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A Multicenter, Randomized, Double-Blinded, Propofol-Controlled, Phase 3 Clinical Study to Evaluate the Efficacy and Safety of HSK3486 Injectable Emulsion for Induction of General Anesthesia in Adults Undergoing Elective Surgery

Tong J Gan, MD[1]; Todd Bertoch, MD[2]; Ashraf S. Habib, MD[3]; Pangke Yan, MD[4]; Rong Zhou, PhD[4]; Yu-Ling Lai, MS[5]; Xiao Liu[4]; William L. Daley, MD, MPH[5]; Adrian W. Gelb, MBChB[6]

[1]Anesthesiology, Critical Care and Pain Medicine Division, University of Texas MD Anderson Cancer Center, Houston, TX; [2]CenExel JBR, Salt Lake City, UT; [3]Department of Anesthesiology, Duke University School of Medicine, Durham, NC; [4]Haisco Pharmaceutical Group Co, Ltd, Shannan, China; [5]Haisco-USA Pharmaceutical Company, Inc, Bridgewater, NJ; [6]Department of Anesthesia and Perioperative Care, University of California San Francisco, San Francisco, CA

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Background

- Propofol is the standard of care for intravenous induction of anesthesia; however, it can cause significant hypotension,[1-3] respiratory depression,[4] and injection site pain[5]
- HSK3486 injectable emulsion is a new chemical entity with pharmacodynamic characteristics of fast onset and quick, stable recovery
- Prior clinical studies have demonstrated HSK3486 to be an effective anesthetic, having a safety profile comparable to that of propofol but with potentially less cardiopulmonary instability and significantly less injection site pain[6-8]
- A phase 3 clinical study was conducted to evaluate the efficacy and safety of HSK3486 for induction of general anesthesia in adults undergoing elective surgery

- **Primary objective: to demonstrate the noninferiority of HSK3486 compared with propofol in successful induction of anesthesia (noninferiority margin of −8%)**

1. Sebel PS, et al. *Anesthesiology*. 1989;71(2):260-277; 2. Chan VW, et al. *J Clin Anesth*. 1996;8(4):317-323; 3. Dundee JW, et al. *Anaesthesia*. 1986;41(5):482-485; 4. Vanlersberghe C, et al. *Handb Exp Pharmacol*. 2008;(182):227-252; 5. Picard P, et al. *Anesth Analg*. 2000;90(4):963-969; 6. Li J, et al. *Basic Clin Pharmacol Toxicol*. 2022;131(2):138-148; 7. Zeng Y, et al. *Eur Rev Med Pharmacol Sci*. 2022;26(4):1114-1124; 8. Luo Z, et al. *CNS Drugs*. 2022;36(3):301-313.

Study design: HSK3486 phase 3 study (NCT04711837)

Population: 255 participants

Induction of general anesthesia in adults undergoing elective surgery with endotracheal intubation

ASA-PS: I-IV
Age: ≥18 years
BMI: ≥18 kg/m²

R 2:1

HSK3486 0.4/0.2 mg/kg (n=170)

0.4 mg/kg IV slow injection over 30 (±5) seconds followed by an additional 0.2 mg/kg dose, if needed

Blinded

Propofol 2.0/1.0 mg/kg (n=85)

2.0 mg/kg IV slow injection over 30 (±5) seconds followed by an additional 1.0 mg/kg dose, if needed

- **Duration of participation**
  - Screening period up to 14 days prior to surgery
  - Study drug administration on day of surgery
  - Follow-up 24 hours post–study drug administration
  - Phone contact 1 week (± 2 days) post–surgery
- **Duration of study enrollment:** February 2021 to April 2022
- **Number of participants included in analyses:**
  - 251 (HSK3486 [n=168]; propofol [n=83])

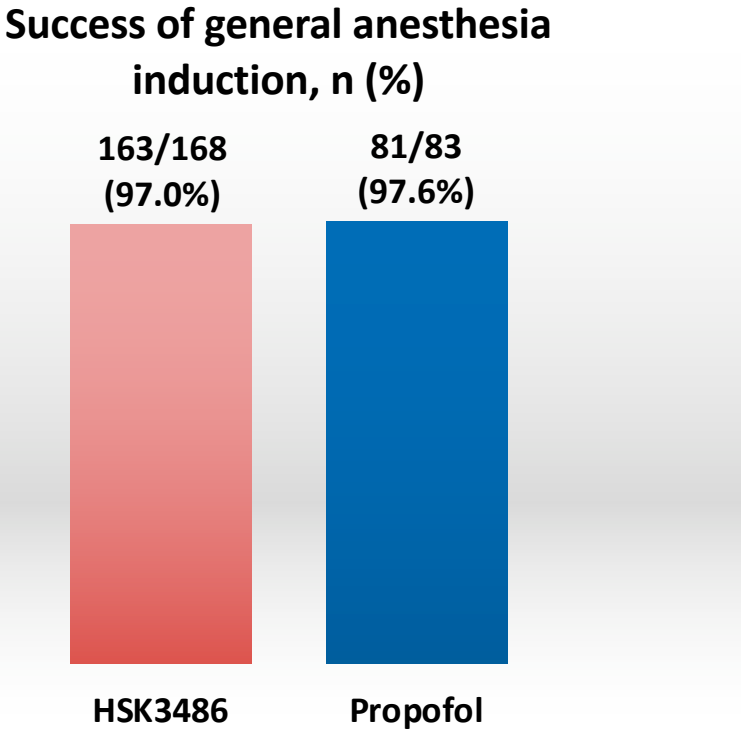
- **Primary endpoint: successful induction of anesthesia**
  - **MOAA/S ≤1 and one or less top-up dose required without using any rescue drugs**
- **Secondary endpoints:**
  - **Proportion with injection site pain on the NRS ≥1**
  - **Proportion with successful induction who maintain desired depth of anesthesia**
- **Safety endpoints: AEs, vital signs, injection site pain**

ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT04711837. Accessed September 2022.
AE, adverse event; ASA-PS, American Society of Anesthesiologists Physical Status; BMI, body mass index; MOAA/S, Modified Observer's Assessment of Awareness/Sedation; NRS, numerical rating scale; R, randomization.

General demographics

	HSK3486 (n=168)	Propofol (n=83)	Total (N=251)
Age, years			
Mean (SD)	48.9 (13.89)	50.9 (14.30)	49.6 (14.03)
Age group, years, n (%)			
<65	141 (83.9)	69 (83.1)	210 (83.7)
≥65	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 (%)			
American Indian or Alaska Native	0	0	0
Asian	4 (2.4)	0	4 (1.6)
Black or African American	36 (21.4)	12 (14.5)	48 (19.1)
Native Hawaiian or other Pacific Islander	0	0	0
White	121 (72.0)	71 (85.5)	192 (76.5)
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)

Primary endpoint results



Primary endpoint		HSK3486 (n=168)	Propofol (n=83)
Success of general anesthesia induction, n (%)[a,b]		**163 (97.0)**	**81 (97.6)**
Difference of proportions success rate, %	−0.57		
95% CI, %	(−5.4 to 4.2)		
Failed to meet success of general anesthesia induction, n (%)		**5 (3.0)**	**2 (2.4)**

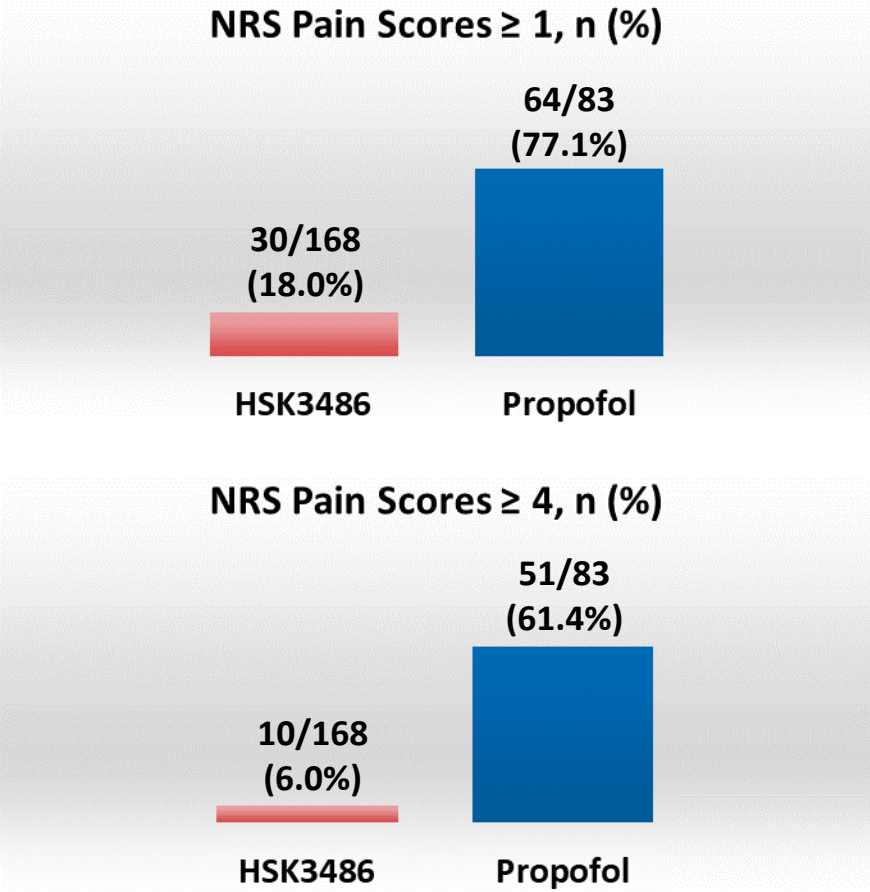
[a] Considered successful if MOAA/S ≤1 and one or less top-up dose required without using any rescue drugs.

[b] Differences in the success rate and CIs are calculated using the Farrington-Manning method with the noninferiority margin of −8%.

- **HSK3486 was demonstrated to be noninferior to propofol as the lower bound of the 95% CI did not cross the boundary of -8%**

MOAA/S, Modified Observer's Assessment of Awareness/Sedation.

Secondary endpoint results



Secondary endpoint		HSK3486 (n=168)	Propofol (n=83)
Participants with pain scores (NRS ≥1)[a] during injection and induction, n (%)		30 (18.0)	64 (77.1)
Difference of proportions pain scores, %	−59.14		
95% CI, %	(−69.9 to −48.4)		
P value	<.0001		
Participants with pain scores (NRS ≥4)[b] during injection and induction, n (%)		10 (6.0)	51 (61.4)
Difference of proportions pain scores, %	−55.46		
95% CI, %	(−66.5 to −44.4)		
P value	<.0001		

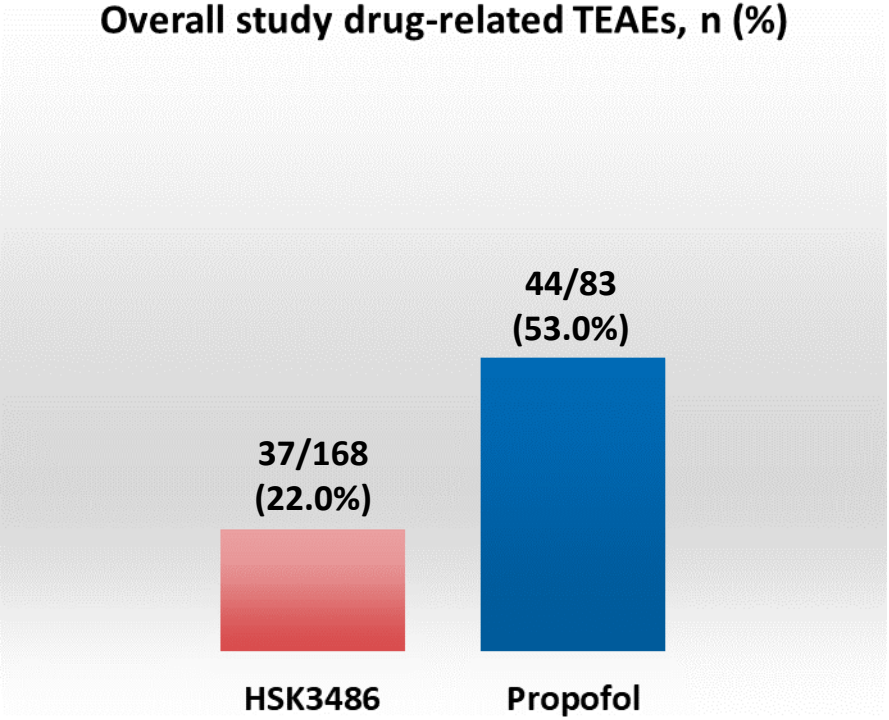
[a] No pain = NRS pain scale of <1; mild pain = NRS pain scale of 1 to 3.

[b] Moderate pain = NRS pain scale of 4 to 6; severe pain = NRS pain scale of 7 to 9; worst pain imaginable = NRS pain scale of 10.

- **HSK3486 was associated with significantly less pain on injection than propofol**
- **There was no difference between HSK3486 and propofol for maintaining desired depth of anesthesia**

NRS, numerical rating scale.

Safety endpoint results



Safety endpoint	HSK3486 (n=168)	Propofol (n=83)
Study drug–related TEAEs, n (%)	37 (22.0)	44 (53.0)

- Overall incidence of TEAEs was numerically higher for propofol

TEAE, treatment-emergent adverse event.

Conclusions

- The study met its primary objective and endpoint, demonstrating noninferiority of HSK3486 compared with propofol for successful induction of anesthesia
- HSK3486 was associated with significantly less pain on injection than propofol
- The overall incidence of study drug–related TEAEs was numerically higher for participants treated with propofol compared with those treated with HSK3486

TEAE, treatment-emergent adverse event.

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Backup slides

Protocol definitions

- Secondary endpoint: proportion of participants with successful induction who maintain **desired depth of anesthesia** in combination with an inhaled anesthetic, and without significant cardiac and respiratory depression between the time of successful induction to 15 minutes post study drug administration. Per protocol:
  - ***Respiratory depression*** includes apnea, defined as absence of thoracic movement lasting >30 seconds, or hypoxia, defined as SpO_2 <90% lasting >30 seconds, or life-threatening apnea or hypoxia requiring immediate intervention
  - ***Cardiac depression*** is defined as SBP <90 mmHg lasting >2 minutes plus requiring medical intervention such as inotropes, vasopressors, or IV fluid resuscitation, or life-threatening hypotension requiring immediate intervention
- **Desired depth of anesthesia** for general elective surgery is defined if all of the following criteria are met:
  - No clinical signs of inadequate depth of anesthesia, such as coughing, laryngospasm, or bronchospasm, and no additional IV rocuronium bromide after routine rocuronium bromide 0.6 mg/kg in response to clinical symptoms, such as gag reflex, movement etc, due to first tracheal intubation
  - No event where any of the SBP, DBP, or MAP increases more than 20% from baseline on 2 consecutive readings in response to any major operational procedures or noxious stimulus in defined period
  - Subjects maintain desired depth of anesthesia for general elective surgery with BIS as an objective assessment (after reaching initial lowest value, BIS remains at a sustainable level of ≤60)
    Note: Target BIS 40 to 60 for general anesthesia
    The BIS sustainable level of ≤60 is defined as ≤1 episode with BIS value observed >60 in defined period
    Video laryngoscopy is strongly recommended during tracheal intubation. Timing of second intubation attempt needs to be recorded

BIS, bispectral index score; DBP, diastolic blood pressure; IV, intravenous; MAP, mean arterial pressure; SBP, systolic blood pressure; SpO_2, oxygen saturation.

Weight demographics

	HSK3486 (n=168)	Propofol (n=83)	Total (N=251)
Weight, kg			
Mean (SD)	83.85 (19.72)	81.87 (20.16)	83.20 (19.85)
BMI, kg/m^2			
Mean (SD)	29.89 (5.80)	29.26 (6.23)	29.68 (5.94)
BMI group, kg/m^2, n (%)			
<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)

BMI, body mass index.

Disease characteristics

	HSK3486 (n=168)	Propofol (n=83)	Total (N=251)
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
Pre-dose BIS, n	167	83	250
Mean (SD)	95.7 (3.69)	95.6 (3.84)	95.7 (3.73)
ASA-PS 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
Class I-II	156 (92.9)	78 (94.0)	234 (93.2)
Class III-IV	12 (7.1)	5 (6.0)	17 (6.8)

ASA-PS, American Society of Anesthesiologists Physical Status; BIS, bispectral index score.

Treatment-emergent adverse events (total >3%)

	HSK3486 (n=168)	Propofol (n=83)	Total (N=251)
Subjects with any TEAE, n (%)	140 (83.3)	72 (86.7)	212 (84.5)
Hypotension	47 (28.0)	27 (32.5)	74 (29.5)
Nausea	46 (27.4)	20 (24.1)	66 (26.3)
Procedural pain	32 (19.0)	19 (22.9)	51 (20.3)
Injection site pain	11 (6.5)	36 (43.4)	47 (18.7)
Asthenia	16 (9.5)	14 (16.9)	30 (12.0)
Vomiting	14 (8.3)	11 (13.3)	25 (10.0)
Hypertension	13 (7.7)	8 (9.6)	21 (8.4)
Dizziness	7 (4.2)	8 (9.6)	15 (6.0)
Blood pressure diastolic increased	12 (7.1)	2 (2.4)	14 (5.6)
Mean arterial pressure increased	10 (6.0)	2 (2.4)	12 (4.8)
Blood pressure systolic increased	8 (4.8)	2 (2.4)	10 (4.0)
Constipation	6 (3.6)	3 (3.6)	9 (3.6)
Urinary retention	5 (3.0)	4 (4.8)	9 (3.6)

TEAE, treatment-emergent adverse event.