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HSK21542 in patients with postoperative pain: two phase 3, multicentre, double-blind, randomized, controlled trials

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HSK21542, a peripherally restricted kappa opioid receptor agonist, was evaluated for efficacy and safety in patients with postoperative pain following abdominal surgery. This was assessed in two phase 3, multicentre, randomized, double-blind, controlled trials (HSK21542-301 [ClinicalTrials.gov identifier, NCT04738357] and HSK21542-303 [ClinicalTrials.gov identifier, NCT05390905]) in China. HSK21542-301 was a dual-arm study comparing HSK21542 1.0 μg/kg with placebo, while HSK21542-303 involved three arms comparing HSK21542 1.0 μg/kg with tramadol 50 mg/dose and placebo. All treatments were administered intravenously. The primary endpoint was the time-weighted summed pain intensity differences over 24 h ($SPID_{0\text{-}24\,h}$). Both HSK21542-301 (least squares [LS] mean [± standard error], −39.1 [1.88] vs −27.4 [1.89]; $P < 0.001$) and HSK21542-303 (−64.0 [2.25] vs −45.9 [2.25]; $P < 0.001$) demonstrated superiority of HSK21542 over placebo in terms of $SPID_{0\text{-}24\,h}$, while HSK21542-303 showed non-inferiority to tramadol (LS mean difference, −1.1; 95% confidence interval, −7.4 to 5.1; $P < 0.001$). Furthermore, HSK21542 had a comparable safety profile to placebo, inducing fewer gastrointestinal adverse events compared with tramadol. Grade ≥3 treatment-emergent adverse events occurred in eight (5.9%) and three (2.3%) patients in the HSK21542 arm of HSK21542-301 and HSK21542-303, respectively. In conclusion, HSK21542 showed potent analgesic effect and was well tolerated in patients who underwent abdominal surgery and experienced postoperative pain.

More than 80% of patients who undergo surgical procedures experience acute postoperative pain, with ~75% of them reporting the severity as moderate, severe, or even extreme[1–3]. Following common operative procedures, persistent pain is experienced by 10–50% of patients after acute postoperative pain, and ~2–10% of these patients may experience severe chronic pain[4,5]. The degree of postoperative pain varies greatly among patients and depends on the type of surgery. Several studies have reported that around 50–90% of patients experienced moderate to severe pain after abdominal surgery[6–8], despite the use of less invasive surgical techniques such as

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laparoscopy. Evidence suggests that less than half of the patients who undergo surgery report adequate postoperative pain relief[2]. Inadequately controlled pain has a detrimental impact on quality of life, function, and functional recovery. It also increases the risk of persistent postoperative pain and complications. Importantly, there is a correlation between the intensity and duration of acute postoperative pain and the likelihood of it developing into a persistent pain state[4,5]. Therefore, it is crucial to explore aggressive, early therapeutic approaches to manage postoperative pain.

Opioids are the widely used and highly effective analgesics for the treatment of pain and related disorders[9]. Through early binding studies and bioassays, three main types of opioid receptors have been identified: mu, delta, and kappa receptors[10–12]. These receptors are commonly found in many parts of the body, including the central and peripheral nervous systems, neuroendocrine cells (pituitary and adrenal), immune cells, ectodermal cells, endothelial cells, and keratinocytes[13–16]. The most commonly used opioids for pain management primarily target the mu opioid receptor (MOR) systems[9]. However, MOR agonists such as morphine and oxycodone often come with deleterious side effects such as respiratory depression, sedation, nausea and constipation, and the development of tolerance that manifests as reduced efficacy following repeated use[17–19]. Furthermore, it has been estimated that millions of people in the United States suffer from substance abuse stemming from the prescription of MOR agonist-based pain relievers[20]. As a result, there is considerable interest in exploring other classes of opioids. In this regard, kappa opioid receptor (KOR) agonists appear to offer a non-addictive alternative for analgesia[17].

Compared with MOR agonists, KOR agonists have a critical role in regulating the reward system by contributing to the negative feedback of dopamine[21]. Unlike MOR agonists, KOR agonists do not cause respiratory depression[22–24]. Almost all early selective KOR agonists are centrally acting, which means they possess excellent analgesic effects but without the side effects of respiratory depression, constipation, addiction, and tolerance[25]. Furthermore, they are effective in counteracting the development of tolerance induced by MOR agonists[25]. However, as KOR signaling is involved in various other functions within the central nervous system, including negative emotional states like aversion, depressive-like behaviors, and drug reinstatement, the clinical application of centrally penetrating KOR agonists is severely limited[24–30]. Peripheral KOR agonists act exclusively in the periphery and rarely cross the blood-brain barrier, avoiding the side effects inherent with traditional, centrally acting, selective KOR agonists. This has been demonstrated through preclinical studies in animal models[15–17,31–34], and in clinical trials where dysphoria or evidence of abuse potential was not observed in patients[23,35,36]. Consequently, there is a recent research trend to design novel peripherally restricted KOR agonists.

HSK21542, with a chemical structure of 7-(D-phenylalanyl-D-phenylalanyl-D-leucyl-D-lysyl)−2-acetyl-2,7-diazaspiro (3.5) nonane, is a novel peripherally restricted KOR agonist[24]. In a preclinical study, HSK21542 demonstrated prolonged analgesic effect with minimal ability to penetrate the blood-brain barrier, providing peripheral analgesia without the central side effects associated with opioids, such as hallucination, addiction, and respiratory depression[24]. The brain/plasma distribution of HSK21542, assessed using liquid chromatography with tandem mass spectrometry assay, showed a concentration ratio of 0.001, suggesting low penetration into the brain tissues. Assessment of sedative effect showed that a low dose of HSK21542 at 0.4 mg/kg did not affect the locomotor activity of mice. There was also no change in respiratory rate measured using whole body plethysmography when HSK21542 was given at 2.0 mg/kg. A subsequent dose-ascending study found that HSK21542 had linear pharmacokinetic characteristics after a single dose or 1-week multiple-dose administration in hemodialysis patients without drug accumulation[37]. HSK21542 at 0.30 μg/kg appears to be a promising therapy for hemodialysis patients with moderate to severe pruritus. Here, we report the results of two phase 3 trials evaluating the efficacy and safety of HSK21542 in adult patients who underwent elective abdominal surgery and experienced postoperative pain.

Results

Patients

In the HSK21542-301 study, a total of 323 patients were screened and 276 patients were randomized 1:1 to receive either HSK21542 or placebo between 24 March 2021 and 30 July 2021. Among these patients, five patients who did not receive the study drug, and four who received the study drug at least once, terminated the study early. The remaining 267 patients (134 in the HSK21542 group and 133 in the placebo group) completed the treatment (Fig. 1). The full analysis set (FAS), per-protocol set (PPS), and safety set (SS) comprised 271, 257, and 271 patients, respectively.

In the HSK21542-303 study, out of 449 screened patients, 387 patients were randomized 1:1:1 to HSK21542, tramadol, or placebo between 9 June 2022 and 29 November 2022. Among the randomized patients, 29 patients terminated the study early, leaving 358 patients (123 in the HSK21542 group, 121 in the tramadol group, and 114 in the placebo group) who completed the treatment (Fig. 1). The FAS, PPS, and SS comprised of 387, 354, and 387 patients, respectively.

Baseline demographics and characteristics were generally balanced across treatment arms in both studies (Table 1). The median age for patients in HSK21542-301 was 49.0 (range, 45.0–52.0) years and 45.0 (range, 37.0–53.0) years in HSK21542-303. The majority of patients were female in both studies (HSK21542-301, 93.4%; HSK21542-303, 84.5%), and mean body mass index (BMI) of the overall population fell within the healthy range (mean [SD], HSK21542-301, 24.1 [3.1] kg/m^2; HSK21542-303, 23.7 [3.2] kg/m^2). The types of abdominal surgical procedures conducted in HSK21542-301 and HSK21542-303 are generally well balanced between groups, as described in Supplementary Table 1. Both studies have been completed.

Efficacy

Primary efficacy endpoint. In the HSK21542-301 trial, the primary efficacy endpoint was the sum of pain intensity differences at rest within 0–24 h post first-dose ($SPID_{0-24\,h}$) between the HSK21542 and placebo groups. The least squares (LS) means (±standard error [SE]) of $SPID_{0-24\,h}$ were −39.1 (1.88) and −27.4 (1.89) in the HSK21542 and the placebo groups (Fig. 2a), respectively; LS mean difference between both groups was −11.7 (95% confidence interval [CI], −17.0 to −6.5, $P < 0.001$). Superiority of HSK21542 over placebo was established as the upper limit of the 95% CI was less than zero. Similar results were obtained in the PPS analysis, where the LS means (±SE) of $SPID_{0-24\,h}$ in the HSK21542 and the placebo groups were −39.2 (1.91) and −28.9 (1.90), respectively, and the LS mean difference between both arms was −10.4 (95% CI, −15.7 to −5.1; $P < 0.001$).

In the HSK21542-303 trial, the LS means (±SE) of $SPID_{0-24\,h}$ in the HSK21542, tramadol, and placebo treatment arms were −64.0 (2.25), −62.9 (2.25), and −45.9 (2.25) (Fig. 2b), respectively. The LS mean difference between HSK21542 and placebo was −18.1 (95% CI, −24.4 to −11.9; $P < 0.001$), indicating the superiority of HSK21542 over placebo. Significant difference in $SPID_{0-24\,h}$ was also seen between the tramadol group and the placebo group, with a LS mean difference of −17.0 (95% CI, −23.2 to −10.7; $P < 0.001$). The LS mean difference between HSK21542 and tramadol was −1.1 (95% CI, −7.4 to 5.1; $P < 0.001$). The upper limit of the 95% CI was less than the non-inferiority margin of 11.03, suggesting that HSK21542 was non-inferior to tramadol. Comparable results were also obtained in the PPS analysis, with LS means of HSK21542, tramadol, and placebo at −66.3 (1.84), −65.7 (1.84), and −51.4 (1.90), respectively. The LS mean difference between HSK21542 and placebo was −15.0 (95% CI, −20.2 to −9.8; $P < 0.0001$), and −0.6 (95% CI, −5.8 to 4.5; $P < 0.001$) between HSK21542 and tramadol.

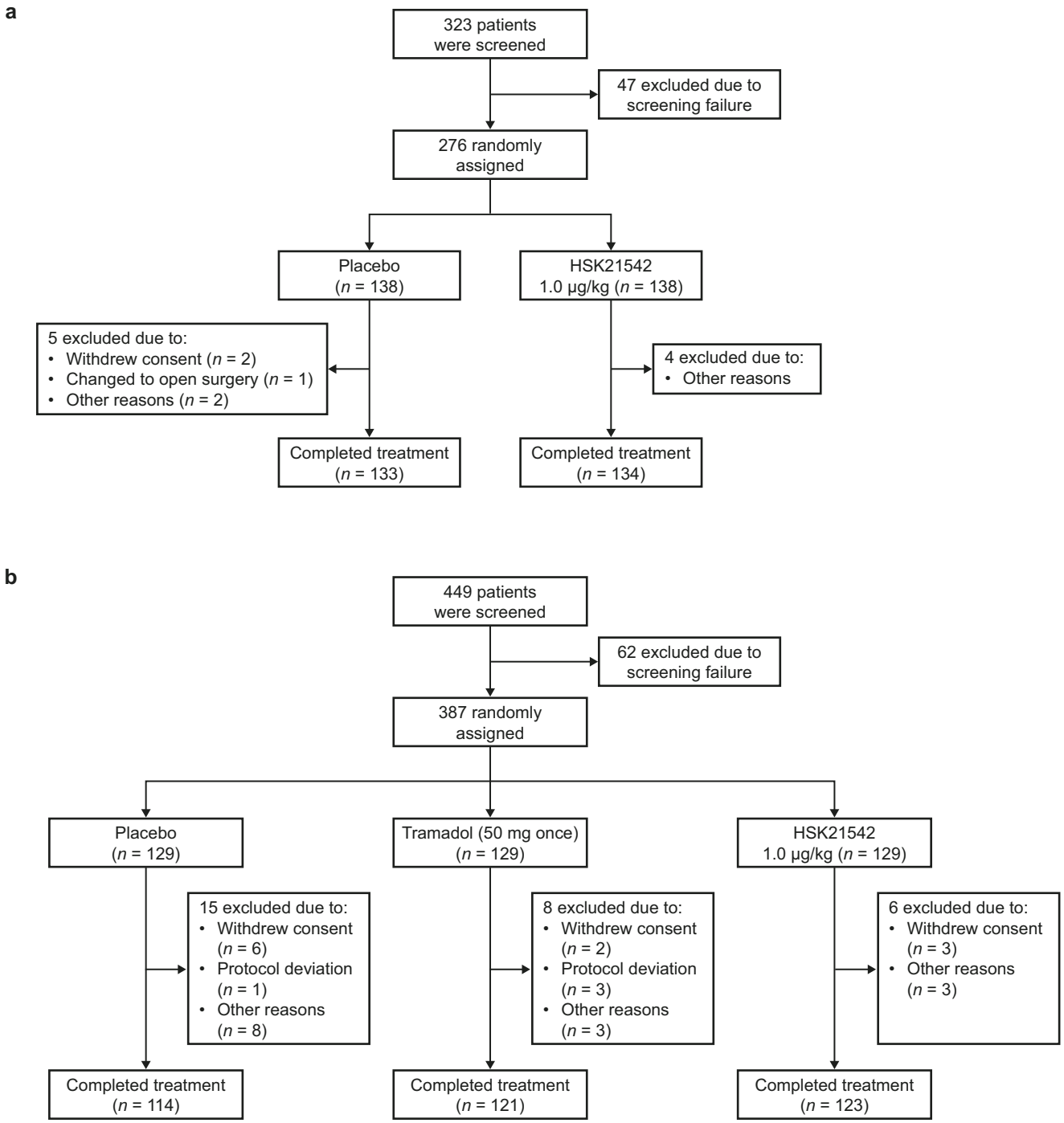

Fig. 1 | Patient disposition. Trial profiles of **a** HSK21542-301 and **b** HSK21542-303.

Secondary efficacy endpoints. The secondary efficacy endpoints for both the HSK21542-301 and HSK21542-303 trials are summarized in Table 2.

In the HSK21542-301 trial, the LS means (±SE) $SPID_{0-12\,h}$ for HSK21542 and placebo were −17.3 (0.92) and −12.0 (0.92), respectively; LS mean difference between both groups was significant ($P < 0.001$; Supplementary Fig. 1a). Within 12 h (29.4 vs 45.2%; $P = 0.002$) and 24 h (33.1 vs 46.7%; $P = 0.009$) after first dose, fewer patients in the HSK21542 group required rescue analgesics (morphine 3 mg administered intravenously) compared with the placebo group. The mean (± standard deviation [SD]) cumulative dose of rescue analgesics used was also significantly lower in the HSK21542 group than in the placebo group within 0–12 h (1.7 [3.45] mg vs 2.5 [3.81] mg; $P = 0.009$) and 0–24 h (2.3 [4.86] mg vs 2.9 [4.22] mg; $P = 0.022$) after first dose. The 25th percentiles of time to initiate rescue analgesics were 3.88 and 0.80 h in the HSK21542 and placebo groups, respectively. The LS mean pain intensity difference (PID) in the HSK21542 group was significantly lower compared with the placebo group at all time points other than at 15 min post first dose (Fig. 3a). Significantly more patients in the HSK21542 group reported a lower pain score of numerical rating scale (NRS) ≤3 within 12 h (49.3 vs 36.3%; $P = 0.006$) and 24 h (48.5 vs 35.6%; $P = 0.007$). Longer mean (±SD) duration of analgesic effect was observed with HSK21542 compared with placebo (22.0 [3.45] h vs 20.3 [4.95] h; $P < 0.001$). Moreover, the mean (±SD) satisfaction score was

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Table 1 | Summary of patient characteristics at baseline for HSK21542-301 and HSK21542-303

	HSK21542 (*n* = 136)	Placebo (*n* = 135)	Total (*N* = 271)	HSK21542 (*n* = 129)	Tramadol (*n* = 129)	Placebo (*n* = 129)	Total (*N* = 387)
Age, median (range), years	49.0 (46.0–53.0)	49.0 (45.0–52.0)	49.0 (45.0–52.0)	46.0 (37.0–53.0)	45.0 (37.0–53.0)	44.0 (36.0–52.0)	45.0 (37.0–53.0)
Sex, *n* (%)							
Male	5 (3.7)	13 (9.6)	18 (6.6)	24 (18.6)	22 (17.1)	14 (10.9)	60 (15.5)
Female	131 (96.3)	122 (90.4)	253 (93.4)	105 (81.4)	107 (82.9)	115 (89.1)	327 (84.5)
Ethnicity, *n* (%)							
Han	130 (95.6)	129 (95.6)	259 (95.6)	117 (90.7)	126 (97.7)	125 (96.9)	368 (95.1)
Others	6 (4.4)	6 (4.4)	12 (4.4)	12 (9.3)	3 (2.3)	4 (3.1)	19 (4.9)
Height, cm	157.6 (5.8)	159.0 (6.0)	158.3 (5.9)	160.4 (7.2)	160.2 (7.3)	159.6 (6.5)	160.1 (7.0)
Weight, kg	59.8 (8.8)	61.2 (9.7)	60.5 (9.2)	61.5 (9.4)	61.5 (11.0)	59.8 (10.1)	60.9 (10.2)
BMI, kg/m^2	24.0 (3.1)	24.2 (3.1)	24.1 (3.1)	23.9 (3.0)	23.9 (3.4)	23.4 (3.2)	23.7 (3.2)
ASA, *n* (%)							
Class I	28 (20.6)	38 (28.1)	66 (24.4)	57 (44.2)	48 (37.2)	58 (45.0)	163 (42.1)
Class II	108 (79.4)	97 (71.9)	146 (53.9)	72 (55.8)	81 (62.8)	71 (55.0)	224 (57.9)
Baseline NRS	3.4 (1.6)	3.2 (1.6)	–	4.5 (0.7)	4.5 (0.8)	4.5 (0.7)	4.5 (0.7)
0–3, *n* (%)	58 (42.6)	73 (54.1)	131 (48.3)	0	0	0	0
4–6, *n* (%)	76 (55.9)	60 (44.4)	136 (50.2)	127 (98.4)	125 (96.9)	126 (97.7)	378 (97.7)
7–10, *n* (%)	2 (1.5)	2 (1.5)	4 (1.5)	2 (1.6)	4 (3.1)	3 (2.3)	9 (2.3)

All continuous variables are presented in mean (±SD), unless otherwise specified. *ASA* American Society of Anesthesiologists, *BMI* body mass index, *NRS* numerical rating scale, *SD* standard deviation.

significantly higher with HSK21542 than placebo among patients (9.0 [1.68] vs 8.4 [1.86]; $P = 0.001$) and physicians (8.9 [1.49] vs 7.8 [2.07]; $P < 0.001$). The PPS analysis was consistent with the FAS for all secondary outcome measures (Table 2).

In the HSK21542-303 trial, the LS means (±SE) $SPID_{0-12\,h}$ for HSK21542, tramadol, and placebo were −28.9 (1.11), −28.7 (1.11), and −19.7 (1.11), respectively. Significant LS mean differences ($P < 0.001$; Supplementary Fig. 1b) were observed between HSK21542 versus placebo and tramadol versus placebo. Fewer patients received rescue analgesics (flurbiprofen axetil 50 mg administered intravenously) in the HSK21542 and tramadol groups compared with placebo within 0–12 h (39.5 vs 34.1 vs 69.0%) and 0–24 h (40.3 vs 35.7 vs 71.3%) after first dose. Mean (±SD) cumulative dose of rescue analgesics used was also lower in the HSK21542 and tramadol groups compared with placebo within 0–12 h (28.7 [40.88] mg vs 26.7 [44.21] mg vs 57.4 [53.80] mg) and 0–24 h (29.8 [42.63] mg vs 29.3 [46.78] mg vs 61.6 [56.08] mg) after first dose. Significant difference ($P < 0.001$) was observed in all assessments of mean cumulative rescue analgesic dose between HSK21542 versus placebo and tramadol versus placebo. The 25th percentile of time to rescue analgesic initiation was 0.82, 1.17, and 0.35 h with HSK21542, tramadol, and placebo, respectively. The LS mean PID in the HSK21542 and tramadol groups was significantly lower compared with the placebo group at all time points (Fig. 3b). Significantly larger proportions of patients in the HSK21542 and tramadol groups reported a lower pain score of NRS ≤3 within 12 h (47.3 vs 51.2 vs 19.4%; both $P < 0.001$) and 24 h (45.0 vs 48.1 vs 17.1%; both $P < 0.001$) compared with placebo. The mean (±SD) duration of analgesic also lasted significantly longer with HSK21542 and tramadol compared with placebo (21.0 [5.87] h vs 21.3 [5.46] h vs 18.2 [7.24] h; both $P < 0.001$). A significantly higher mean (±SD) satisfaction score was observed among patients who received HSK21542, but not tramadol, when compared with the placebo group (8.7 [1.67] vs 8.5 [1.58] vs 8.2 [1.91]; HSK21542 vs placebo, $P = 0.019$; tramadol vs placebo, $P = 0.379$). However, the mean (±SD) satisfaction scores were higher in both the HSK21542 group and the tramadol group compared with placebo among physicians (8.6 [1.51] vs 8.4 [1.42] vs 7.6 [1.99]; HSK21542 vs placebo, $P < 0.001$; tramadol vs placebo, $P = 0.002$). The PPS analysis was consistent with the FAS for all secondary outcome measures (Table 2).

Safety. The safety profiles of HSK21542-301 and HSK21542-303 are summarized in Table 3. All laboratory abnormalities, changes to vital signs or electrocardiograms (ECGs) that were either normal before treatment or clinically insignificant before treatment but became clinically significant after treatment were reported as adverse events.

There were 194 (71.6%) treatment-emergent adverse events (TEAEs) reported in the HSK21542-301 trial; 94 (69.1%) occurred in the HSK21542 group and 100 (74.1%) in the placebo group. Of these, 19 (14.0%) and 25 (18.5%) were considered related to treatment. The majority of the TEAEs were mild to moderate in severity. Grade ≥3 TEAEs occurred in nine (3.3%) patients; eight in the HSK21542 group and one in the placebo group. No deaths were reported in either treatment arm. The overall incidence and types of TEAEs in the HSK21542 group were similar to those in the placebo group. Of note, the incidence of nausea (17.6 vs 27.4%) and vomiting (15.4 vs 32.6%) was lower with HSK21542 compared with placebo. Most of the TEAEs were resolved without requiring treatment. The number of patients who required an antiemetic within 24 h post first dose was 16 (11.8%) and 44 (32.6%) in the HSK21542 and placebo groups, respectively. Three patients in the HSK21542 group had serious adverse events which were unrelated to the study treatment. One patient from the placebo arm discontinued treatment and subsequently withdrew from the study due to TEAEs. There were several laboratory abnormalities possibly related to the study drug. In the HSK21542 group, these included five cases of decreased thyroid-stimulating hormone, three cases of decreased blood potassium, two cases of decreased free triiodothyronine, one case of decreased blood urea, and one case of hypokalemia. In the placebo group, there were two cases of hypokalemia and one case of decreased blood potassium that were possibly treatment-related. All other laboratory abnormalities were unrelated to the study drug. Most patients' vital signs remained stable throughout the study. Two cases of elevated blood pressure were reported in the HSK21542 group, whereas the placebo group had two cases of elevated blood pressure, two cases of decreased heart rate, and one case of elevated body temperature. None of these events were related to study

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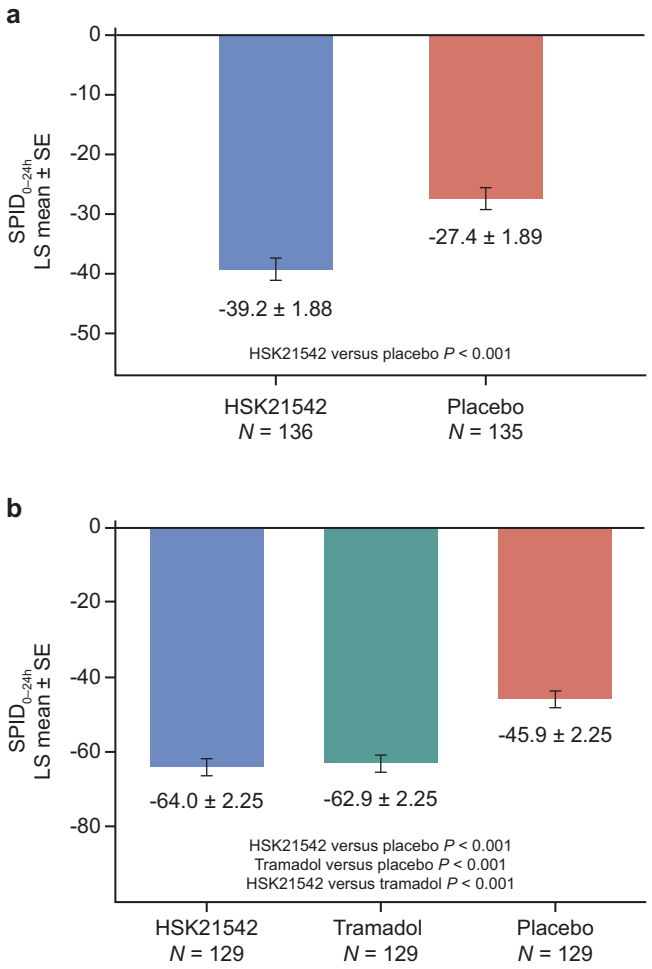

Fig. 2 | Primary efficacy endpoint. $SPID_{0-24\,h}$ after the postoperative administration of the first dose in **a** HSK21542-301 and **b** HSK21542-303. An ANCOVA model was constructed with the treatment group as a fixed effect and the baseline NRS score as a covariate. The *P* value of the HSK21542 group and the tramadol group in HSK21542-303 was based on the non-inferiority margin of 11.03. LS least squares, SE standard error, SPID summed pain intensity difference.

treatment or met the criteria for adverse events. Abnormal ECG readings reported at 15 min ± 30 s post first dose (0 vs 3 cases), day 2 (1 case each), and day 3 (5 vs 3 cases) were determined to be unrelated to the study drug.

A total of 265 (68.5%) TEAEs were reported in the HSK21542-303 trial, of which 76 (58.9%), 108 (83.7%), and 81 (62.8%) occurred in the HSK21542, tramadol, and placebo groups, respectively. The overall incidence of TEAEs in the HSK21542 group was similar to that in the placebo group, but lower than the tramadol group. Most TEAEs were grade 1–2 in severity. The number of grade ≥3 TEAEs in the HSK21542, tramadol, and placebo groups were three (2.3%), six (4.7%), and four (3.1%), respectively. Notably, the incidence of nausea (10.1 vs 41.9 vs 20.2%) and vomiting (8.5 vs 38.0 vs 16.3%) was significantly lower with HSK21542 compared with tramadol or placebo. Drug-related TEAEs occurred in 33 (25.6%), 74 (57.4%), and 40 (31.0%) patients in the HSK21542, tramadol, and placebo groups, respectively. Fifteen (11.6%) patients in the HSK21542 group had decreased thyroid-stimulating hormone levels, 11 (8.5%) of which were related to treatment. One patient each in the tramadol and placebo groups experienced a serious adverse event. Three patients (two in the tramadol group and one in the placebo group) experienced TEAEs that led to study withdrawal. No deaths were reported in any of the study arms. Antiemetics were administered to 12 (9.3%), 54 (41.9%), and 29 (22.5%) patients within 24 h post first dose in the HSK21542, tramadol, and placebo groups, respectively. All clinically significant abnormal laboratory test (routine blood test, blood biochemistry, urinalysis, and blood electrolyte test) results that met the criteria for reporting as adverse events were documented. The majority of these were classified as either grade 1 or 2 in severity. Abnormal vital signs detected at either 15 min ± 30 s post first dose (diastolic blood pressure: 0 vs 2 vs 2 cases; heart rate: 0 vs 0 vs 1 case; respiratory rate: 0 vs 1 vs 0 case; systolic blood pressure: 0 vs 0 vs 2 cases) or during the follow-up period (diastolic blood pressure: 0 vs 0 vs 3 cases; heart rate: 1 vs 1 vs 0 case; systolic blood pressure: 0 vs 0 vs 1 case) were deemed not related to treatment. Similarly, abnormal ECG readings reported at 15 min ± 30 s post first dose (2 vs 0 vs 3 cases) and during the follow-up period (3 vs 3 vs 2 cases) were unrelated to the study drug.

Pharmacokinetics. In the pharmacokinetics analysis set (PKS, $n = 136$) of the HSK21542-301 trial, the mean plasma concentrations in the HSK21542 group were 7.4681 ± 3.8908 ng/mL at 30 s to 5 min post-administration following surgery, and 0.8763 ± 2.0854 ng/mL between 5:00 AM and 9:00 AM on day 2. Plasma concentration of HSK21542 peaked sharply after post-surgical administration, then declined to relatively low levels by the morning of day 2. The pharmacokinetic data from HSK21542-301 was used to develop a population pharmacokinetic model, which was recently published in a separate study[38].

Subgroup analyses in HSK21542-303. Subgroup analyses were performed in the HSK21542-303 trial to assess the efficacy endpoints stratified by NRS score (Supplementary Table 2) and age (Supplementary Table 3).

In the subgroup analysis based on NRS score, there were more primary and secondary efficacy endpoints that met statistically significant differences between the HSK21542 and tramadol groups compared with the placebo group in the NRS 4–6 points subgroup than the 7–10 subgroup. In the subgroup analysis based on age, there were more primary and secondary efficacy endpoints that met significant differences between the HSK21542 and tramadol groups compared with placebo in patients aged <65 years than 65–70 years.

Discussion

In these two phase 3 trials, HSK21542 demonstrated superior efficacy in treating postoperative pain compared with placebo. The first trial (HSK21542-301) focused on patients who underwent elective laparoscopic surgery, while the second trial (HSK21542-303) involved patients who underwent elective abdominal surgery, including laparoscopic procedures, under general anesthesia. In the latter trial, HSK21542 not only proved superior to placebo but also showed non-inferiority to tramadol in managing postoperative pain. PPS analysis of the primary endpoint produced consistent results with the FAS in both studies.

Compared with placebo, HSK21542 was proven to have a potent analgesic effect in both the randomized studies, as evidenced by lower $SPID_{0-24\,h}$, PID across all time points except at 15-min post first dose, a longer duration of analgesia effect, and a smaller proportion of patients requiring rescue analgesics. This led to high satisfaction scores among patients and physicians, further underscoring the notion that the abatement of postoperative pain intensity seen with HSK21542 treatment was associated with a positive effect on postoperative recovery, which was important for patients. More than 30% improvement in $SPID_{0-24\,h}$ with HSK21542 compared with placebo was observed in both studies. This magnitude of improvement was consistent with other trials of novel analgesics such as VX-548 ($Na_V1.8$ inhibitor), meloxicam (COX-2 inhibitor), and oliceridine (μ-receptor G-protein pathway modulator) that utilized SPID24 as an efficacy endpoint in abdominoplasty and bunionectomy[39–41].

Table 2 | Summary of secondary efficacy endpoints for HSK21542-301 and HSK21542-303

	HSK21542-301			HSK21542-303				
	HSK21542 FAS, *n* = 136; PPS, *n* = 128	Placebo FAS, *n* = 135; PPS, *n* = 129	*P* value	HSK21542 FAS, *n* = 129; PPS, *n* = 121	Tramadol FAS, *n* = 129; PPS, *n* = 120	Placebo FAS, *n* = 129; PPS, *n* = 113	*P* value (HSK21542 vs placebo)	*P* value (tramadol vs placebo)
FAS set								
$SPID_{0-12h}$	−17.3 (0.92)	−12.0 (0.92)	<0.001	−28.9 (1.11)	−28.7 (1.11)	−19.7 (1.11)	<0.001	<0.001
Rescue analgesic received$_{0-12\,h}$, *n* (%)	40 (29.4)	61 (45.2)	0.002	51 (39.5)	44 (34.1)	89 (69.0)	<0.001	<0.001
Rescue analgesic received$_{0-24\,h}$, *n* (%)	45 (33.1)	63 (46.7)	0.009	52 (40.3)	46 (35.7)	92 (71.3)	<0.001	<0.001
Cumulative rescue analgesic dose$_{0-12\,h}$, mg	1.7 (3.45)	2.5 (3.81)	0.009	28.7 (40.88)	26.7 (44.21)	57.4 (53.80)	<0.001	<0.001
Cumulative rescue analgesic dose$_{0-24\,h}$, mg	2.3 (4.86)	2.9 (4.22)	0.022	29.8 (42.63)	29.3 (46.78)	61.6 (56.08)	<0.001	<0.001
Time to rescue analgesic initiation, h								
P25 (95% CI)	3.88 (1.03, 14.18)	0.80 (0.48, 1.65)	0.017	0.82 (0.52, 2.23)	1.17 (0.53, 4.57)	0.35 (0.30, 0.38)	<0.001	<0.001
P50 (95% CI)	– (–, –)	– (4.55, –)		– (–, –)	– (–, –)	0.62 (0.50, 2.12)		
P75 (95% CI)	– (–, –)	– (–, –)		– (–, –)	– (–, –)	– (9.03, –)		
NRS ≤$3_{12\,h}$, *n* (%)	67 (49.3)	49 (36.3)	0.006	61 (47.3)	66 (51.2)	25 (19.4)	<0.001	<0.001
NRS ≤$3_{24\,h}$, *n* (%)	66 (48.5)	48 (35.6)	0.008	58 (45.0)	62 (48.1)	22 (17.1)	<0.001	<0.001
Duration of analgesic effect, h	22.0 (3.45)	20.3 (4.95)	<0.001	21.0 (5.87)	21.3 (5.46)	18.2 (7.24)	<0.001	<0.001
Patient satisfaction score	9.0 (1.68)	8.4 (1.86)	0.001	8.7 (1.67)	8.5 (1.58)	8.2 (1.91)	0.019	0.379
Physician satisfaction score	8.9 (1.49)	7.8 (2.07)	<0.001	8.6 (1.51)	8.4 (1.42)	7.6 (1.99)	<0.001	0.002
PPS set								
$SPID_{0-12\,h}$	−17.3 (0.94)	−12.5 (0.94)	<0.001	−29.8 (0.98)	−29.8 (0.99)	−21.6 (1.02)	<0.001	<0.001
Rescue analgesic received$_{0-12h}$, *n* (%)	39 (30.5)	58 (45.0)	0.006	46 (38.0)	39 (32.5)	74 (65.5)	<0.001	<0.001
Rescue analgesic received$_{0-24\,h}$, *n* (%)	44 (34.4)	60 (46.5)	0.021	47 (38.8)	41 (34.2)	77 (68.1)	<0.001	<0.001
Cumulative rescue analgesic dose$_{0-12h}$, mg	1.8 (3.53)	2.5 (3.86)	0.021	27.7 (40.80)	23.3 (39.39)	48.2 (45.77)	<0.001	<0.001
Cumulative rescue analgesic dose$_{0-24\,h}$, mg	2.4 (4.98)	2.9 (4.21)	0.052	28.9 (42.70)	26.0 (42.68)	53.1 (49.68)	<0.001	<0.001
Time to rescue analgesic initiation, h								
P25 (95% CI)	3.69 (0.63, 13.27)	0.95 (0.48, 1.65)	0.037	1.15 (0.57, 3.88)	1.89 (0.60, 12.73)	0.37 (0.32, 0.47)	<0.001	<0.001
P50 (95% CI)	– (–, –)	– (3.98, –)		– (–, –)	– (–, –)	1.03 (0.57, 4.08)		
P75 (95% CI)	– (–, –)	– (–, –)		– (–, –)	– (–, –)	– (16.28, –)		
NRS ≤$3_{12\,h}$, *n* (%)	62 (48.4)	46 (35.7)	0.008	59 (48.8)	63 (52.5)	24 (21.2)	<0.001	<0.001
NRS ≤$3_{24\,h}$, *n* (%)	61 (47.7)	45 (34.9)	0.009	56 (46.3)	59 (49.2)	21 (18.6)	<0.001	<0.001
Duration of analgesic effect, h	22.1 (3.35)	20.5 (4.82)	0.001	22.0 (4.15)	22.4 (3.09)	19.9 (5.40)	<0.001	<0.001
Patient satisfaction score	9.0 (1.71)	8.4 (1.89)	<0.001	8.7 (1.68)	8.5 (1.59)	8.3 (1.85)	0.049	0.602
Physician satisfaction score	8.8 (1.52)	7.9 (2.03)	<0.001	8.6 (1.53)	8.4 (1.43)	7.6 (2.01)	<0.001	0.005

All continuous variables are presented in mean (±SD), unless otherwise specified.

FAS full analysis set, *NRS* numerical rating scale, *PPS* per-protocol set, *P25* 25th percentile; *P50* 50th percentile, *P75* 75th percentile, *SD* standard deviation, *SPID* summed pain intensity difference. The rescue analgesic morphine 3 mg was administered intravenously in HSK21542-301, while flurbiprofen axetil 50 mg was administered intravenously in HSK21542-303. Additional doses of rescue analgesic could be administered if needed.

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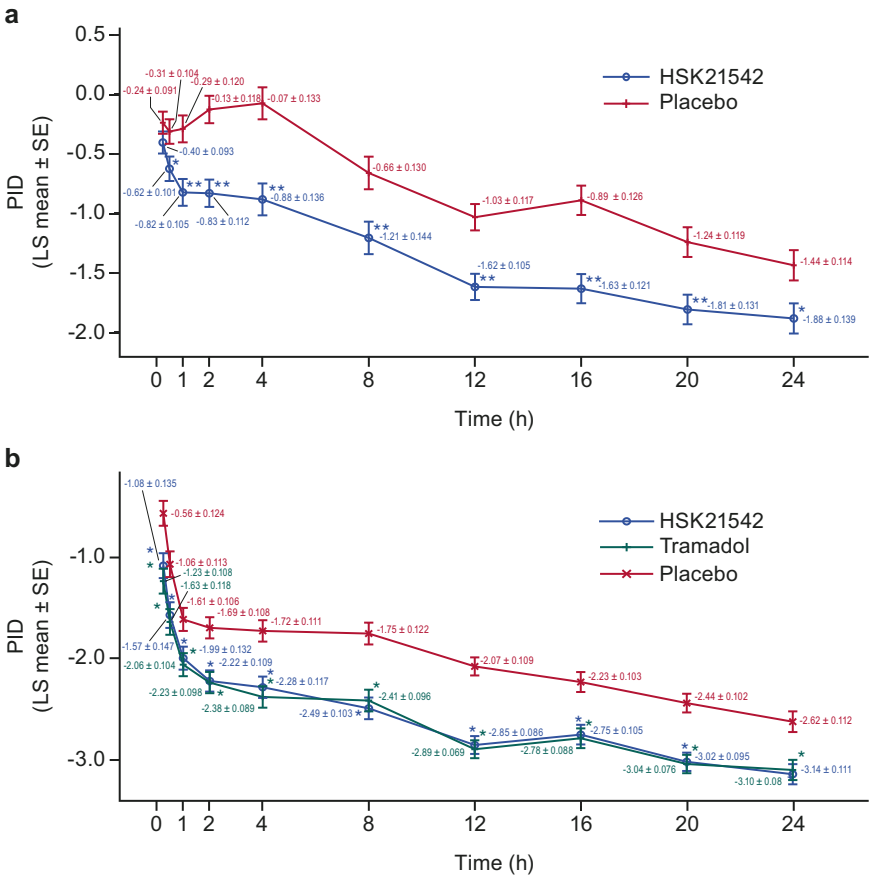

Fig. 3 | LS mean PID. Postoperative pain intensity differences at each time point in **a** HSK21542-301 and **b** HSK21542-303. The ANCOVA model was constructed with the treatment group as the fixed effect and the baseline NRS score as the covariate. *$P < 0.05$. **$P < 0.01$. LS least squares, PID pain intensity difference, SE standard error.

Table 3 | Treatment-emergent adverse events in the safety set of HSK21542-301 and HSK21542-303

	HSK21542-301		HSK21542-303		
	HSK21542 (*n* = 136)	Placebo (*n* = 135)	HSK21542 (*n* = 129)	Tramadol (*n* = 129)	Placebo (*n* = 129)
Any AE	94 (69.1)	100 (74.1)	76 (58.9)	108 (83.7)	81 (62.8)
Drug-related TEAE	19 (14.0)	25 (18.5)	33 (25.6)	74 (57.4)	40 (31.0)
SAE	3 (2.2)	0	0	1 (0.8)	1 (0.8)
≥ Grade 3 TEAE	8 (5.9)	1 (0.7)	3 (2.3)	6 (4.7)	4 (3.1)
AEs ≥5%					
Vomiting	21 (15.4)	44 (32.6)	11 (8.5)	49 (38.0)	21 (16.3)
Nausea	24 (17.6)	37 (27.4)	13 (10.1)	54 (41.9)	26 (20.2)
Fever	9 (6.6)	13 (9.6)	6 (4.7)	10 (7.8)	9 (7.0)
Inflammation	11 (8.1)	5 (3.7)	1 (0.8)	1 (0.8)	0
Anemia	9 (6.6)	9 (6.7)	13 (10.1)	16 (12.4)	10 (7.8)
Decreased thyroid-stimulating hormone	5 (3.7)	0	15 (11.6)	0	0
Decreased serum potassium	8 (5.9)	11 (8.1)	3 (2.3)	3 (2.3)	2 (1.6)
Hypokalemia	2 (1.5)	2 (1.5)	6 (4.7)	10 (7.8)	12 (9.3)
Decreased lymphocyte count	8 (5.9)	2 (1.5)	0	0	0
Hematuria	8 (5.9)	10 (7.4)	3 (2.3)	2 (1.6)	2 (1.6)

AE adverse event, *NR* not reported, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event.

Developing peripherally restricted KOR agonists has been challenging, with many early compounds discontinued due to unwanted side effects or unfavorable clinical efficacy at doses that spare centrally mediated activity[21,42]. HSK21542 is a peripherally restricted KOR agonist that has demonstrated the ability to attenuate nociceptive transmission by acting on KORs located in the viscera. This mode of action has been proven clinically effective in reducing pain without causing centrally mediated side effects[42]. Preclinical study to evaluate the biological activity and selectivity of HSK21542 has suggested that it produces potent analgesic effects in animal models, acting as a ligand of KOR with higher affinity without detectable activity at the MOR, delta opioid receptor, or any other targets associated with abuse

potential[24]. More recently, another peripherally restricted KOR agonist, the peptide-based CR845, has shown good analgesic and antipruritic effects in clinical trials[35,43,44]. At present, CR845 is approved for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in patients undergoing hemodialysis[45], and has been investigated in pain management in a phase 2 study on bunionectomy with 51 patients, where adverse events such as nausea, vomiting, paresthesia, and somnolence were observed[35]. CR845 has also been investigated in abdominal surgery for its analgesic effect and safety[46]. When CR845 was compared with HSK21542, the latter appeared to have higher potency and longer acting effects in mice, possibly due to its higher affinity to KOR[24]. In addition, the brain-plasma distribution study showed that HSK21542 has limited ability to penetrate the central nervous system. The pharmacokinetics of HSK21542 are well documented, with the half-life of the novel analgesic ranging between 1.5 to 2 h, and the majority of the compound excreted through urine was unchanged[47,48]. These findings suggest HSK21542 has a possible safety advantage compared with centrally penetrating KOR agonists and MOR agonists, offering an effective alternative for pain management.

In general, the incidence of TEAEs for HSK21542 was similar to placebo and lower than that of tramadol. HSK21542 was associated with fewer gastrointestinal adverse events, such as nausea and vomiting, compared with tramadol, resulting in lower cumulative use of antiemetics. Although the incidence of decreased thyroid-stimulating hormone only occurred in the HSK21542 arms of both studies, there were no clinical symptoms or manifestations related to the change in thyroid function observed, and the condition was resolved within a week without further intervention. Most of the other safety parameters (laboratory tests, vital signs, physical examination, and ECG) were stable, and most abnormal measurements did not meet the adverse event criteria or were related to the study drug.

Postoperative nausea and vomiting (PONV) are common complications after surgery, particularly in abdominal surgery[49–52]. PONV commonly occurs within 24 to 48 h after surgery, and can have negative effects, including water and electrolyte imbalance, wound dehiscence, incisional hernia formation, or aspiration pneumonia. Analgesics such as opioids and tramadol could increase the risk of PONV[49]. HSK21542, as a peripheral restricted KOR agonist, rapidly distributes in the gastrointestinal tract after administration and acts on the vagus nerve. This mechanism changes the regulation of the central system's gastrointestinal stimulation signals, improving early intestinal dilatation and gas formation caused by gastrointestinal discomfort after abdominal surgery or anesthesia[53]. As such, the incidence of PONV was considerably lower in patients receiving HSK21542 compared with those receiving tramadol or placebo.

Both HSK21542-301 and HSK21542-303 had several strengths. First, both were randomized controlled studies. Second, HSK21542-303 incorporated a multimodal analgesia regimen, which is usually used to treat postoperative pain in the clinic, reflecting clinical practice accurately in a trial setting. One limitation was that both studies enrolled patients who were undergoing elective abdominal surgery, so the effects of HSK21542 on patients with other types of pain need further evaluation. The results were also not generalizable to the non-Chinese population. Another limitation was that the safety and efficacy of HSK21542 were assessed at only 8 ± 1 days after surgery and did not consider the development of chronic pain. Therefore, longer follow-up evaluations would be necessary to assess the generalizability of this treatment. The study was also not able to elucidate the patient group that received the most clinical benefit from HSK21542, given that there were fewer patients with a baseline NRS 7–10 pain score or aged 65–70 years old. Lastly, pain could be underestimated as movement-evoked pain, which is usually more intense and functionally relevant, was not measured.

In conclusion, treatment with HSK21542 led to a significant reduction in postoperative pain intensity among patients undergoing elective abdominal surgery (including laparoscopic surgery) under general anesthesia. Additionally, HSK21542 exhibited prolonged analgesic effects, less use of cumulative rescue analgesics, high satisfaction scores among patients and physicians compared with placebo, and fewer gastrointestinal adverse events compared with tramadol or placebo. Based on both studies, it is recommended to administer HSK21542 at a dose of 1.0 μg/kg at 0, 8, and 16 h.

Methods

Study design and patients

HSK21542-301 (ClinicalTrials.gov Identifier: NCT04738357) and HSK21542-303 (ClinicalTrials.gov Identifier: NCT05390905) were two phase 3, multicenter, randomized, double-blind, placebo-controlled (HSK21542-303 also has a positive tramadol control arm) studies evaluating the efficacy and safety of HSK21542 in the management of postoperative pain (Fig. 1). Both studies were registered at www.clinicaltrials.gov. HSK21542-301 was conducted in 26 clinical centers with the first patient enrolled on March 24, 2021, and last patient enrolled on July 30, 2021, while HSK21542-303 was conducted in 21 clinical centers with the first patient enrolled on June 9, 2022, and last patient enrolled on November 29, 2022, all located in China (Supplementary Table 4). The primary objective of both studies was to assess efficacy, while safety served as the secondary objective. HSK21542-301 enrolled patients who underwent elective laparoscopic surgery, whereas HSK21542-303 included patients who underwent elective abdominal operations under general anesthesia. A full account of the eligibility criteria for both HSK21542-301 and HSK21542-303 are available in the protocol as Supplementary Information.

The inclusion criteria of HSK21542-301 included patients who underwent elective laparoscopic surgery under general anesthesia with an expected operation duration of 1–5 h; American Society of Anesthesiologists classification I–II; aged between 18–70 years; BMI between 18–40 kg/m^2; must not have undergone major surgery within the past 3 months that would affect postoperative pain assessment; and agree to participate in this trial and voluntarily sign the informed consent form. The inclusion criteria of HSK21542-303 were similar to HSK21542-301, with the key differences being the inclusion of patients who underwent elective abdominal surgery (including laparoscopic surgery) under general anesthesia and those who had a NRS pain score of ≥4 points at rest within 4 h postoperatively as assessed by the investigators.

Key exclusion criteria for both HSK21542-301 and HSK21542-303 included history of cardiovascular, respiratory, neurological, and psychiatric diseases; history of allergy to opioids, such as urticaria, or allergic to intraoperative anesthetics (propofol/sevoflurane), muscle relaxants (cisatracurium), and antiemetics (tropisetron) used in the study; prior use of opioid and non-opioid analgesics with the interval between the last administration and randomization shorter than five half-lives of the drug or the duration of response; consecutive use of opioid analgesics for any reason of more than 10 days within 3 months before screening; use of drugs with unknown half-lives that affect the analgesic effects within 14 days before randomization; prior use of diuretics and compound drugs containing diuretics with the interval between the last administration and randomization shorter than five half-lives of the drug or the duration of response; and underwent major surgery that would affect postoperative pain assessment within 3 months.

Ethics

The studies adhered to the principles outlined in the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent according to local requirements before

participating in the study. The trial protocols and any amendments were reviewed by the independent ethics committee or institutional review board (see Supplementary Table 4 and the Inclusion and Ethics section below for the comprehensive list). All protocol deviations or violations that occurred during the study were reported to the medical ethics committee of each center as required.

Inclusion and ethics

The HSK21542-301 study was reviewed and approved by all relevant local ethics committees and institutional review boards, listed below: The Human Research Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine; Clinical Research Ethic Committee, Renmin Hospital of Wuhan University; Ethics Committee of The First Hospital of Jilin University; Ethics Committee of The First People's Hospital of Liuzhou; Henan Provincial People's Hospital Ethics Committee for Drug (Device) Clinical Trials; Clinical Research Sub-Ethics Committee of Medical Ethics Committee, The First Affiliated Hospital of Nanhua University; Clinical Medical Ethics Review Committee of Xiangya Hospital, Central South University; Sichuan Academy of Medical Sciences-Sichuan Provincial People's Hospital Drug (device) Ethics Committee; Drug Clinical Trial Ethics Committee of The Affiliated Hospital of Zunyi Medical University; Institutional Review Board of the First Affiliation Hospital of Jinan University; Drug Clinical Trial Ethics Committee of Dalian University Affiliated Zhongshan Hospital; Ethics Committee of The Affiliated Hospital of Zhejiang University; Medical Ethics Committee of West China Second Hospital of Sichuan University; Ethics Committee of The Second People's Hospital of Yibin City; Ethics Committee of Huazhong University of Science and Technology; Harbin Medical University Cancer Hospital Ethics Committee; Ethics Committee of The Third Xiangya Hospital of Central South University; Medical Ethics Committee, Beijing Obstetrics and Gynecology Hospital, Capital Medical University; Ethics Committee of Lianyungang First People's Hospital; Ethics Committee Subcommittee of Southern Medical University Tenth Affiliated Hospital, Dongguan City People's Hospital; Ethics Committee of Cangzhou People's Hospital; Ethics Committee of Wuxi People's Hospital, Nanjing Medical University Affiliated; First Affiliated Hospital of Ningbo University Clinical Trial Ethics Committee for Drugs and Medical Devices; Clinical Medical Research Ethics Committee of the First Affiliated Hospital of Bengbu Medical College; Ethics Committee in Clinical Research of the First Hospital of Wenzhou Medical University; Chinese People's Liberation Army Northern Theater Command General Hospital Medical Ethics Committee. The HSK21542-303 study was reviewed and approved by all relevant local ethics committees and institutional review boards, listed below: Medical Ethics Committee of Union Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology; Henan Provincial People's Hospital Drug (device) Clinical Trial Ethics Committee; Sichuan Provincial People's Hospital Drug (device) Clinical Trial Ethics Committee; Cangzhou City People's Hospital Drug Clinical Trial Ethics Committee; Medical Ethics Committee of the First Affiliated Hospital of the University of South China; Liuzhou People's Hospital Medical Ethics Committee; Ethics Committee of Drug Clinical Trial, the First Affiliated Hospital of Wenzhou Medical University; Medical Ethics Committee of Affiliated Hospital of Xuzhou Medical College; Chengdu Third People's Hospital Drug Clinical Trial Ethics Committee; Guangyuan First People's Hospital Clinical Trial Ethics Committee; Wuhan University People's Hospital Clinical Research Ethics Committee; Ethics Committee of Wuhan Third Hospital; Ethics Committee of Wuhan Central Hospital; Ethics Committee of the Third Xiangya Hospital, Central South University; Wuxi People's Hospital Clinical Trial Ethics Committee; Dongguan City People's Hospital Medical Ethics Committee Branch; Medical Ethics Committee of Affiliated Hospital of Guizhou Medical University; Clinical Trial Ethics Committee of the First Affiliated Hospital of Jinan University; Academic Ethics Committee of Shaoxing People's Hospital; Ethics Committee of National Drug Clinical Trial Institution, Yibin Second People's Hospital; Clinical Trial Ethics Committee of the Fourth Affiliated Hospital of Harbin Medical University.

Randomization and masking

In HSK21542-301, patients were randomized 1:1 to receive either HSK21542 1.0 μg/kg or placebo. In HSK21542-303, patients were randomized 1:1:1 to receive HSK21542 1.0 μg/kg, tramadol 50 mg/dose, or placebo. All treatments in both studies were administered intravenously. The tramadol dose used was within the recommended dosage of 50–100 mg by the intravenous route, and the 50-mg dose has been reported to be well tolerated and achieve high satisfaction in postoperative pain relief[54]. This centrally acting MOR agonist inhibits serotonin and norepinephrine uptake, inhibiting pain transmission[55]. It is mainly excreted via the kidneys and has a half-life of about 6 h[55]. The randomization process employed an interactive web response system to assign patients a random number and corresponding treatment. Patients, study investigators, and study site personnel were masked to the treatment allocation throughout the study, in both trials. The inclusion of the placebo controls in both studies ensures that any observed differences in effect can be attributed to the investigational drug, given that placebo analgesia in pain management studies is a well-documented phenomenon in literature[56,57]. The HSK21542 and placebo packages were identical in appearance to maintain the blinding. The placebo contains all components of HSK21542 except for the active ingredient. It includes glacial acetic acid and sodium acetate for pH buffering, as well as water as a solvent. The study treatment remained blinded unless essential for urgent medical treatment or as required by regulations. The blinding of the treatments and the randomization process were managed by statisticians who were unblinded. Unblinding of the results was performed after data cleaning and locking upon trial completion.

In HSK21542-303, an additional unblinded team was also involved in the administration and management of the study drugs along with the testing of patient blood samples. Communication between the blinded and unblinded teams was not allowed to prevent the trial from being compromised.

Procedures

Dosing schedule. In HSK21542-301, during the surgery, patients received propofol 1.0–2.0 mg/kg, sufentanil 0.4 μg/kg, and cisatracurium 0.1–0.2 mg/kg for anesthesia induction. Remifentanil 0.1–0.5 μg/kg/min was given for anesthesia maintenance. Depending on the hemodynamic change of the patient during the surgery, propofol, remifentanil, and cisatracurium could be administered, as required, according to the investigator's assessment. Sufentanil 0.1 μg/kg was given 15–30 min before the last suture of incision closure was completed. Propofol was discontinued 5–10 min before suturing was completed, and remifentanil was immediately stopped within 2 min after the end of suturing. Modified observer's assessment of alertness and sedation (MOAA/S) was performed at 5- ± 1-min intervals. When the patient reached a fully alert state (MOAA/S score of five points for three consecutive times), the first NRS score was recorded within 15 min. The first dose of study drug was administered within 5 min after obtaining the first NRS score. This was recorded as time 0. However, if the patient complained of pain before reaching full alertness (i.e., obtaining three consecutive MOAA/S scores of five points) with a resting NRS score of ≥4 points, the study drug could be administered in advance. Subsequent treatment doses were given at 8 and 16 h ± 15 min after the first dose, with each intravenous injection completed within 2 min ± 5 s. The study design and timeline of procedures for HSK21542-301 are illustrated in Supplementary Fig. 2.

In HSK21542-303, during surgery, propofol 1.0–2.0 mg/kg and sufentanil 0.2–0.3 μg/kg were given to induce anesthesia. Remifentanil

was supplemented as needed, and cisatracurium 0.1–0.2 mg/kg was used as a muscle relaxant. Either propofol alone or in combination with sevoflurane was administered for anesthetic maintenance during the surgery. Cisatracurium and remifentanil 0.1–0.5 μg/kg/min were given, as needed. These treatments were adjusted according to the hemodynamic change of the patient. Sufentanil at a dose of 0.03–0.08 μg/kg was administered 15–30 min before the last suture of incision closure. Sevoflurane and propofol were discontinued 20–30 min and 5–10 min before the end of suturing, respectively. Remifentanil was also stopped immediately (within 2 min), after the end of the suturing. MOAA/S assessment was conducted at 5- ± 1-min intervals, and once the score reached five points, the NRS was assessed under resting conditions within 5 min. The first dose of study drug administered within 10 min after randomization and obtaining the first NRS score of ≥4 (within 4 h postsurgery) was recorded as time 0. Treatment was administered using an intravenous pump at 8-h intervals ±15 min for a total of three doses. The study design and timeline of procedures for HSK21542-303 is illustrated in Supplementary Fig. 3.

Rescue analgesic use. After receiving the first dose of the study drug, if the patient complained of pain with a resting NRS score of ≥4 points, they could receive morphine 3 mg (HSK21542-301) or flurbiprofen axetil 50 mg (HSK21542-303) intravenously as an initial dose. The recommended interval between two rescue analgesic doses was ≥2 h for HSK21542-301 and ≥3 h for HSK21542-303, while the interval between administering the rescue analgesic and study drug stated in both studies was recommended to be ≥1 h. Rescue analgesics could be administered at any time, if needed, in both studies; additional use of rescue analgesics or higher doses could be given if the pain remained severe, as deemed appropriate by the investigator. In HSK21542-303, the time from the patient receiving a NRS score to the actual administration of the flurbiprofen axetil injection should not exceed 30 min; if pain relief was not achieved after ≥4 doses of rescue medication, the investigator would consider withdrawing the patient from the study to receive other appropriate analgesic treatments. The nonsteroidal anti-inflammatory drug, flurbiprofen axetil, was chosen in HSK21542-303 as the rescue medication with the safety of the patient as a key consideration, because tramadol, in the positive control group, is an opioid drug with side effects similar to those of morphine. The resting NRS score prior to the use of rescue analgesics, time of administration, and amount used were recorded.

Antiemetic. Prophylactic antiemetic therapy was not allowed during the study period. After the administration of the first dose of the study drug, investigators could administer antiemetic drugs based on the occurrence of nausea and vomiting. Tropisetron 2.5 mg was the preferred choice, with additional doses not exceeding 10 mg within 24 h, if necessary. If tropisetron proved ineffective, alternative antiemetic drugs could be used. The use of antiemetics was a secondary endpoint assessed as part of the safety evaluation in both studies.

Assessment. In both studies, the NRS score of resting pain (sitting or lying still) was assessed at various time points, including pre-dose, post first dose (15 min, 30 min, 1, 2, 4, and 8 h), post second dose (12 and 16 h), and post third dose (20 and 24 h). If the patient was not awake at the assessment time point, the current NRS score would be the same as the previous score if the previous score was <2, or recorded as 2 if the previous score was ≥2. The NRS is scored from 0–10 (0 meaning "no pain" and 10 meaning the "worst pain imaginable").

Blood samples were collected at each assessment time point to measure the serum concentration of HSK21542. Postoperative satisfaction with analgesia, as evaluated by patients and investigators, was assessed 24 h after the first dose. Patients were followed up via telephone on day 8 ± 1 post first dose, and adverse events were closely monitored from the time of informed consent until the end of the follow-up period.

Outcome measures

The primary endpoint for both studies was the time-weighted SPID over the 24-h period ($SPID_{0-24\,h}$) for each treatment arm, a measure derived from the NRS pain score reported from 11 time points at baseline (postsurgery after randomization [time 0], 15, 30 min; and 1, 2, 4, 8, 12, 16, 20, and 24 h post loading dose). Time-weighted SPID is the cumulative sum of the product of the PID at each time point multiplied by the time difference (the time difference is the current time point minus the previous time point). The following formula is used to calculate SPID: $SPID_{0\text{-}t} = PID_{t1}*(t1 - 0) + PID_{t2}*(t2 - t1) + \ldots + PID_{tn}*(tn - tn\text{-}1)$; $SPID_{0\text{-}t}$ represents the time-weighted cumulative pain intensity difference of resting pain from the first postoperative medication to time point t, t is 12 and 24 h, PID_{tn} represents the pain intensity difference at rest at the nth time, and tn is the actual time of the NRS measurement of resting pain score, including unplanned time points. SPID is an accepted measurement for pain by the United States Food and Drug Administration and European Medicines Agency that combines both magnitude and duration of relief into a single score[58,59].

Secondary endpoints for HSK21542-301 included $SPID_{0-12\,h}$ (the time-weighted SPID at rest within 0–12 h after the first postoperative administration in each group), cumulative use of rescue analgesics (morphine) within 0–12 h or 0–24 h after the first postoperative administration in each group, percentage of subjects not using remedial analgesics, and start time of remedial analgesic use, and PID at rest at each scoring time point after the first postoperative administration in each group; proportion of patients with resting pain score NRS ≤3 at 12 or 24 h after the first postoperative administration in each group; duration of analgesia after the first postoperative administration in each group; and postoperative satisfaction with analgesia at 24 h, rated on a scale of 0–10, with 0 being dissatisfied and 10 being satisfied, by patients and investigators. Secondary endpoints for HSK21542-303 included time-weighted SPID at rest within 0–24 h after the first administration in the tramadol group and the placebo group, cumulative use of rescue analgesic medication (flurbiprofen axetil injection) within 0–12 or 0–24 h after the first administration, percentage of unused rescue analgesic medication, and time to initiation of rescue analgesic medication; $SPID_{0-12h}$; PID at rest at each scoring time point after the first administration; NRS score at each scoring time point after the first administration; proportion of subjects with resting pain score NRS ≤3 at 0–12 or 0–24 h after the first administration, duration of analgesia after the first administration within 24 h after the first postoperative administration, and postoperative satisfaction with analgesia at 24 h. PID is measured by subtracting the baseline NRS score from the pain intensity at the assessed time point.

Safety and tolerability for both studies were assessed through the occurrence of adverse events, physical examination, clinical laboratory tests, electrocardiogram, vital signs, and the use of antiemetic drugs within 24 h after the first postoperative analgesic administration throughout the treatment and 8-day follow-up period. TEAEs were defined as any adverse event that began or worsened in severity after the first dose of the study drug, and within 8 days after the last dose. The severity of adverse events was graded according to the Common Terminology Criteria for Adverse Events v5.0.

Plasma concentrations of HSK21542 were assessed between 30 s and 5 min after the completion of the first post-surgical dose administration, and between 5:00 AM and 9:00 AM on the morning following surgery in HSK21542-301. As for HSK21542-303, plasma concentrations of HSK21542 were assessed at four time points: between 30 s and 5 min after the completion of the second dose, 1 h ± 15 min after the second dose, 4 h ± 1 h after the second dose, and

within 1 h before the third dose. However, if the second dose is administered after 8:00 PM on the day of surgery, blood samples will be collected at four different time points relative to the third dose: between 30 s and 5 min after the completion of the third dose, 1 h ± 15 min after the third dose, 4 h ± 1 h after the third dose, and between 8 to 12 h after the third dose.

Statistical analysis

Categorical variables were expressed as a frequency (percentage), and logistic regression was used to assess the significant differences between groups. Continuous variables were expressed as mean ± SD and the Shapiro–Wilk test was used to test for normality. Analysis of covariance (ANCOVA) was used to assess the significant differences between groups in normally distributed continuous variables. For non-normally distributed continuous variables, values were presented as median (25th, 75th percentiles), and differences between groups were calculated using the Wilcoxon rank-sum test. $SPID_{0-12\,h}$ and $SPID_{0-24\,h}$ were analyzed by ANCOVA with group as fixed effects and baseline NRS score as the covariate.

Data for each study were analyzed independently. The efficacy analyses were conducted in the FAS based on the intent-to-treat population, which included all randomized patients who received at least one dose of treatment. A sensitivity analysis was performed in the PPS, which included all patients in the FAS with good compliance, complete data on primary efficacy endpoints, and no significant study protocol deviations. Safety endpoint analyses were based on the SS, which included all randomized patients who received at least one dose of treatment with data on safety evaluation. Subgroup analyses for the efficacy endpoints by baseline NRS score and age were conducted in HSK21542-303 to evaluate the therapeutic effect of HSK21542 in different populations. The PKS included all randomized subjects who have received at least one dose of the study drug with at least one measurable concentration, and who have also not experienced a protocol deviation affecting the pharmacokinetics data. All data were analyzed using SAS EG version 8.3 (SAS Institute, Cary, NC, USA) or later.

The sample size determination for HSK21542-301 was estimated based on the primary efficacy results of an earlier phase 2 study, where the mean (±SD) $SPID_{0-24\,h}$ difference between HSK21542 1.0 μg/kg and placebo was −17.97 (44.68). Enrolling 138 patients in each treatment arm was expected to provide 90% power to detect a difference in the primary endpoint, using a two-sided significance level of 0.05 and considering a 5% loss to follow-up. The sample size calculation for the HSK21542-303 study was based on assumptions of a mean difference (SD) of 2.68 (22.55) in $SPID_{0-24\,h}$ between the HSK21542 group and the tramadol group, with a non-inferiority boundary of 11.03; a sample size of 116 in each group would provide 80% power to detect a difference between the two groups at a two-sided significance level of 0.05. In addition, a sample size of 116 in each group would provide 98% power to detect a LS mean difference of −17.43 (SD 32.79) in $SPID_{0-24\,h}$ between the HSK21542 group and the placebo group at a two-sided significance level of 0.05; based on a previous study[60], assuming an effect size of 0.68 between the tramadol group and the placebo group, a sample size of 116 in each group would provide 99% power to detect the difference between these two groups at a two-sided significance level of 0.05. Assuming a 10% dropout rate, the planned sample size was 129 in each group.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The datasets used and/or analyzed during the current study are included in this article or as supplementary material. Due to ethical and legal concerns for patient privacy, individual participant data cannot be made public. Any de-identified patient-level data requests are available from the corresponding authors upon request and subjected to approval by the study management committee and data transfer agreements. A signed data access agreement with the sponsor is required before accessing shared data. Requests for data access will be processed within 4 weeks, and access will be granted for a month. The study protocol and statistical analysis plan are available in the Supplementary Information file. Source data are provided with this paper.

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Author contributions

Y.Z., Y.X., M.Yan., and X.C. contributed to the conception and design of the study. Y.Z., Y.X., Q.L., M.Yang, S.W., X.H., H.X., Y.L., Z.Q., Z.G., J.Z., Y.W., J.W., H.W., Y.M., Z.X., H.Z., K.J., P.Z., Z.W., L.W., L.L., Z.C., H.J., G.W., J.C., Z.Z., X.C., and M.Yan contributed to patient enrollment and were responsible for the acquisition and analysis of data. Y.Z., Y. X., M.Yan, and X.C. were involved in the analysis and data interpretation. Y.Z., Y.X., M.Yan., and X.C. wrote the first draft of the manuscript. All authors contributed to the manuscript revision, reviewed, and approved the final version for submission.

Competing interests

The authors declare no competing interests.

Additional information

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