Kaplan–Meier estimates (medians with 95% two-sided CIs). The change in BIS after study drug administration up to 15 min was summarized descriptively by group.

Results

A total of 377 participants were screened, with 122 excluded (Supplemental Digital Content, eFigure 2, https://links.lww.com/ALN/D421, Diagram of participant disposition). Overall, 255 participants were randomized: 170 participants to the HSK3486 group and 85 to the propofol group. A total of 251 participants were treated in the study and were included in the analyses (HSK3486, n = 168; propofol, n = 83). Four participants were excluded from the analyses and were considered not treated, *i.e.*, they did not receive the appropriate randomization drug; 2 participants (HSK3486, n = 1; propofol, n = 1) dropped out before dosing and 2 participants (HSK3486, n = 1; propofol, n = 1) received the rescue drug, propofol, instead of the appropriate top-up dose due to procedural error. Neither of the two incorrectly dosed participants needed rescue drug per protocol.

Data across the sites were pooled for analyses. Site effect was tested as a sensitivity analysis, and results showed no significant effect.

Baseline characteristics were generally balanced between the groups (table 1). However, most participants were women (70.1%), White (76.5%), and not Hispanic or Latino (70.1%). Mean age of study participants was 49.6 yr (range, 20 to 85 yr), and 83.7% of participants were less than 65 yr of age. Mean height and weight were 167.11 cm and 83.2 kg, respectively. BMI ranged from 18.3 to 50.5 kg/m^2; 16.7% of participants had a BMI of 35 kg/m^2 or greater.

Participants were classified based on difficulty of tracheal intubation using the modified Mallampati score,[18] stratified into class I (n = 134; 53.4%), II (n = 116; 46.2%), or III

Table 1. Baseline Demographics and Disease Characteristics

	HSK3486 (n = 168)	Propofol (n = 83)	Total (n = 251)
Mean age ± SD, yr	48.9 ± 13.89	50.9 ± 14.30	49.6 ± 14.03
Age group, n (%)			
< 65 yr	141 (83.9)	69 (83.1)	210 (83.7)
≥ 65 yr	27 (16.1)	14 (16.9)	41 (16.3)
Sex, n (%)			
Male	49 (29.2)	26 (31.3)	75 (29.9)
Female	119 (70.8)	57 (68.7)	176 (70.1)
Race, n (%)			
White	121 (72.0)	71 (85.5)	192 (76.5)
Black or African American	36 (21.4)	12 (14.5)	48 (19.1)
American Indian or Alaska Native	0	0	0
Asian	4 (2.4)	0	4 (1.6)
Native Hawaiian or other Pacific Islander	0	0	0
Multiple, other, or not reported	7 (4.2)	0	7 (2.8)
Ethnicity, n (%)			
Hispanic or Latino	45 (26.8)	23 (27.7)	68 (27.1)
Not Hispanic or Latino	118 (70.2)	58 (69.9)	176 (70.1)
Unknown	5 (3.0)	2 (2.4)	7 (2.8)
Mean body weight ± SD, kg	83.85 ± 19.72	81.87 ± 20.16	83.20 ± 19.85
Mean body mass index ± SD, kg/m^2	29.89 ± 5.81	29.25 ± 6.23	29.68 ± 5.95
Body mass index group, n (%), kg/m^2			
< 35	141 (83.9)	68 (81.9)	209 (83.3)
≥ 35	27 (16.1)	15 (18.1)	42 (16.7)
≤ 40	156 (92.9)	79 (95.2)	235 (93.6)
> 40	12 (7.1)	4 (4.8)	16 (6.4)
Modified Mallampati score, n (%)			
Class I	93 (55.4)	41 (49.4)	134 (53.4)
Class II	75 (44.6)	41 (49.4)	116 (46.2)
Class III	0	1 (1.2)	1 (0.4)
Class IV	0	0	0
Mean predose Bispectral Index score ± SD, n*	95.7 ± 3.69, 167	95.6 ± 3.84, 83	95.7 ± 3.73, 250
ASA Physical Status group, n (%)			
Class I	70 (41.7)	34 (41.0)	104 (41.4)
Class II	86 (51.2)	44 (53.0)	130 (51.8)
Class III	12 (7.1)	5 (6.0)	17 (6.8)
Class IV	0	0	0
I to II	156 (92.9)	78 (94.0)	234 (93.2)
III to IV	12 (7.1)	5 (6.0)	17 (6.8)

*One participant was missing a response for this parameter in the HSK3486 group.
ASA, American Society of Anesthesiologists.

(n = 1; 0.4%; table 1). The mean predose BIS was 95.7 (range, 79 to 98). A total of 234 participants (93.2%) had ASA-PS classification of I to II; none had IV. Baseline disease characteristics were comparable between the treatment groups. Induction success rate was 97.0% (163 of 168 participants) for HSK3486 and 97.6% (81 of 83 participants) for propofol (table 2). The treatment difference in the success rate was −0.57% (95% CI, −5.4 to 4.2%). Because the lower bound of the 95% CI did not cross the noninferiority boundary of −8%, the primary endpoint was achieved, and HSK3486 was deemed significantly noninferior to propofol for successful induction of anesthesia.

A total of 156 participants in the HSK3486 group and 78 in the propofol group had ASA-PS of I to II. The induction success rate in this subgroup was 96.8% (n = 151) for HSK3486 and 97.4% (n = 76) for propofol. HSK3486 was noninferior to propofol in the induction of general anesthesia in participants with ASA-PS classification of I to II (difference of proportions, –0.64%; 95% CI, –5.7 to 4.4%). All participants in the HSK3486 and propofol groups with an ASA-PS of III to IV had successful anesthetic induction; thus, a comparison between groups was not evaluable.

A total of 141 participants in the HSK3486 group and 69 in the propofol group were less than 65 yr old. The induction success rate was 97.2% (n = 137) and 97.1% (n = 67) in the HSK3486 and propofol groups, respectively. HSK3486 (n = 27) was noninferior to propofol (n = 14) in the induction of general anesthesia in participants aged less than 65 yr (difference of proportions, 0.06%; 95% CI, –5.3 to 5.4%). In participants aged 65 yr or more, HSK3486 did not demonstrate noninferiority to propofol in the induction of general anesthesia (difference of proportions, –3.70%; 95% CI, –13.9 to 6.5%).

Table 2. Success Rate of Anesthesia Induction

	Difference of Proportions	HSK3486 (n = 168)	Propofol (n = 83)
Success of general anesthesia induction, n (%)*		163 (97.0)	81 (97.6)
Success rate of general anesthesia induction†			
Difference of proportions, %	−0.57		
95% CI, %	(−5.4 to 4.2)		
Failure to induce general anesthesia, n (%)‡		5 (3.0)	2 (2.4)

*Considered successful if Modified Observer's Assessment of Alertness/Sedation score was 1 or less, 1 or fewer top-up doses was required, and no rescue drugs were used. †Differences in the success rate and CI are calculated using the Farrington–Manning method, with a noninferiority margin of −8%. ‡Reasons for not successfully inducing general anesthesia were not necessarily mutually exclusive.

A total of 141 participants in the HSK3486 group and 68 in the propofol group had BMI of less than 35 kg/m^2. The induction success rate for participants with BMI of less than 35 kg/m^2 was 96.5% (n = 136) and 97.1% (n = 66) in the HSK3486 and propofol groups, respectively. HSK3486 was noninferior to propofol in the induction of general anesthesia in participants with a BMI of less than 35 kg/m^2 (difference of proportions, −0.60%; 95% CI, −6.1 to 4.8%). All participants in the HSK3486 (n = 27) and propofol (n = 15) groups with a BMI of 35 kg/m^2 or greater had successful anesthetic induction; thus, a comparison between groups was not evaluable.

The mean ± SD NRS pain score during study drug administration on day 1 was 0.5 ± 1.45 in the HSK3486 group (median, 0) and 4.7 ± 3.51 in the propofol group (median, 5), indicating no pain and moderate pain, respectively. During injection, the proportion of participants with at least mild pain (defined as NRS score of 1 or greater) and at least severe injection-site pain (defined as NRS score of 4 or greater) were significantly lower with HSK3486 *versus* propofol: 18.0% *versus* 77.1% (95% CI, −69.9 to −48.4%; $P < 0.0001$) and 6.0% *versus* 61.4% (95% CI, −66.5 to −44.4%; $P < 0.0001$; fig. 2; Supplemental Digital Content, eTable 1, https://links.lww.com/ALN/D421, Injection pain scores by NRS).

The proportions of participants with successful induction for the secondary composite endpoint were 48.2% and 50.6% for the HSK3486 and propofol groups, respectively. This difference was not statistically significant ($P = 0.8780$). Median time to successful induction was 0.75 min and 0.62 min for HSK3486 and propofol, respectively (Supplemental Digital Content, eFigure 3, https://links.lww.com/ALN/D421, Kaplan–Meier curve). Median time to loss of eyelash reflex was 0.92 min for HSK3486 and 0.80 min for propofol (Supplemental Digital Content, eFigure 4, https://links.lww.com/ALN/D421, Kaplan–Meier curve). Neither difference was clinically meaningful.

The proportions of participants who demonstrated no clinical signs of inadequate depth of anesthesia (such as coughing, laryngospasm, and bronchospasm) and did not require additional intravenous rocuronium bromide after routine administration were 89.3% and 95.2% with HSK3486 and propofol, respectively. Fewer participants who received HSK3486 *versus* those who received propofol (78.0% *vs.* 91.6%) had evidence of inadequate depth of anesthesia, as assessed by blood pressure increase of greater than 20% from baseline within 15 min after study drug administration. Similar proportions of HSK3486- and propofol-administered participants had no substantial respiratory depression before receiving rocuronium bromide (95.8% *vs.* 96.4%, respectively) and no substantial cardiac depression requiring intervention (93.5% and 94.0%, respectively).

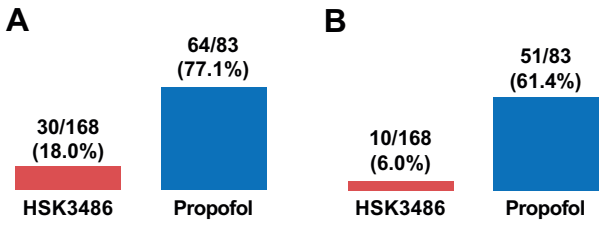
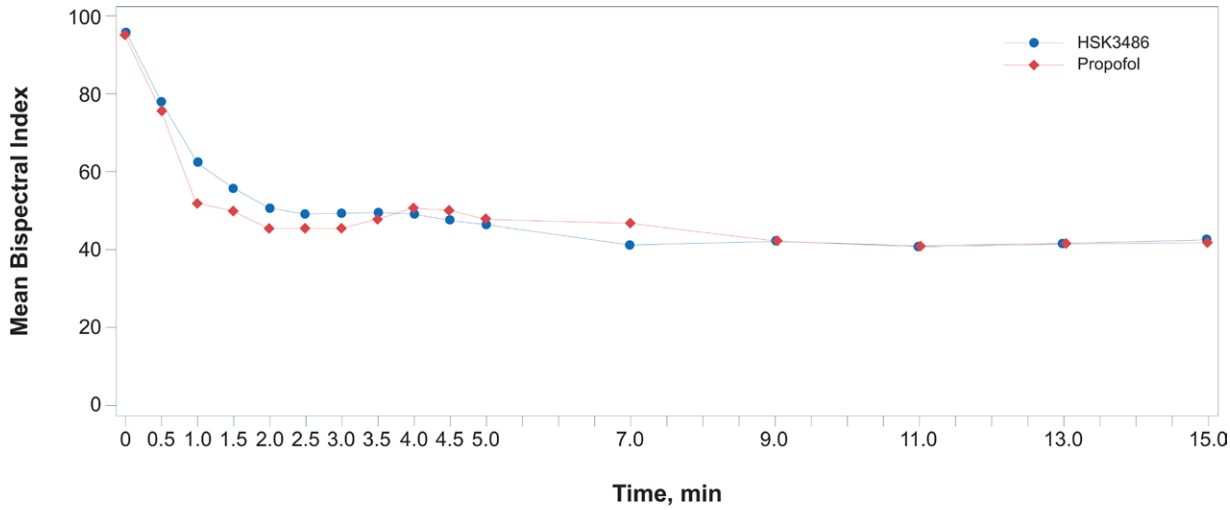


Fig. 2. Pain scores during injection and induction per Numerical Rating Scale. (*A*) Participants with pain scores of 1 or greater and (*B*) participants with pain scores of 4 or greater. Statistical significance tested at $\alpha = 0.035$ level: $P < 0.0001$ for pain scores of 1 or greater and pain scores of 4 or greater. The locations of intravenous administration for participants were as follows: dorsum of hand (HSK3486, n = 136 [81.0%]; propofol, n = 70 [84.3%]), antecubital fossa (HSK3486, n = 20 [11.9%]; propofol, n = 8 [9.6%]), and forearm (HSK3486, n = 6 [3.6%]; propofol, n = 3 [3.6%]).

Mean ± SD baseline BIS for participants who met BIS criteria for depth of anesthesia was 95.5 ± 4.09 in the HSK3486 group (n = 127; 76.0%) and 95.6 ± 3.80 in the propofol group (n = 52; 62.7%). A similar pattern in mean BIS was observed for the HSK3486 and propofol groups through the anesthesia period (fig. 3). The frequency of BIS of 60 or less by measurement time point for each group is shown in Supplemental Digital Content, eTable 2 (https://links.lww.com/ALN/D421).

HSK3486 and propofol were generally well tolerated. No abuse-related adverse events were reported. Treatment-emergent adverse events (those categorized as unlikely related or not related to study drug) were reported for



HSK3486	n=167	n=165														
Time	Baseline	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	7.0	9.0	11.0	13.0	15.0
Mean	95.6	77.9	62.3	55.7	50.7	49.2	49.5	49.5	49.1	47.5	47.1	41.1	42.3	40.9	41.6	42.5
SD	3.77	20.35	19.64	16.91	15.13	15.27	14.20	14.80	15.32	13.77	13.16	11.21	10.72	11.26	10.98	11.13

Propofol	n=83	n=83														
Time point	Baseline	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	7.0	9.0	11.0	13.0	15.0
Mean	95.4	76.1	52.4	50.3	45.8	46.0	45.8	48.3	51.1	50.6	47.9	47.1	42.3	40.9	41.6	42.1
SD	4.18	21.09	17.00	17.05	13.52	13.91	13.86	14.41	15.18	13.74	12.61	13.19	10.72	11.26	10.98	11.82

Fig. 3. Mean Bispectral Index (BIS). Baseline BIS values were recorded before administration of study drug. BIS was monitored continuously, and values were recorded at the following time points after completion of initial study drug administration: every 30 ± 10 s until 5 min, then every 2 min ± 30 s until 15 min, and then every 15 ± 5 min until 60 ± 10 min after study drug administration. No procedural intervention occurred due to the BIS value, as all decisions regarding successful induction were based on the Modified Observer's Assessment of Alertness/Sedation scores. One participant in the HSK3486 group was missing a response for the Baseline parameter.

140 participants (83.3%) in the HSK3486 group and 72 participants (86.7%) in the propofol group (Supplemental Digital Content, eTable 3, https://links.lww.com/ALN/D421, Summary of adverse events). Most treatment-emergent adverse events were considered mild or moderate; hypotension (HSK3486, 28.0%; propofol, 32.5%), nausea (HSK3486, 27.4%; propofol, 24.1%), procedural pain (HSK3486, 19.0%; propofol, 22.9%), and injection-site pain (HSK3486, 6.5%; propofol, 43.4%) were the most common overall.

No treatment-emergent adverse events led to discontinuation of the study drug, withdrawal from study, or death. No serious treatment-emergent adverse events occurred in the HSK3486 group. Three participants in the propofol group experienced serious treatment-emergent adverse events (pulmonary embolism, abdominal wall hematoma, biliary colic, urinary retention, and femur fracture) that were judged to be unlikely related or unrelated to study drug.

The overall proportion of participants who experienced treatment-emergent adverse events related to study drug was lower in the HSK3486 group *versus* the propofol group (22.0% *vs.* 53.0%, respectively); when injection-site pain was excluded, the incidence was 17.9% for HSK3486 and 14.5% for propofol (table 3; fig. 4).

See Supplemental Digital Content, eFigure 5 (https://links.lww.com/ALN/D421) for mean change from baseline in SBP and DBP. Changes from baseline in blood pressure and HR were comparable for HSK3486 *versus* propofol at 30 min or less after study drug administration.

Discussion

HSK3486 was noninferior to propofol for anesthetic induction, with an HSK3486 success rate of 97%. HSK3486 was comparable to propofol for rapid induction of general anesthesia and desired depth of anesthesia, as analyzed based on clinical signs, physiologic parameters, and BIS values. Additionally, the three subgroup analyses showed that HSK3486 was noninferior to propofol in participants with ASA-PS of I to II, age less than 65 yr, and BMI less than 35 kg/m^2. In the subgroups for ASA-PS of III to IV and BMI 35 kg/m^2 or greater, 100% of participants had successful anesthesia induction.

HSK3486 did not demonstrate noninferiority to propofol in participants aged 65 yr or more, due to small sample sizes

Table 3. Treatment-emergent Adverse Events Related to Study Drug

Participants, n (%)	HSK3486 (n = 168)	Propofol (n = 83)	Total (n = 251)
Total treatment-emergent adverse events related to study drug	37 (22.0)	44 (53.0)	81 (32.3)
Total treatment-emergent adverse events related to study drug excluding injection-site pain	30 (17.9)	12 (14.5)	42 (16.7)
Treatment-emergent adverse events related to study drug with incidence >1%			
Injection-site pain	11 (6.5)	36 (43.4)	47 (18.7)
Hypotension	11 (6.5)	5 (6.0)	16 (6.4)
Hypertension	6 (3.6)	3 (3.6)	9 (3.6)
Blood pressure diastolic increased	3 (1.8)	1 (1.2)	4 (1.6)
Blood pressure systolic increased	3 (1.8)	1 (1.2)	4 (1.6)
Hypoxia	3 (1.8)	0	3 (1.2)
Mean arterial pressure increased	2 (1.2)	1 (1.2)	3 (1.2)
Dizziness	1 (0.6)	1 (1.2)	2 (0.8)
Nausea	2 (1.2)	0	2 (0.8)
Cardiovascular insufficiency	0	1 (1.2)	1 (0.4)
Heart rate increased	0	1 (1.2)	1 (0.4)
Hepatocellular injury	0	1 (1.2)	1 (0.4)
Hyperacusis	0	1 (1.2)	1 (0.4)

Adverse events were coded using the Medical Dictionary for Regulatory Activities version 25.0. Adverse events related to study drug were considered by the investigator as definitely or likely related to study drug. Adverse events with missing/unknown relationship were considered as definitely related to study drug in overall count.

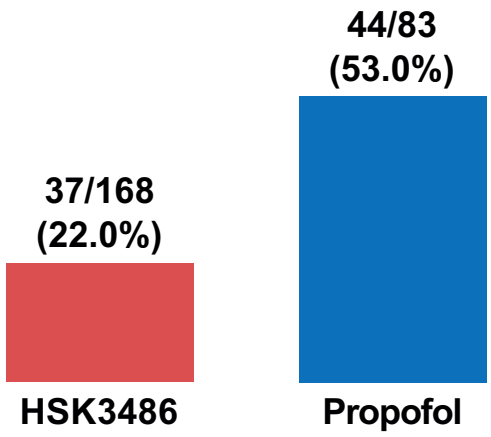


Fig. 4. Study drug-related treatment-emergent adverse events. Adverse events related to study drug were considered by the investigator as definitely or likely related to study drug and included injection-site pain.

(n = 27 for HSK3486; n = 14 for propofol). A study comparing safety and efficacy in healthy participants aged less than 65 and 65 yr or more demonstrated that HSK3486 had a remarkably stable respiratory profile in individuals aged 65 yr or more, with no spontaneous reports of injection-site pain and pharmacokinetic properties similar to those of propofol; additionally, time to recovery was comparable to that in participants administered HSK3486.[17] Thus, results from these studies (current and previous) support future larger clinical studies of HSK3486 in participants 65 yr of age or more.

Injection-site pain is among the most frequently reported adverse reactions associated with propofol, with an incidence of 25 to 74% in adults.[19] Injection-site pain associated with propofol results in side effects such as anxiety and discomfort and can affect hemodynamic stability during induction.[15] In the current study, the incidence of injection-site pain was significantly lower in participants who received HSK3486 *versus* those who received propofol ($P < 0.0001$), a result consistent with data from previous clinical studies.[8,13,14,16,17]

Intravenous lidocaine is commonly used to attenuate injection-site pain during propofol administration.[20] In the current study, however, lidocaine was not administered before or with the study drug to avoid confounding effects on the injection-site pain evaluation. In a small subset of participants (7 of 251 participants; fewer than 3%), lidocaine was administered after the surgical procedure and before or after transfer to PACU: intravenously in 3, intradermally in 2, and intramuscularly in 2. The first injection-site pain evaluation occurred after administration of study drug and before the participant losing consciousness, while the second occurred after transfer to PACU and was intended to assess recall effects. Both questions were specific to pain at the injection site, with the first as an immediate response and the second as a recall of the immediate response. Therefore, responses are not expected to have been affected by administration of lidocaine after the surgical procedure.

The difference in incidence of injection-site pain in the current study could be attributable to differences in concentrations of HSK3486 and propofol in the aqueous phase of the injection solution, with a higher concentration of propofol contributing to greater pain on injection.[21] Recent evidence suggests that the stronger hydrophobicity of HSK3486 compared with propofol results in a lower concentration of unbound drug in the aqueous phase of the emulsion and decreased injection-site pain.[12,14] Injection-site pain associated with propofol adds to the pain load of patients already undergoing considerable physiologic stress

with surgery. Thus, the reduced proportion of participants experiencing pain with HSK3486 was clinically meaningful and greatly contributed to improved patient comfort during induction. Furthermore, HSK3486 and propofol were well-tolerated, aligning with the results from previous safety and efficacy studies.[8,13]

Propofol's antiemetic effects are well documented and associated with a low incidence of postoperative nausea and vomiting.[22,23] The current study did not evaluate the antiemetic effects of HSK3486 or propofol; participants were given antiemetics such as 5-hydroxytryptamine receptor subtype 3 antagonists and/or dexamethasone following best-practice guidelines. However, given the structural similarity between propofol and HSK3486, the comparable rates of nausea (27.4% with HSK3486 *vs.* 24.1% with propofol) and vomiting (8.3% with HSK3486 *vs.* 13.3% with propofol), although vomiting was not judged to be a treatment-emergent adverse event related to study drug, are not surprising. The question of whether HSK3486, like propofol,[24,25] can be administered postoperatively for antiemesis may warrant future investigation.

Cardiovascular responses are sensitive indicators of noxious stimuli such as tracheal intubation during general anesthesia.[26,27] Propofol is known to depress HR and blood pressure,[28,29] emphasizing the clinical relevance of evaluating hemodynamic effects during and after HSK3486 and propofol administration. In the current study, hemodynamic parameters appeared stable throughout, and HSK3486 and propofol had comparable hemodynamic profiles, consistent with previous reports.[30] The most common treatment-emergent adverse event was hypotension (28.0% with HSK3486 *vs.* 32.5% with propofol), and the most frequent cardiovascular treatment-emergent adverse events included hypertension (7.7% with HSK3486 *vs.* 9.6% with propofol) and DBP increases (7.1% with HSK3486 *vs.* 2.4% with propofol; Supplemental Digital Content, eTable 3, https://links.lww.com/ALN/D421, Summary of adverse events). HSK3486 demonstrated a stable respiratory profile and a low incidence of respiratory depression, consistent with previous clinical trials,[8,13,14,31] and comparable to anesthetic effects for propofol.

Although HSK3486-304 was larger and more demographically heterogenous than previous studies, possible limitations included the demographic characteristics of the population, which was primarily female, White, and not Hispanic or Latino, and the small subgroup sample sizes for 65 yr or more and BMI of 35 kg/m^2 or more. These limitations may warrant clinical validation with increased diversity and subgroup sample sizes.

In conclusion, the primary efficacy results of this study indicate that HSK3486 was noninferior to propofol in the induction of general anesthesia and that HSK3486 demonstrated substantially lower rates of injection-site pain than propofol. The overall incidence of treatment-emergent adverse events related to study drug, when injection-site pain was excluded, was similar for HSK3486 and propofol. HSK3486 was associated with similar hemodynamic effects *versus* propofol during induction and maintenance of anesthesia.

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Competing Interests

Drs. Yan, Zhou, Liu, Daley, and Lai are employees and shareholders of Haisco. Dr. Gelb is the immediate past president of World Federation of Societies of Anaesthesiologists (London, United Kingdom) and has a consulting relationship with Haisco. Dr. Gan has received honoraria from Haisco. Dr. Habib has received research support from Pacira Pharmaceuticals (Tampa, Florida), Haisco, and Heron Therapeutics (San Diego, California); he has served on the advisory board for Heron Therapeutics, Merck (Rahway, New Jersey), MDoloris Medical Systems (Loos, France), and Vertex Pharmaceuticals (Boston, Massachusetts). Dr. Essandoh has a consulting relationship with Boston Scientific (Boston, Massachusetts) and is an advisory board member for S4 Medical (Roselle Park, New Jersey). The other author declares no competing interests.

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Supplemental Digital Content

Efficacy of HSK3486 and Propofol for Anesthesia Induction Study Supplement, https://links.lww.com/ALN/D421
Section S1: Supplemental tables
Section S2: Supplemental figures
Section S3: Supplemental methods
Section S4: Site information
Section S5: Supplement references

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