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CLINICAL TRIAL REPORT

Generic Intravenous Amisulpride (QLG2069) for the Prevention of Postoperative Nausea and Vomiting in Adults: A Phase III, Multicenter, Randomized, Placebo-Controlled Study

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Background: The dopamine D2/D3 antagonist amisulpride has demonstrated its superiority and efficacy in prophylaxis of postoperative nausea and vomiting (PONV). Given the branded intravenous amisulpride (Barhemsys®) has not been approved in China, there is unmet clinical need for amisulpride. Our primary objective was to ascertain the efficacy and safety of the generic intravenous amisulpride (QLG2069) in the prophylaxis of PONV.

Methods: In this phase III, multicenter, randomized, double-blind, placebo-controlled study, 551 adult Chinese patients (with ≥2 Apfel risk factors for PONV) undergoing elective laparoscopic gynecological or abdominal surgery were randomly allocated in a 1:1 ratio to receive either generic intravenous amisulpride or placebo. The primary endpoint was the complete response (CR) rate, defined as the proportion of patients demonstrating neither emetic episodes (vomiting/retching) nor requiring rescue antiemetics throughout the 24-hour postoperative window.

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Results: Totally, 542 patients (amisulpride group: n=275; placebo group: n=267) were included in the full analysis set. Amisulpride demonstrated significantly higher CR rate compared to placebo (53.82% vs 40.07%; P=0.0011) within 24-h postoperative period. Patients treated with intravenous amisulpride exhibited significantly lower incidence of moderate-to-severe nausea (28.36% vs 37.08%; P=0.0266) and emesis (44.73% vs 57.30%; P=0.0030) compared to the incidence in the placebo group. The proportion of patients without nausea was numerically higher (45.09%) in the amisulpride group compared to that in the placebo group (37.45%), although the difference did not reach statistical significance (P=0.0685). No significant difference in the proportions of patients receiving rescue medication was noticed between the two groups (21.09% vs 28.09%; P=0.0569). The incidence of adverse events were comparable in two groups.

Conclusion: The generic intravenous amisulpride was safe and effective in prophylaxis of PONV in Chinese patients with moderate-to-high risk of PONV to were undergoing laparoscopic gynecological or abdominal surgery.

Keywords: generic intravenous amisulpride, postoperative nausea and vomiting, complete response

Introduction

Postoperative nausea and vomiting (PONV) is the most prevalent postoperative adverse event subsequent to laparoscopic surgery and anesthesia.[1,2] Currently, the incidence of PONV is estimated to be 30% in the general surgical population and predicted to 60%–80% in patients considered to be at high risk.[3,4] PONV is a distressing condition that can cause complications like gastrointestinal disturbances, electrolyte imbalances, elevated intracranial pressure, and aspiration pneumonia.[5–7] Moreover, it has the potential to extend the length of stay in the post-anesthesia care unit (PACU), trigger unplanned hospital admissions, and escalate healthcare expenditures.[8,9]

Until 2001, droperidol, a dopamine D2-antagonist, was extensively employed for the prophylaxis of PONV. However, following a boxed warning by the Food and Drug Administration (FDA) due to reported cases of torsade de pointes (TdP), a serious cardiac arrhythmia caused by QT interval prolongation, the utilization of droperidol underwent a substantial decline.[10] Furthermore, other dopamine antagonists, notably haloperidol, have also demonstrated the potential to prolong the QT interval. It is worth noting that the intravenous formulation of haloperidol for antiemetic use has not yet received approval from the FDA.[11]

Intravenous amisulpride, a highly selective dopamine D2/D3 receptor antagonist, has emerged as a valuable therapeutic option for PONV prophylaxis. Its distinct safety profile includes favorable QT interval characteristics, negligible extrapyramidal toxicity, and a low incidence of TdP.[12] In 2020, the intravenous formulation of amisulpride (Barhemsys®) received US FDA approval for the prophylaxis of PONV, marking a significant milestone nearly three decades after its oral counterpart firstly approved for acute and chronic schizophrenia management in the 1980s.[13] When administered as monotherapy prophylaxis (5 mg) or combined with antiemetics targeting distinct pathways, intravenous amisulpride demonstrates effective 24-hour postoperative PONV prevention in patients with moderate-to-high Apfel risk for PONV, with favorable safety and superior efficacy.[4,14–17] Furthermore, a single 10-mg dose of intravenous amisulpride served as an effective rescue therapy for breakthrough PONV following failed prophylaxis.[5] These evidence-based applications expand the therapeutic armamentarium for PONV prophylaxis and management in adult surgical populations.

Intravenous amisulpride (Barhemsys®) remains unapproved in China, creating an unmet clinical need for evidence-based PONV prophylaxis and management. Generic formulations, which demonstrate therapeutic equivalence to originator drugs while offering substantial cost-saving potential for healthcare systems,[18–20] require regulatory authorization contingent on pharmaceutical equivalence and bioequivalence to reference products.[21] Development of generic intravenous amisulpride represents a strategic approach to bridge this therapeutic gap. Qilu Pharmaceutical Co., Ltd (China) has advanced this initiative through successful development of generic intravenous amisulpride (QLG2069). Pharmaceutical quality analyses have confirmed consistency between the generic formulation and reference product (Barhemsys®) (unpublished data).

Aligning with the guidelines issued by FDA[22] and European Medicines Agency (EMA)[23], Center for Drug Evaluation (CDE) of China has granted a bioequivalence study waiver for healthy volunteers. Pursuant to CDE requirements (*Clinical Technical Requirements for Drugs Marketed Overseas but Not Marketed in China*), this Phase III trial was

designed to evaluate therapeutic equivalence in efficacy and safety between generic intravenous amisulpride (QLG2069) and the reference product for PONV prophylaxis.[24]

Material and Methods

Patient Eligibility

Patients were eligible if they were aged 18–75 years with body mass index values between 18–30 kg/m² and body weight exceeding 45 kg, male or female. Participants were required to possess at least two Apfel risk factors for PONV (female gender, nonsmoking status, prior history of PONV or motion sickness, and anticipated postoperative opioid administration).[9,25] Eligible surgical candidates included those scheduled for laparoscopic gynecological procedures or abdominal surgeries under general anesthesia (propofol was restricted to induction only, prohibited for maintenance of general anesthesia), utilizing inhalational agents (sevoflurane) for maintenance (minimum duration ≥1 hour). Participants needed to maintain American Society of Anesthesiologists (ASA) physical status classification I–III. Patients were excluded if they were scheduled for intrathoracic, transplant, or neurosurgical procedures where PONV might compromise patient safety. Additional exclusion criteria included: requirement for postoperative nasogastric/orogastric intubation, preexisting vestibular disorders or chronic dizziness, gastrointestinal/neurological pathologies predisposing to emesis, and recent (within 7 days preoperative) use of antiemetic medications or prophylactic antiemetic regimens. Complete eligibility specifications are detailed in Supplementary Table S1.

Study Design and Treatment

This was a phase III, multicenter, randomized, double-blind, placebo-controlled study (Clinicaltrials.gov identifier: NCT05822713, registration on April 9, 2023; ChinaDrugTrials.org.cn identifier: CTR20230868, registration on November 10, 2022) and was conducted at 42 clinical centers across China (Supplementary Table S2). This study was firstly approved by the Ethics Committee of the main site (No. 2022PHC037-002) followed by subsequent approvals from local ethics committees at all participating sites. The study was conducted in accordance with the international standards of good clinical practice and the principles of the Declaration of Helsinki. All enrolled participants provided written informed consent prior to study procedures.

Eligible patients were randomly allocated in a 1:1 ratio to receive either generic intravenous amisulpride (manufactured by Qilu Pharmaceutical Co., Ltd., China) or placebo. An independent statistician implemented computer-generated randomization through an Interactive Web Response System (IWRS; Almac Clinical Technologies, UK), with stratification based on PONV risk factor categories (2, 3, 4). Amisulpride (5 mg, Qilu Pharmaceutical Co., Ltd., China) or placebo (2 mL) was administered as a slow intravenous injection within 1 to 2 min during induction of anesthesia. Safety monitoring included standardized assessments at postoperative day 4 (±1 day), with supplementary telephone follow-up through day 7 when required.

Investigational products were formulated to be visually and physically identical, with matched organoleptic properties and indistinguishable primary packaging. In this double-blind trial, all participants and research staff remained blinded to treatment allocation, except for an independent unblinded statistician conducting prespecified interim analyses. Rescue antiemetics from a distinct pharmacological class could be administrated at the discretion of investigator based on the severity and patient clinical performance, or on patient request for any episode of vomiting or/and nausea.

Study Assessments and Endpoints

All emetic events (including vomiting and retching episodes), nausea occurrences, and rescue medication administrations were prospectively recorded by patients during the initial 24-hour postoperative phase. Vomiting was characterized by forceful expulsion of gastric contents through oral/nasal routes, while retching referred to nonproductive rhythmic contractions of abdominal musculature without gastric content expulsion.[6] Nausea was operationally defined as a self-reported aversive psychophysical experience associated with emetic urge but lacking expulsive motor components. Nausea severity was quantified using a validated 10-cm VAS with terminal anchors at 0 (no symptoms) and 10 (worst

imaginable symptoms). Moderate-to-severe nausea was prospectively defined as VAS scores ≥4, a threshold supported by previous pharmacokinetic-pharmacodynamic modeling.[26] The primary efficacy endpoint was the complete response (CR) rate, defined as the proportion of patients demonstrating neither emetic episodes (vomiting/retching) nor requiring rescue antiemetics throughout the 24-hour postoperative window. The secondary efficacy endpoints included the nausea-free rates, the incidence of moderate-to-severe nausea, emesis occurrence rates, rescue medication utilization rates, and the time-to-treatment failure, calculated from surgical wound closure to first emetic event or rescue medication administration, whichever occurred first.

Safety was evaluated by adverse events (AEs), serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs) with severity and potential relationship to study drugs. AE surveillance extended from investigational product administration through postoperative day 7 via structured telephone follow-up. AEs refer to any clinically detectable undesirable medical occurrence (including laboratory anomalies) temporally associated with, though not necessarily causally related to, the investigational product. All events were systematically coded using MedDRA (v26.0) with preferred terms and System Organ Class classifications. Standardized preoperative evaluations and postoperative reassessments included: vital sign measurements (blood pressure, heart rate, respiratory rate, temperature); physical examinations; Laboratory panels (complete blood count, comprehensive metabolic profile, urinalysis, prolactin quantification); 12-lead electrocardiography. Clinically significant abnormalities (classified as mild, moderate, or severe severity) were included in safety analyses.

Statistical Analysis

The sample size calculation was based on previous stduy demonstrating CR rates of 39% in placebo-controlled arms versus 52% in amisulpride-treated cohorts.[14] A superiority design required 490 participants to detect this 13% absolute difference with one-sided α=0.025 (aligned with ICH E9 guidance for superiority trials) and 80% power (β=0.20). To account for potential 5% attrition due to protocol deviations or loss to follow-up, the final enrollment target was increased to 516 subjects (258 per arm), ensuring adequate statistical power throughout the trial duration.

All randomized patients who have received ≥1 dose of the investigation product following the intention-to-treat (ITT) principle were included in full analysis set (FAS) and safety set (SS). The per-protocol set (PPS) comprised FAS subjects without major protocol violations affecting efficacy outcomes. Baseline demographics and clinical characteristics were summarized using appropriate descriptive statistics: continuous variables were expressed as median (interquartile range, IQR) or mean ± standard deviation (SD), based on distribution normality assessed by Shapiro–Wilk testing, while categorical variables were reported as frequencies (%). For the primary efficacy endpoint (CR rate), two-sided 95% confidence intervals (CIs) were calculated using the Clopper-Pearson exact method. Between-group comparisons employed stratified Cochran-Mantel-Haenszel (CMH) tests adjusted for PONV risk factor counts. Secondary binary endpoints were analyzed via Miettinen-Nurminen score methods with continuity correction. Time-to-treatment failure distributions were estimated using Kaplan-Meier methodology, with between-arm differences assessed through Log rank tests and corresponding hazard ratios derived from Cox proportional hazards models. Prespecified subgroup analyses for the primary efficacy endpoint were performed to explore potential differential estimated treatment effects in corresponding subgroups. All statistical procedures were executed in SAS 9.4 (SAS Institute Inc., Cary, NC), with two-tailed p-values <0.05 considered statistically significant unless otherwise specified for confirmatory endpoints.

The reporting of this trial strictly adheres to the CONSORT 2010 guidelines, with the completed checklist provided as supplementary material. Sensitivity analyses included both FAS and PPS population evaluations to confirm robustness of primary findings.

Result

Patient Disposition and Baseline Characteristics

From March 29, 2023, to August 31, 2023, 643 patients were screened, with 551 meeting inclusion criteria and undergoing 1:1 randomization to receive either amisulpride (N=277) or placebo (N=274). Nine randomized patients

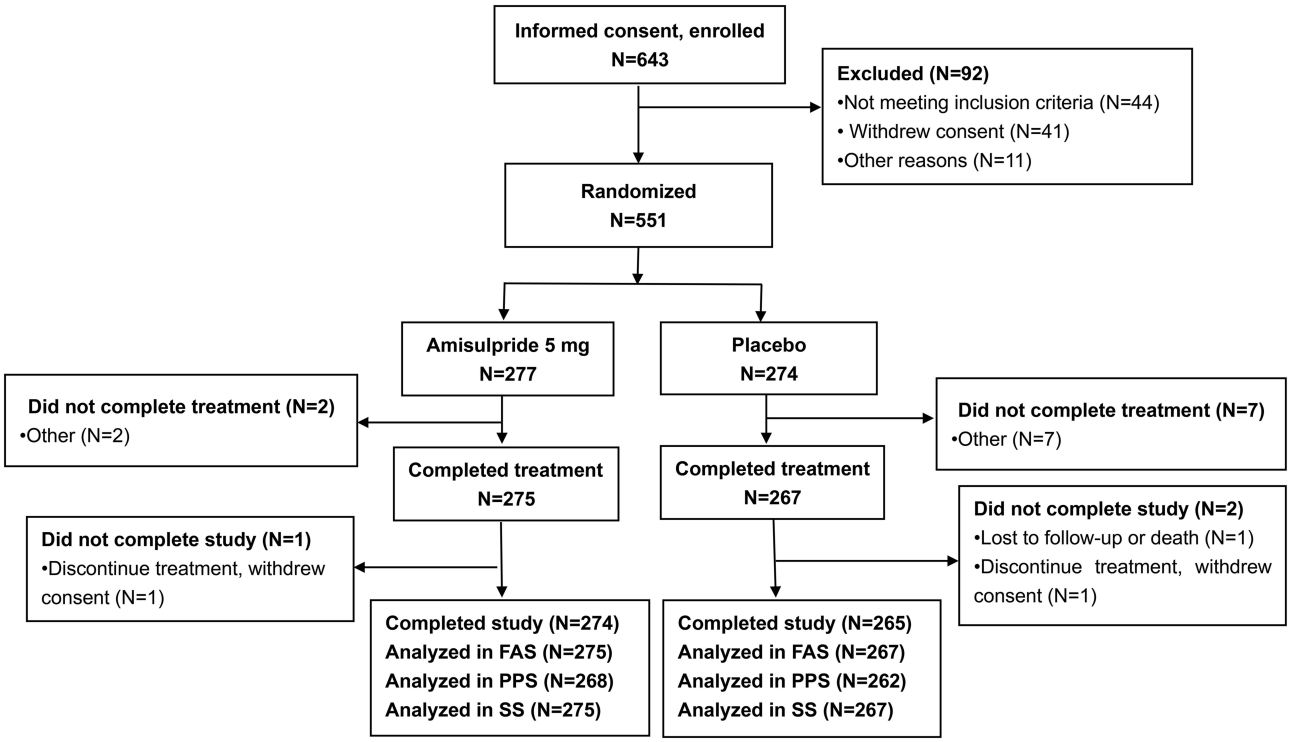

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) diagram of patient disposition.
Abbreviations: FAS, full analysis set; PPS, per-protocol set; SS, safety set.

withdrew prior to treatment initiation, resulting in 542 evaluable patients (amisulpride: N=275; placebo: N=267) included in the FAS. Of the patients in FAS, 12 patients were excluded for major protocol deviations, and a total of 530 patients were included in the PPS population (amisulpride group: N=268; placebo group: N=262). Patient disposition is shown in Figure 1. Baseline characteristics in the FAS populations were well balanced between the two groups, without notable clinical differences between groups (Table 1). The cohort comprised predominantly Chinese Han females (90%), with

Table 1 Baseline Demographic and Clinical Characteristics of Full Analysis Set (FAS) Populations

Characteristics	Amisulpride (N=275)	Placebo (N=267)
Age (y), median (range)	43.0 (19–67)	44.0 (20–71)
Sex, n (%)		
Male	18 (6.55)	17 (6.37)
Female	257 (93.45)	250 (93.63)
BMI (kg/m^2) median (range)	23.05 (18.14–29.94)	23.62 (18.37–29.97)
Ethnicity, n (%)		
Chinese-Han	247 (89.82)	238 (89.14)
Others	28 (10.18)	29 (10.86)
ASA status, n (%)		
Grade I	96 (34.91)	96 (35.96)
Grade II	176 (64.00)	170 (63.67)
Grade III	3 (1.09)	1 (0.37)
Baseline PONV risk, N (%)		
History of PONV/motion sickness	59 (21.45)	60 (22.47)
Nonsmoker	268 (97.45)	252 (94.38)
Expected postoperative opioid use, n (%)	217 (78.91)	215 (80.52)

(*Continued*)

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Table 1 (Continued).

Characteristics	Amisulpride (N=275)	Placebo (N=267)
No. PONV risk factors *, n (%)		
2 PONV risk factors	57 (20.73)	57 (21.35)
3 PONV risk factors	185 (67.27)	177 (66.29)
4 PONV risk factors	33 (12.00)	33 (12.36)
Surgical procedure classification, n (%)		
Gynecological	234 (85.09)	224 (83.90)
Abdominal	41 (14.91)	43 (16.10)
Surgical technique		
Laparoscopic, n (%)	274 (99.64)	266 (99.63)
Open, n (%)	1 (0.36)	1 (0.37)
Duration of surgery (min), mean ± SD	102.766±47.251	104.987±51.131
Duration of inhalational anesthesia (min), mean ± SD	112.391±47.165	116.020±51.361

Notes: *PONV risk factors are (i) female, (ii) nonsmoker, (iii) history of PONV or motion sickness, and (iv) expected postoperative opioid use.
Abbreviations: BMI, Body mass index; PONV, postoperative nausea and vomiting; ASA, American Society of Anesthesiologists.

median age of 43 years (IQR 35–52) in the amisulpride group versus 44 years (IQR 36–53) in placebo recipients. Notably, 60% of participants exhibited ≥3 established PONV risk factors. Surgical characteristics revealed 80% undergoing gynecological procedures, and nearly all had laparoscopic procedures. No clinically meaningful between-group differences (>10% absolute difference) were observed in any predefined baseline variable.

Primary Efficacy Endpoint

In FAS population, amisulpride demonstrated significantly higher CR rate compared to placebo (53.82% [95% CI 47.73–59.82] vs 40.07% [95% CI 34.15–46.22]; risk difference 13.91% [95% CI 5.64–22.17], P=0.0011) within 24-h postoperative period (Table 2). The PPS analysis corroborated these findings. CR was achieved by 53.36% [95% CI 47.19–59.45] in the amisulpride group versus 40.46% [95% CI 34.46–46.67] in placebo group (risk difference 13.14% [95% CI 4.79–21.50], P=0.0023) within 24-h postoperative period in the PPS population (Supplementary Table S3). Furthermore, the superiority of amisulpride over placebo was evident across subgroups. These subgroups exhibited therapeutic effect consistent with the main analysis (Figure 2 and Supplementary Figure S1).

Table 2 Efficacy Results in 24-h Postoperative Period in Full Analysis Set (FAS) Populations

	Amisulpride (N=275)	Placebo (N=267)	Risk Difference (95% CI)	P-value
Total CR, n (%), 95% CI	148 (53.82), 47.73–59.82	107 (40.07), 34.15–46.22	13.91 (5.64–22.17)	0.0011
Subgroup CR, n/N* (%), 95% CI				
2 PONV risk factors	36/57 (63.16), 49.34–75.55	28/57 (45.90), 33.06–59.15	17.26 (−0.81–34.20)	0.0601
3 PONV risk factors	99/185 (53.80), 46.32–61.17	69/177 (39.88), 32.53–47.59	13.92 (3.55–23.98)	0.0085
4 PONV risk factors	13/33 (38.24), 22.17–56.44	10/33 (30.30), 15.59–48.71	7.93 (−14.90–29.95)	0.4942
Nausea-free, n (%), 95% CI	124 (45.09), 39.11–51.18	100 (37.45), 31.63–43.56	7.70 (−0.54–15.95)	0.0685
Moderate-to-severe nausea, n (%), 95% CI	78 (28.36), 23.11–34.09	99 (37.08), 31.27–43.18	−8.92 (−16.75–-1.08)	0.0266
Emesis, n (%), 95% CI	123 (44.73), 38.75–50.82	153 (57.30), 51.13–63.31	−12.71 (−21.03–-4.40)	0.0030
Rescue medication utilization, n (%), 95% CI	58 (21.09), 16.42–26.39	75 (28.09), 22.78–33.89	−7.04 (−14.29–0.21)	0.0569
Time-to-treatment-failure (h), median (95% CI)	2.00 (1.72–2.50)	1.73 (1.42–2.00)	0.83# (0.66–1.06)	0.1362

Notes: *Number of patients in each subgroup. #Hazard ratio = amisulpride group/placebo group.
Abbreviations: CR, complete response; CI, confidence interval; PONV, postoperative nausea and vomiting.

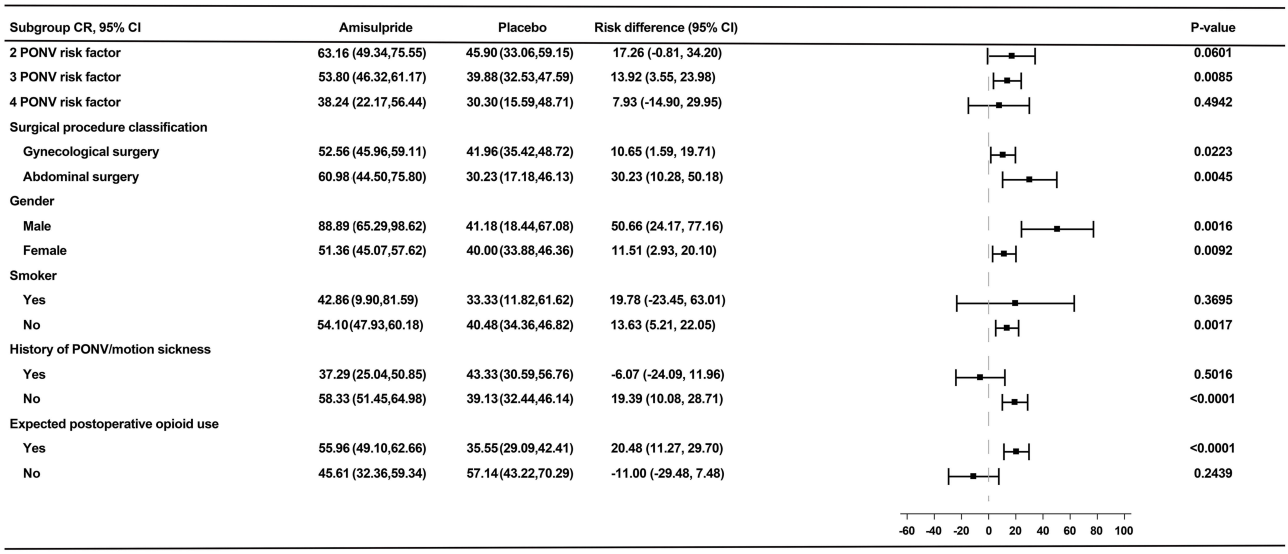

Figure 2 Forest plot of subgroup analysis in full analysis set (FAS) populations.
Abbreviations: CI, confidence interval; PONV, postoperative nausea and vomiting.

Secondary Efficacy Endpoints

In FAS population, 45.09% (124/275; 95% CI 39.11–51.18) patients in the amisulpride group remained nausea-free during the 24-hour postoperative period, compared with 37.45% (100/267; 95% CI 31.63–43.56) in the placebo group (risk difference 7.70% [95% CI −0.54–15.95], P=0.0685). The incidence of moderate-to-severe nausea was significantly reduced in the amisulpride-treated group compared to the incidence in placebo group (28.36% [95% CI 23.11–34.09] vs 37.08% [95% CI 31.27–43.18]; risk difference −8.92% [95% CI −16.75–-1.08], *P*=0.0266; Table 2). Postoperative emesis episodes within 24 hours occurred less frequently in amisulpride group than the placebo group (44.73% [95% CI 38.75–50.82] vs 57.30% [95% CI 51.13–63.31]; risk difference 12.71% [95% CI: −21.03–-4.40]; P=0.0030). No significant differences in the proportion of patients who received rescue medication were detected between the two groups (21.09% [95% CI: 16.42–26.39] vs 28.09% [95% CI: 22.78–33.89]; risk difference −7.04% [95% CI: −14.29–0.21]; P=0.0569). Kaplan-Meier estimates revealed prolonged time-to-treatment failure with amisulpride (median 2.00 h vs 1.73 h; hazard ratio (HR): 0.83 [95% CI 0.66–1.06], P=0.1362). Early separation of Kaplan-Meier curves occurred within the first postoperative hour (log-rank P=0.012 at 1 h), with sustained divergence persisting through 17 hours (Figure 3). Sensitivity analyses in the PPS population confirmed these temporal patterns (Supplementary Table S3 and Supplementary Figure S2).

Safety

TEAEs are systematically summarized in Table 3. Most TEAEs were of mild to moderate severity during the study. The number of TEAEs were 227 in 82.55% of patients in the amisulpride group versus 214 in 80.15% of patients in the placebo group. Comparable incidence rates were observed for clinically important AEs (53.82% [148/275] vs 53.56% [143/267]) and drug-related important AEs (16.00% [44/275] vs 14.43% [38/267]) between groups. The safety profiles were similar in treatment-related AEs (TRAEs) with incidence ≥1%, except for hyperprolactinemia which demonstrated a notably higher incidence with amisulpride (16.73% [46/275] vs 11.24% [30/267]). Among the TEAEs (incidence ≥5%), the elevated blood prolactin, anemia and abdominal distension were more prevalent in the amisulpride group. A single amisulpride recipient discontinued due to procedural pain, which was deemed as not

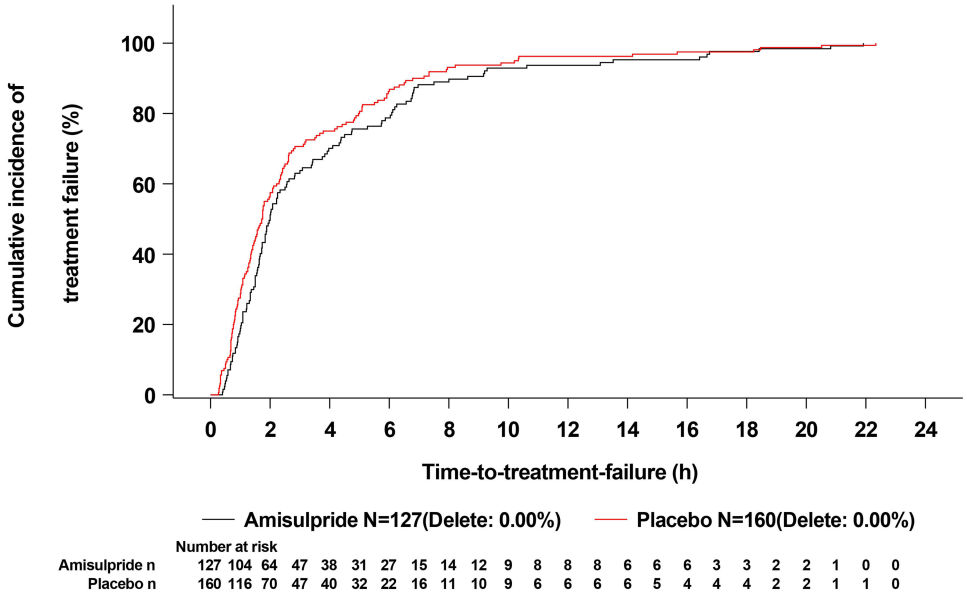

Figure 3 Kaplan-Meier curves of time-to-treatment failure in full analysis set (FAS) populations.

related to amisulpride treatment. Five serious adverse events (1.87%) occurred exclusively in the placebo group, including postoperative hemorrhage (n=2) and intestinal obstruction (n=3). No treatment-related discontinuations or death occurred during the study period.

Table 3 Summary of Treatment-Emergent Adverse Events

	Amisulpride (N=275)	**Placebo (N=267)**
All AE [n (%)]	227 (82.55)	214 (80.15)
At least one TEAE [n (%)]	227 (82.55)	214 (80.15)
Mild TEAE	126 (45.82)	103 (38.58)
Moderate TEAE	96 (34.91)	107 (40.07)
Severe TEAE	5 (1.82)	4 (1.50)
TRAEs [n (%)]	119 (43.27)	95 (35.58)
SAE [n (%)]	0	5 (1.87)
Drug-related SAE [n (%)]	0	1 (0.37)
Important AE [n (%)]	148 (53.82)	143 (53.56)
Drug-related important AE [n (%)]	44 (16.00)	38 (14.43)
AE resulted in study withdrawal [n (%)]	1 (0.36)	0
AE led to concomitant treatment [n (%)]	148 (53.82)	143 (53.56)
Drug-related AE led to concomitant treatment [n (%)]	44 (16.00)	38 (14.23)
TEAEs occurring in ≥5% of either group [n (%)]		
Procedural pain	50 (18.18)	47 (17.60)
Blood prolactin increased	47 (17.09)	32 (11.99)
Anemia	46 (16.73)	33 (12.36)
Hypotension	26 (9.45)	23 (8.61)
Hypokalemia	24 (8.73)	20 (7.49)
Incision site	21 (7.46)	23 (8.61)
Heart rate decreased	19 (6.91)	21 (7.87)

(*Continued*)

Table 3 (Continued).

	Amisulpride (N=275)	Placebo (N=267)
QT interval prolongation	19 (6.91)	16 (5.99)
Abdominal distension	18 (6.55)	10 (3.75)
Hypertension	17 (6.18)	10 (3.75)
Wound complication	16 (5.82)	18 (6.74)
Pyrexia	14 (5.09)	17 (6.37)
Procedural hypotension	10 (3.64)	16 (5.99)

Abbreviations: AE, adverse event; SAE, serious adverse event, TEAE, treatment emergent adverse event; TRAEs, treatment-related adverse events; SOC, System Organ Classes; PT, Preferred Term.

Discussion

This phase III, multicenter, randomized, double-blind, placebo-controlled study met its primary endpoint, demonstrating the superiority of generic intravenous amisulpride (QLG2069) 5 mg over placebo for PONV prophylaxis in Chinese patients with ≥2 Apfel risk factors undergoing laparoscopic gynecologic/abdominal surgery. The generic intravenous amisulpride significantly improved CR rate, reduced the incidence of moderate-to-severe nausea and vomiting, and doubled nausea-free proportions compared to placebo. Consistent therapeutic effects were maintained across all PONV risk strata. Safety analyses revealed comparable profiles of generic intravenous amisulpride (QLG2069) to the reference product (Barhemsys®) in prior study. No unexpected safety signals emerged. Notably, some patients still experienced PONV even after receiving intravenous amisulpride, thereby necessitating recourse to rescue antiemetics. This underscores the probable imperative for multimodal prophylaxis in higher-risk patients, which aligns with current international guidelines.[4] Overall, we believe these findings can inform global strategies for PONV prevention and management, particularly in resource-limited settings.

The trial design incorporated rigorous patient protection measures: exclusion of high-risk surgical candidates and protocol-mandated rescue antiemetic. In this study, the observed 59.93% PONV incidence in our placebo cohort demonstrated remarkable concordance with historical controls in moderate-to-high risk populations, confirming appropriate risk stratification and protocol adherence.[15] This methodological consistency was further evidenced by the CR rate achieved with generic amisulpride, which was comparable to that observed with branded amisulpride in prior study.[15,16] In the FAS, the 13.91% absolute CR improvement over placebo within the 24-h postoperative period not only replicates the therapeutic window of reference amisulpride (10–13%) but also surpasses serotonin antagonists in similar risk cohorts: versus ondansetron 4 mg (44.1%) and ramosetron 0.3 mg (52.9%).[15,16,27] Consistent with Apfel's risk model (baseline risk: +20% per factor; prophylaxis effect: 20–25% reduction per agent),[4,28] amisulpride demonstrated dose-response-appropriate efficacy. The incidence of PONV in the amisulpride group was 46.2% among patients with three Apfel risk factors and 61.76% among those with four.[2,16] Furthermore, sensitive analysis found consistent efficacy in PPS population. This population-level consistency substantiates the generalizability of findings beyond the trial setting.

Prior research has demonstrated the superior efficacy of dopamine D2 receptor antagonists in managing nausea compared to vomiting control.[11] Our study substantiated this observation, revealing a significantly lower incidence of moderate-to-severe nausea (28.36%) versus vomiting (44.73%). Notably, postoperative nausea emerges as the primary determinant of prolonged hospitalization, serving both as the strongest predictor of delayed discharge and the leading contributor to unplanned readmissions.[3,29]

Secondary endpoint analysis established amisulpride's clinical superiority over placebo, evidenced by its significant reduction in moderate-to-severe nausea/vomiting episodes during the initial 24 hours following surgery. While statistical significance was not achieved in rescue medication utilization or time-to-treatment failure metrics, a persistent positive trend favoring amisulpride was observed across these parameters. Pharmacodynamic characteristics were further elucidated through Kaplan-Meier analysis, where marked divergence of survival curves indicates rapid therapeutic onset with intravenous amisulpride. This kinetic profile holds critical clinical relevance: timely resolution of emetic

symptoms facilitates accelerated postoperative recovery, enabling earlier patient mobilization and discharge readiness from high-acuity PACU. Such optimized recovery trajectories simultaneously enhance patient outcomes and institutional resource allocation efficiency.[5,30]

Phase III clinical trials have previously established the favorable tolerability profile of intravenous amisulpride for PONV prophylaxis in adult populations.[15,16] Our findings corroborate this safety profile, demonstrating non-inferiority to placebo in QT interval prolongation incidence (6.91% vs 5.99%), a critical advantage over conventional dopamine antagonists with known cardiac risks.[11] The most prevalent TEAEs associated with amisulpride administration included nausea, procedural pain, and abdominal distension, consistent with established pharmacovigilance data.[5,15,16,31] Consistent with the known endocrine effects of dopamine receptor antagonists, amisulpride therapy induced serum prolactin elevation.[7] However, this biochemical alteration showed no clinical correlation with hyperprolactinemia-related complications, particularly in the context of a single-dose treatment in this study. This was primarily because the increase in prolactin levels was minimal, remaining within the normal range for nonpregnant females after treatment, and did not result in any clinical sequelae. Comparative analysis revealed numerically higher incidence rates of serum prolactin elevation, anemia, and abdominal distension in the amisulpride group versus placebo. Notably, while the observed frequency of serum prolactin elevation exceeded historical data from PONV prevention studies, the between-group risk differential remained comparable (5.1% vs 6.9%) to previous reports.[15]

There were some limitations that we should be aware. Firstly, one evident limitation is the female-predominated cohort (typical in PONV research due to gender-specific risk profiles), limits generalizability to male patients, though clinical relevance is attenuated by males' inherently lower PONV susceptibility. Secondly, exclusion of patients who underwent other types of surgeries, such as thoracic, urological, and neurosurgical surgeries, restricts extrapolation of findings to these specialized surgical contexts. Thirdly, while the monotherapy design was methodologically essential for evaluating the equivalence in PONV prophylaxis and safety, this approach raises ethical considerations by potentially withholding guideline-recommended combination prophylaxis for surgical populations with ≥2 Apfel risk factors for PONV.

Conclusion

In summary, the generic intravenous amisulpride (QLG2069) demonstrated efficacy and safety for PONV prophylaxis in Chinese surgical populations with moderate-to-high (≥2) Apfel risk factors for PONV. While supporting its first-line application, this confirmative phase III provides evidence for the approval of the generic intravenous amisulpride for PONV prophylaxis and a new option for PONV prophylaxis for Chinese patients.

Data Sharing Statement

The original contributions presented in the study are included in the article/Supplementary Materials, further inquiries can be directed to the corresponding authors by Email fengyi@pkuph.edu.cn.

Ethics Approval and Informed Consent

This study was firstly approved by the Ethics Committee of the main site (No. 2022PHC037-002) followed by subsequent approvals from local ethics committees at all participating sites (Supplementary Table S2). The study was conducted in accordance with the international standards of good clinical practice and the principles of the Declaration of Helsinki. All enrolled participants provided written informed consent prior to study procedures.

Consent for Publication

The subjects gave written informed consent for the publication of any associated data and accompanying images.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Wen Ouyang and Yi Feng equally contributed to this paper and thus shared the co-corresponding authorship.

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Disclosure

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References

1. Klenke S, Frey UH. Genetic variability in postoperative nausea and vomiting: a systematic review. *Eur J Anaesthesiol*. 2020;37(11):959–968. doi:10.1097/EJA.0000000000001224
2. Kumar A, Singh A, Brashier D, Karan A, Sharma S, Pratap U. Amisulpride: tackling postoperative nausea and vomiting not a nightmare any more. *Int J Basic Clin Pharmacol*. 2020;9(7):1167. doi:10.18203/2319-2003.ijbcp20202552
3. Corcoran TB, Martin C, O'Loughlin E, et al. Dexamethasone and clinically significant postoperative nausea and vomiting: a prespecified substudy of the randomised perioperative administration of dexamethasone and infection (PADDI) trial. *Br J Anaesth*. 2022;129(3):327–335. doi:10.1016/j.bja.2022.05.018
4. Gan TJ, Belani KG, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. *Anesthesia Analgesia*. 2020;131(2):411–448. doi:10.1213/ane.0000000000004833
5. Habib AS, Kranke P, Bergese SD, et al. Amisulpride for the rescue treatment of postoperative nausea or vomiting in patients failing prophylaxis: a randomized, Placebo-controlled phase III trial. *Anesthesiology*. 2019;130(2):203–212. doi:10.1097/ALN.0000000000002509
6. Yan S, Xu M, Zou X, et al. Acupuncture combined with ondansetron for prevention of postoperative nausea and vomiting in high-risk patients undergoing laparoscopic gynaecological surgery: a randomised controlled trial. *United Eur Gastroenterol J*. 2023;11(6):564–575. doi:10.1002/ueg2.12421
7. Hu C, Ou X, Teng Y, et al. Sedation effects produced by a ciprofol initial infusion or bolus dose followed by continuous maintenance infusion in healthy subjects: a phase 1 trial. *Adv Ther*. 2021;38(11):5484–5500. doi:10.1007/s12325-021-01914-4
8. Kovac AL. Update on the management of postoperative nausea and vomiting. *Drugs*. 2013;73(14):1525–1547. doi:10.1007/s40265-013-0110-7
9. Stoops S, Kovac A. New insights into the pathophysiology and risk factors for PONV. *Best Pract Res Clin Anaesthesiol*. 2020;34(4):667–679. doi:10.1016/j.bpa.2020.06.001
10. McKeage K, Simpson D, Wagstaff AJ. Intravenous droperidol: a review of its use in the management of postoperative nausea and vomiting. *Drugs*. 2006;66(16):2123–2147. doi:10.2165/00003495-200666160-00009
11. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2014;118(1):85–113. doi:10.1213/ANE.0000000000000002
12. Fox GM, Albayaty M, Walker JL, Xue H, Darpo B. Intravenous amisulpride does not meaningfully prolong the QTc interval at doses effective for the management of postoperative nausea and vomiting. *Anesthesia Analgesia*. 2021;132(1):150–159. doi:10.1213/ANE.0000000000004538
13. Coukell AJ, Spencer CM, Benfield P. Amisulpride: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of schizophrenia. *CNS Drugs*. 1996;6:237–256. doi:10.2165/00023210-199606030-00006
14. Kranke P, Eberhart L, Motsch J, et al. I.V. APD421 (amisulpride) prevents postoperative nausea and vomiting: a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Anaesth*. 2013;111(6):938–945. doi:10.1093/bja/aet251
15. Gan TJ, Kranke P, Minkowitz HS, et al. Intravenous amisulpride for the prevention of postoperative nausea and vomiting: two concurrent, randomized, double-blind, Placebo-controlled Trials. *Anesthesiology*. 2017;126(2):268–275. doi:10.1097/ALN.0000000000001458
16. Kranke P, Bergese SD, Minkowitz HS, et al. Amisulpride prevents postoperative nausea and vomiting in patients at high risk: a randomized, double-blind, Placebo-controlled Trial. *Anesthesiology*. 2018;128(6):1099–1106. doi:10.1097/ALN.0000000000002133
17. Kang C, Shirley M. Amisulpride: a review in post-operative nausea and vomiting. *Drugs*. 2021;81(3):367–375. doi:10.1007/s40265-020-01462-1
18. Haas JS, Phillips KA, Gerstenberger EP, Seger AC. Potential savings from substituting generic drugs for brand-name drugs: medical expenditure panel survey, 1997–2000. *Ann Intern Med*. 2005;142(11):891–897. doi:10.7326/0003-4819-142-11-200506070-00006
19. Kesselheim AS, Avorn J, Sarpatwari A. The high cost of prescription drugs in the United States: origins and prospects for reform. *JAMA*. 2016;316(8):858–871. doi:10.1001/jama.2016.11237
20. Gagne JJ, Choudhry NK, Kesselheim AS, et al. Comparative effectiveness of generic and brand-name statins on patient outcomes: a cohort study. *Ann Intern Med*. 2014;161(6):400–407. doi:10.7326/M13-2942
21. Desai RJ, Sarpatwari A, Dejene S, et al. Differences in rates of switchbacks after switching from branded to authorized generic and branded to generic drug products: cohort study. *BMJ*. 2018;361:k1180. doi:10.1136/bmj.k1180

22. Food and Drug Administration, Department of Health and Human Services. Code of Federal Regulations. Sec 320.22 (b)(1). Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-320/subpart-B/section-320.22. Accessed August 18, 2025.
23. European Medicines Agency. Guideline on the investigation of bioequivalence. *Committee for Medicinal Products for Human Use (CHMP)*. 2010:106–133.
24. Clinical technical requirements for drugs marketed overseas but not marketed in China. Available from: https://www.nmpa.gov.cn/xxgk/ggtg/ypggtg/ypqtggtg/20201016145016178.html. Accessed August 18, 2025.
25. Pierre S, Benais H, Pouymayou J. Apfel's simplified score may favourably predict the risk of postoperative nausea and vomiting. *Can J Anesthesia*. 2002;49(3):237–242. doi:10.1007/BF03020521
26. Boogaerts JG, Vanacker E, Seidel L, Albert A, Bardiau FM. Assessment of postoperative nausea using a visual analogue scale. *Acta Anaesthesiol Scand*. 2000;44(4):470–474. doi:10.1034/j.1399-6576.2000.440420.x
27. Choi YS, Sohn HM, Do SH, Min KT, Woo JH, Baik HJ. Comparison of ramosetron and ondansetron for the treatment of established postoperative nausea and vomiting after laparoscopic surgery: a prospective, randomized, double-blinded multicenter trial. *Ther Clin Risk Manag*. 2018;14:601–606. doi:10.2147/TCRM.S159211
28. Apfel CC, Korttila K, Abdalla M, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med*. 2004;350(24):2441–2451. doi:10.1056/NEJMoa032196
29. Green G, Jonsson L. Nausea: the most important factor determining length of stay after ambulatory anaesthesia. A comparative study of isoflurane and/or propofol techniques. *Acta anaesthesiologica scandinavica*. 1993;37(8):742–746. doi:10.1111/j.1399-6576.1993.tb03801.x
30. Habib AS, Chen YT, Taguchi A, Hu XH, Gan TJ. Postoperative nausea and vomiting following inpatient surgeries in a teaching hospital: a retrospective database analysis. *Curr Med Res Opin*. 2006;22(6):1093–1099. doi:10.1185/030079906X104830
31. Candiotti KA, Kranke P, Bergese SD, et al. Randomized, double-blind, Placebo-Controlled Study of intravenous amisulpride as treatment of established postoperative nausea and vomiting in patients who have had no prior prophylaxis. *Anesth Analg*. 2019;128(6):1098–1105. doi:10.1213/ANE.0000000000003733