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ORIGINAL RESEARCH

A Phase I Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of QP002 for the Treatment of Post-Operative Pain After Tension-Free Repair of Open Unilateral Inguinal Hernia

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Background: QP002 Long-acting local anaesthetic with bupivacaine and low-dose meloxicam as active ingredients for postoperative regional analgesia. The objective of the present study was to evaluate the safety, tolerability, and pharmacokinetics (PK) and pharmacodynamics (PD) of QP002 for postoperative analgesia following tension-free repair of an open unilateral inguinal hernia.

Methods: This was a multicentre, randomised, double-blind, positive-controlled trial. Patients were randomly assigned to receive a single injection of QP002 (five dose groups) with 0.25% bupivacaine hydrochloride 75 mg after open unilateral tension-free repair of an inguinal hernia. Pharmacokinetic parameters were evaluated by obtaining pharmacokinetic characteristic blood samples before and 120 hours after administration, at a total of 20 sampling points. Adverse events occurring after treatment were recorded from baseline to postoperative day 27 follow-up.

Results: A total of 40 patients with unilateral inguinal hernia were included in this study. In comparison to 0.25% bupivacaine hydrochloride 75 mg, the results demonstrate that QP002 was well tolerated, with no additional adverse events (AEs) observed and no instances of serious adverse events (SAEs). QP002 demonstrated prolonged absorption and clearance of bupivacaine, including a longer time to reach peak plasma concentration and a terminal elimination half-life. The peak plasma concentrations of 240 mg/7.2 mg QP002 (C_{max} 250.33 ng/mL) were similar to those of 0.25% bupivacaine hydrochloride 75 mg (C_{max} 258.40 ng/mL). Cumulative pain intensity scores at 24 hours postoperatively in the exercise state (NRS-A-$AUC_{0\text{-}24}$) were lower in the QP002 dose groups than in the 0.25% bupivacaine hydrochloride 75 mg, with P = 0.0165 in the 320 mg/9.6 mg QP002 and P = 0.0435 in the 400 mg/12 mg QP002.

Conclusion: QP002 demonstrated favorable safety profiles and exhibited distinct extended-release pharmacokinetic (PK) characteristics in single-ascending-dose administration. High doses of QP002 showed potential for postoperative incisional infiltration to control pain. Future studies will further explore its efficacy and safety in broader clinical applications.

Keywords: QP002, phase I trial, pharmacokinetic, safety

Introduction

Acute postoperative pain has always been a significant problem in postoperative patient recovery. Despite the combined application of analgesic drugs with different mechanisms of action and a variety of analgesic methods, up to 46% of

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patients in the Chinese population still experience inadequate postoperative analgesia.[1] Opioids remain the mainstay of treatment for postoperative pain.[2] However, given the potential risks of respiratory depression, addiction, and tolerance associated with opioids,[3–5] multimodal combined analgesia is often used in clinical practice to reduce the incidence of these side effects.[6] Incisional infiltration analgesia, a component of multimodal analgesia, has been shown to reduce the use of postoperative opioids and to provide a significant analgesic effect.[7] However, the duration of analgesia resulting from a single injection of conventional local anaesthetics is limited to 8 to 12 hours, falling short of the prolonged analgesia (72 hours) required for postoperative pain management.[8] This underscores the critical need for the development of novel local anaesthetics to address these limitations and enhance the efficacy of acute postoperative pain management.

QP002 is a slow-release formulation comprising bupivacaine and low-dose meloxicam as active ingredients. Bupivacaine functions as a slow-release incisional analgesic, while meloxicam exerts an incisional anti-inflammatory effect through selective inhibition of cyclooxygenase-2 (COX-2) to maintain normal pH at the incision.[9] It has been demonstrated that the efficacy of incisional infiltration analgesia is diminished by a decrease in pH at the incision, and that maintenance of normal pH at the incision during incisional infiltration of local anaesthetics has the effect of improving the analgesic effect of local anaesthetics.[10,11] In practice, QP002 is applied to the incision to administer the drug, thus avoiding the adverse events of local anaesthetic drugs mistakenly entering the blood vessels. It should be noted that the safety and pharmacokinetic characteristics of QP002 in humans have not yet been studied. A multicentre, randomised, double-blind, positive-controlled, dose-escalation study was conducted on QP002 to preliminarily explore the safety and pharmacokinetics of QP002.

Methods

This multicentre, randomised, double-blind, positive-controlled, dose-escalation study had been conducted in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and local laws and regulations. The study had been approved by the Drug (Device) Trial Ethics Committee of the Sichuan Academy of Medical Sciences and the Sichuan Provincial People's Hospital (approval number: Lunshen (Drug) Zi 2022 No. 39–1). It had undergone dual registration at chinadrugtrials.org.cn (CTR20222587) and www.chictr.org.cn (ChiCTR2300075673). Prior to participation in the study, written informed consent had been obtained from all subjects.

A total of 40 subjects had been enrolled in this trial, with 5 dose groups, each comprising 8 subjects. Study subjects had been recruited from 20 October 2022 (when the first subject was enrolled) to 10 July 2023 (when the last subject was withdrawn from the group). Subjects in each dose group had received QP002 and 0.25% bupivacaine hydrochloride injection 75 mg in a 3:1 ratio, where the doses of QP002 (bupivacaine mg/meloxicam mg) were 80 mg/2.4 mg, 160 mg/4.8 mg, 240 mg/7.2 mg, 320 mg/9.6 mg, and 400 mg/12 mg.

Subjects

The study subjects, who had undergone an open, tension-free repair of unilateral inguinal hernia under general anaesthetic, comprised males with a body mass index (BMI) greater than 50 kg/m² and non-pregnant/lactating females with a BMI between 18.0 and 30 kg/m², aged between 18 and 75 years inclusive, with an American Society of Anaesthesiologists (ASA) classification of I–II.

Exclusion criteria: (1) those with a history of allergy or contraindication to amide local anaesthetics, non-steroidal anti-inflammatory drugs (NSAIDs), or any of the excipients of QP002; (2) those at high risk of bleeding or with a history of significant bleeding; (3) those undergoing other concomitant surgical procedures (eg bilateral inguinal hernia repair). (4) A history of comorbid severe systemic disease or a history of malignancy with known widespread metastases; (5) A history of substance abuse or smoking (>5 cigarettes/day within 3 months prior to randomisation), or a history of alcohol consumption (>14 units of alcohol per week within 3 months prior to) (6) Individuals who have used drugs with analgesic effects (within five half-lives prior to randomisation) or have participated in any clinical trial of medication or medical devices within one month prior to randomisation. (7) Other conditions deemed by the investigator to be unsuitable for participation in this trial.

The complete inclusion and exclusion criteria had been provided in Appendix S1.

Study and Reference Drugs

QP002, an oleogel formed by castor oil as a slow-release carrier, was canned in a pre-filled syringe (1 mL: bupivacaine 80 mg with meloxicam 2.4 mg), purchased from Nanjing Delova Biotech Co., Ltd. (Delova Biotech). No configuration was necessary for the treatment group, which was instilled directly into the incision. Bupivacaine hydrochloride injection, 37.5 mg/vial (0.75%, 5 mL), was procured from Shanghai Chaohui Pharmaceutical Co. Two 5 mL vials of 0.75% bupivacaine hydrochloride injection were combined with saline to create a 30 mL solution of 0.25% bupivacaine hydrochloride, which was then administered locally via syringe in the positive control group.

Study Procedure

This Phase I, once-dosed, dose-escalation study consists of four periods designed to study the safety, tolerability, and PK and PD of QP002 injection in open unilateral tension-free inguinal hernia repair. The study had comprised four periods: screening (days −7 to −1), preparation (days −1 to 1), treatment (days 1 to 6), and follow-up (days 7 to 27). The subjects had been divided into two groups: those with a straight hernia and those with an indirect inguinal hernia. A total of 40 subjects had been randomly assigned to either the QP002 treatment group (n = 6) or the bupivacaine hydrochloride control group (n = 2) in five dose groups (in ascending order of dose) of 8 subjects each. The next dose group trial had been conducted only after completion of a safety assessment in the previous group. Subjects had been assigned sequential random numbers in the order of enrolment via the interactive web response randomization system and had received medication according to the drug number assigned by the system. To ensure impartiality, independent evaluation investigators, sponsors, and subjects had been blinded. As QP002 and bupivacaine hydrochloride were distinguishable based on their appearance, investigators performing drug infiltration were not included in the protocol-specific post-operative outcome assessment.

Propofol and remifentanil had been utilized for the induction and maintenance of general anesthesia throughout the surgical procedure. Intravenous anesthesia or combined anesthesia by sedation and inhalation had been employed during the anesthetic period. However, it had been inadvisable to combine this method with other anesthesia modalities (eg, intrathecal anesthesia, nerve block, etc). Additionally, inotropics and other anesthesia adjuvants had been employed at the discretion of the anesthesiologist. Once the fixation of the patch had been complete, the administration operation had been performed by applying 1/2 volume of QP002 or multipoint infiltration injections of 1/2 volume of bupivacaine hydrochloride injection (no fewer than 4 points had been recommended) around the patch and at the internal ring opening. Subsequently, the abdominal external oblique tendon membrane had been sutured, and a half-volume of QP002 or multiple-point infiltration injections of a half-volume of bupivacaine hydrochloride injection (no fewer than four points had been recommended) had been applied to the abdominal external oblique tendon membrane suture and surrounding tissues. Finally, a layer-by-layer suture of the fascial and epidermal layers had been performed. Following administration, venous blood had been collected at predetermined time points for laboratory testing and safety assessment. Subjects had been discharged from the hospital after completing the safety assessment on Day 6. Thereafter, study subjects had been requested to complete log cards on Days 7 through 27 and to receive weekly telephone follow-up visits on Days 13, 20, and 27.

Safety Assessments

Adverse events occurring after treatment (TEAE), defined as any adverse event (AE) and serious adverse event (SAE) occurring after study drug administration, were recorded from baseline to postoperative day 27 follow-up. Safety was evaluated on days 3 and 6 at baseline through the assessment of clinical laboratory parameters, including routine blood and urine tests, haematological and biochemical profiles. Additionally, incision response was graded according to the Southampton Incision Scoring System (Table S1). A 12-lead ECG was performed at 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 96, and 120 hours after administration to assess cardiotoxicity associated with high plasma bupivacaine exposure. At 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 96, and 120 hours after administration, 12-lead ECG assessments were conducted to evaluate heart rate and PR intervals, QRS durations, QT intervals, QTcF, and RR intervals were recorded, as well as the change in these values from the pre-administration period to each of the post-administration time points, in order to assess the

cardiotoxicity associated with high plasma bupivacaine exposure. Furthermore, CNS-LAST was evaluated in conjunction with 12-lead ECG, with the symptoms of associated AEs classified according to the CNS-LAST 5-level grading system (Table S2) to facilitate comprehensive symptom assessment. All AEs were coded in accordance with the MedDRA version 25.0 (or subsequent iterations).

PK Evaluations

Blood samples for QP002 PK analysis were collected at 0 h (within 2 h before drug administration) and at 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, 15 h, 18 h, 21 h, 24 h, 36 h, 48 h, 60 h, 72 h, 96 h, and 120 h after drug administration. The samples were then subjected to centrifugation at room temperature. The samples were subject to centrifugation within one hour of the conclusion of the sample collection process, with a rate of 1700 g at 4°C for a period of 10 minutes. Following this procedure, the plasma was then stored in a temperature of −80°C in preparation for further analytical assessment.

PD Evaluations

The principal indication for QP002 is postoperative analgesia. Therefore, the primary indicator of postoperative PD is the area under the drug-time curve (AUC) of pain intensity scores at varying time points following administration of the drug ($AUC_{0\text{-}72\ h}$). The numeric rating scale (NRS; 0 = no pain, 10 = worst pain) will be employed to quantify pain experienced at the instant of awakening from anaesthesia, as well as at 1, 2, 6, 8, 10, 12, 15, 18, 21, 24, 30, 36, 48, 60, 72, 96 and 120 hours post-administration of the drug. Secondary metrics for PD included the consumption of opioids, the proportion of subjects who did not use opioids, the time to the first receipt of remedial analgesic medication, and the overall analgesic satisfaction scores of subjects. Intravenous morphine 2 mg was administered as postoperative rescue analgesia in patients experiencing breakthrough pain within 120 hours of surgery. The maximum cumulative dose of morphine was 60 mg on day 1, and two consecutive treatments were spaced at least 15 minutes apart.

Statistical Analysis

PK parameters were calculated using a non-compartmental analysis via the utilisation of Phoenix WinNonlin 8.3 or subsequent software iterations. SAS 9.4 or subsequent software iterations were employed for the generation of blood concentration-time plots, the execution of ancillary data processing, and the performance of summary analyses. The baseline was defined as the result of the final test, assessment, or calculation conducted prior to the administration of the test drug. Subjects who receive bupivacaine injections at each dosage level will be combined into a single group for the purpose of performing relevant statistical analyses. Continuous variables will be statistically described using measures such as the number of cases (n), mean, standard deviation (SD), median, lower quartile (Q1), upper quartile (Q3) and minimum and maximum values. Categorical variables will be described statistically using measures such as frequency and frequency, incidence/composition ratios. NRS pain intensity scores were not recorded when the subject was sleeping, and when the subject was not receiving analgesia, the resulting missing NRS ratings were uniformly recorded as 3. If analgesia was used, the NRS pain intensity scores for the 4 h post-analgesia (including the scheduled sleep state scoring time point during the 4 h post-analgesia) was replaced by the last preanalgesia NRS pain intensity scores. NRS scores at 0 h were imputed as 0, and all other missing data for NRS pain scores were imputed using the last observation carried forward.

The sample size is considered according to the actual situation. In accordance with the stipulations set forth in the Technical Guidelines for Clinical Pharmacokinetic Studies of Chemical Drugs (Appendix S2), a minimum of 8 and a maximum of 12 cases per dose group is typically required for single-administration pharmacokinetic studies. Furthermore, the inclusion of both male and female subjects is recommended, in principle, to ensure a comprehensive analysis. Therefore, the intention was to incorporate forty subjects of both sexes who were undergoing open unilateral tension-free hernia repair, for inguinal or rectal hernia (proposed Lichtenstein procedure), into five dose groups comprising eight cases each.

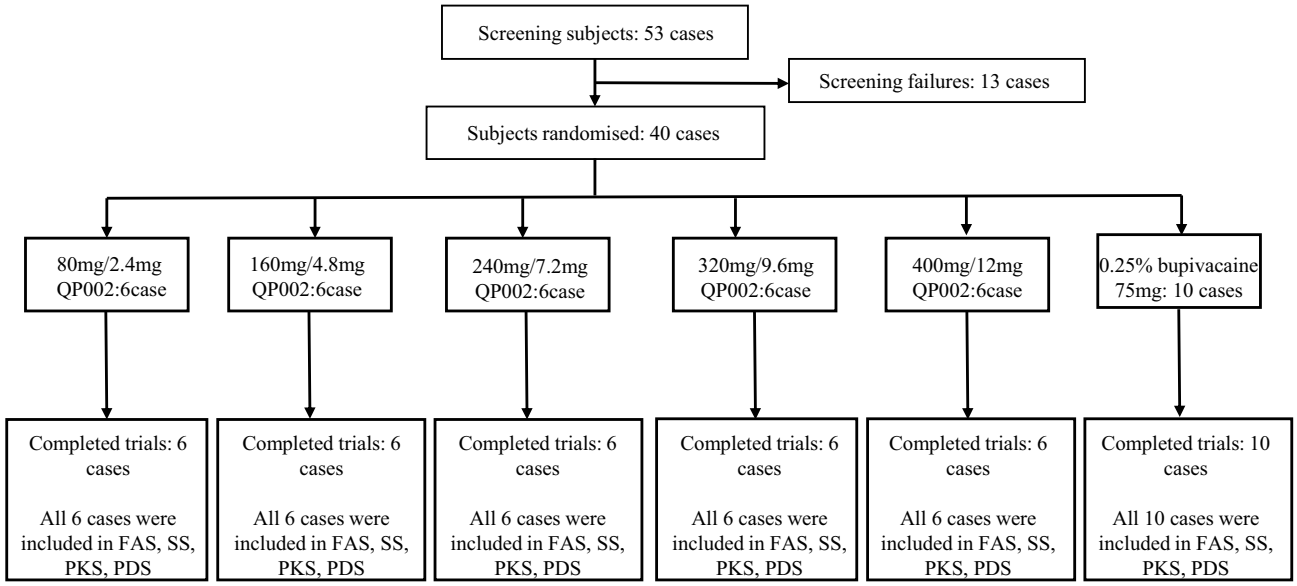

Figure 1 Subject Distribution Flowchart.

Results

Demographic Characteristics

A total of 53 subjects were screened for this study, of which 13 failed the screening process and 40 subjects were randomized Figure 1, all subjects completed the trial and their demographic baseline is shown in Table 1. The subjects were included in the Full Analysis Set (FAS), the Safety Analysis Set (SS), the Pharmacokinetic Analysis Set (PKS), and the Pharmacodynamic Analysis Set (PDS) (Table 2). All groups were composed of Han Chinese individuals with similar mean age and BMI, and ASA grades of I and II. The overall proportion of male subjects (92.5%) was higher than that of females (7.5%), and this difference in male-to-female ratio was attributable to the characteristics of inguinal hernia disease (which is more prevalent in males than in females). However, the gender ratios were similar between the groups. The baseline vital signs, physical examination and electrocardiographic data were similar in all groups, as were the length of surgery and time to awakening (Table S3).

Table 1 Demographics of Enrolled Subjects (FAS)

Variables	QP002 Experimental Drug Group					0.25% Bupivacaine 75 mg N = 10
	80 mg/2.4 mg QP002 N = 6	160 mg/4.8 mg QP002 N = 6	240 mg/7.2 mg QP002 N = 6	320 mg/9.6 mg QP002 N = 6	400 mg/12 mg QP002 N = 6	
Age (yr), min-max	57, 24-73	38.7, 22-59	52.2, 24-72	56.5, 39-66	55, 28-71	43.4, 25-61
Height (cm), mean (SD)	163.3(6.62)	173.5(3.83)	167.7(10.86)	163.0(4.34)	166.0(7.21)	166.8(4.57)
Weight (kg), mean (SD)	61.57(7.047)	64.77(2.618)	65.75(13.118)	62.50(8.116)	63.00(4.417)	64.63(7.770)
BMI (kg m^{-2}), mean (SD)	23.05(1.940)	21.55(1.642)	23.18(2.621)	23.48(2.319)	22.90(1.801)	23.16(1.909)
Male, n (%)	6, (100%)	6, (100%)	5, (83.3%)	5, (83.3%)	6, (100%)	9, (90%)
Han ethnicity, n (%)	6, (100%)	6, (100%)	6, (100%)	6, (100%)	6, (100%)	10, (100%)
ASA, n (%)						
I	3, (50%)	3, (50%)	3, (50%)	2, (33.3%)	1, (16.7%)	3, (30%)
II	3, (50%)	3, (50%)	3, (50%)	4, (66.7%)	5, (83.3%)	7. (70%)

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Table 2 Statistical Analysis Set of Subjects

FAS:	All subjects dosed with the study drug (QP002 or 0.25% bupivacaine hydrochloride injection) according to ITT guidelines.
SS:	All subjects receiving study drug (QP002 or 0.25% bupivacaine hydrochloride injection) with at least one post-baseline safety assessment.
PKS:	All subjects receiving QP002 or 0.25% bupivacaine HCl injection, with no observable effect on PK behaviour during the sampling period, with at least one evaluable PK parameter, and no major protocol deviation or breach.
PDS:	All subjects administered the test drug (QP002 or 0.25% bupivacaine hydrochloride injection) with at least one measurable post-administration PD.

Safety

Of the 40 subjects included in this trial with SS, a total of 34 cases of 94 adverse effects (AEs) were observed. Of these, 15 (37.5%) were classified as moderate, while the remainder were classified as mild (Table 3). With the exception of one subject who experienced one adverse event (AE) that was regressed to persistent (blood fibrinogen elevated to 2.2 times the upper limit of normal), the remaining subjects demonstrated either complete recovery or improvement. Additionally, no AEs resulted in withdrawal from the trial. The type and incidence of adverse events (AEs) in the QP002 groups at different doses did not differ from those in the injection group. Furthermore, no dose-level correlation was observed for AEs between the QP002 dose groups. Of the AEs with an incidence of ≥5% pooled by system organ class (SOC) and preferred term (PT), the AE test group exhibited a lower incidence than the control group in the majority of subgroups (Table S4).

The majority of subjects exhibited graded "0", "IA", and "IC" for incision site reaction at all time points, and the results were consistent across all groups (Table 3). In the 160 mg/4.8 mg QP002 and injection groups, one case exhibited an incision site reaction classification of "IIIA" on Day 6 (*Table S5*). This was reported as an adverse event (AE) and was determined to be unrelated to the test drug. Each subject was evaluated for the occurrence of LAST symptoms on 12 occasions following administration of the test substance. The majority of subjects exhibited no symptoms at any given time point.

No notable variations were observed in the laboratory test values, vital signs, physical examination findings, or electrocardiogram results among the subjects in the follow-up period, extending from the pre-dose baseline to day 27 post-dose. Additionally, the proportions of subjects exhibiting abnormal conditions remained largely consistent across the groups (*Tables S6–S8*).

Pharmacokinetic Characteristics

The T_{max} for the QP002 dose groups ranged from approximately 15 to 20 hours, with the exception of the 80 mg/2.4 mg QP002 group, which had a T_{max} of approximately 10 hours. The systemic exposure was observed to be smaller for the injection group compared to the QP002 group, with a notable earlier peak time of approximately one hour. This was found to be significantly different from the T_{max} observed for each QP002 dose group. The C_{max} of bupivacaine in the injectable group was 258.40 ng/mL, which was comparable to the C_{max} of 250.33 ng/mL observed in the 240 mg/7.2 mg QP002 group. The $t_{1/2}$ of bupivacaine in the injection group was approximately 6 h, which was shorter than that of the QP002 dose groups (Table 4).

Table 3 Summary of Adverse Event Occurrences (SS)

Adverse Event, n (%)	QP002 Experimental Drug Group					0.25% Bupivacaine 75 mg N = 10
	80 mg/2.4 mg QP002 N = 6	160 mg/4.8 mg QP002 N = 6	240 mg/7.2 mg QP002 N = 6	320 mg/9.6 mg QP002 N = 6	400 mg/12 mg QP002 N = 6	
Total	6(100%)	5(83.3%)	5(83.3%	4(66.7%)	5(83.3%	9(90%)
Mild	3(50%)	4(66.7%)	2(33.3%)	2(33.3%)	4(66.7)	4(40%)
Moderate	3(50%)	1(16.7%)	3(50%)	2(33.3%)	1(16.7)	5(50%)
Severe	0	0	0	0	0	0

Table 4 Summary of PK Parameters of Bupivacaine in Each Group After Single Administration (PKS)

PK Parameters	80 mg/2.4 mg QP002 N = 6	160 mg/4.8 mg QP002 N = 6	240 mg/7.2 mg QP002 N = 6	320 mg/9.6 mg QP002 N = 6	400 mg/12 mg QP002 N = 6	0.25% Bupivacaine 75 mg N = 10
T_{max}(h)	9.79(9.11)	14.27(6.18)	17.94(5.01)	19.87(3.63)	16.94(4.14)	0.94(0.48)
C_{max}(ng/mL)	133.15(49.41)	173.83(51.15)	250.33(68.78)	315.00(151.99)	349.50(104.61)	258.40(71.11)
AUC_{0-t}(h*ng/mL)	3531.37(1736.91)	4907.17(2245.06)	10,031.43(3631.24)	11,746.42(7070.72)	14,043.56(6756.60)	2505.46(839.10)
$AUC_{0-\infty}$(h*ng/mL)	3570.05(1745.12)	4931.56(2243.37)	10,111.97(3650.83)	11,791.97(7083.90)	14,089.65(6775.45)	2526.29(849.49)
$\%AUC_{ex}$(%)	1.43(0.95)	0.57(0.37)	0.80(0.63)	0.47(0.29)	0.34(0.21)	0.79(0.45)
λ_z(1/h)	0.076(0.02)	0.08(0.03)	0.054(0.01)	0.07(0.01)	0.07(0.02)	0.13(0.05)
$t_{1/2}$(h)	9.87(2.745)	9.13(2.40)	13.62(3.97)	10.35(1.90)	10.70(2.97)	5.87(2.41)
Vz/F(L)	478.19(474.06)	471.51(174.90)	517.53(242.44)	523.09(244.27)	503.45(249.52)	258.38(69.88)
CL/F(L/h)	36.50(39.41)	38.27(15.91)	26.09(8.03)	35.76(18.00)	33.07(11.96)	33.03(11.48)
MRT_{0-t}(h)	19.20(5.03)	19.95(5.68)	30.00(6.07)	26.67(6.43)	28.40(6.31)	10.89(3.50)

Note: All values are the mean (SD).

Abbreviations: Tmax, time point corresponding to the arrival at maximum blood concentration; Cmax, maximum measured blood concentration; AUC0-t, the area under the blood concentration curve from 0 to the last measurable time point; AUC0-∞, Area under the blood concentration curve from 0 to infinity; %AUCex, percentage of residual area; λz1/h, apparent terminal elimination rate constant, obtained by taking a semi-log linear regression from the elimination phase concentration point; t1/2, apparent terminal elimination half-life; CL/F mL/h, apparent clearance rate; Vz/F mL, apparent volume of distribution of the elimination phase; MRT0-t, Mean Residence Time.

The PK parameters Cmax, AUC_{0-t} and $AUC_{0-\infty}$ of bupivacaine in each dose group of QP002 demonstrated a dose-dependent increase, as illustrated in Figure 2. The slope β of C_{max} of bupivacaine in the dose range of 80 mg~400 mg was 0.65, exhibiting a trend of dose linearity. The slopes β of AUC_{0-t} and $AUC_{0-\infty}$ were The values were 0.96 and 0.95respectively, indicating linear pharmacokinetic characteristics. No significant differences were observed in the $\%AUC_{ex}$, λz, $t_{1/2}$, CL/F, V_z/F, and MRT_{0-t} of bupivacaine between dose levels in each group.

No statistically significant differences were observed between the group comparisons of meloxicam's time to maximum concentration (T_{max}), which was approximately 15–18 hours in all cases. Furthermore, a dose-dependent increase in the pharmacokinetic parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ was evident for meloxicam in each dose group, as depicted in Figure 3. The AUC_{ex}, λ_Z, $t_{1/2}$, CL/F, Vz/F and MRT_{0-t} values for meloxicam exhibited no statistically significant differences between dose levels (Table 5). The Meloxicam dose-exposure within the range of 2.4 mg to 12 mg displayed a linear kinetic profile.

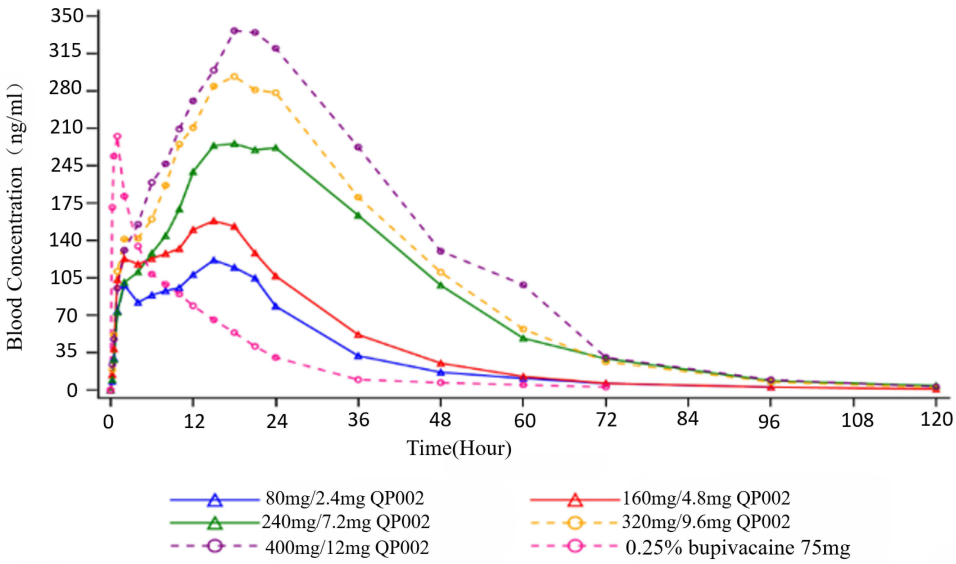

Figure 2 Linear superposition of the mean blood concentration-time curves of bupivacaine in each group after a single administration (PKS).

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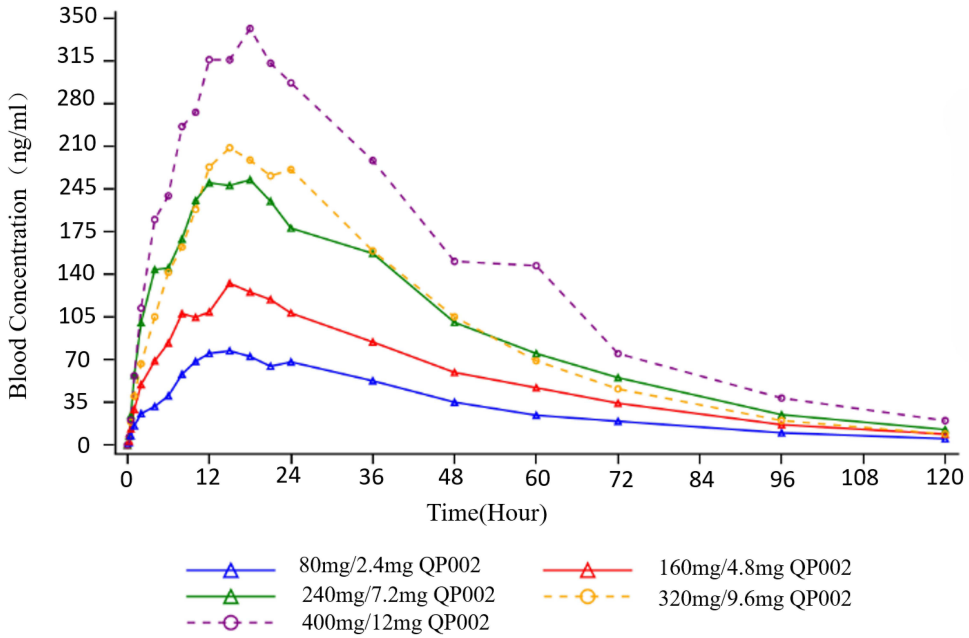

Figure 3 Linear superimposed plot of the mean blood concentration-time curve of meloxicam in each group after a single dose (PKS).

Pharmacodynamics Characteristics

A total of 40 open unilateral inguinal hernia repair subjects completed the study. Subject characteristics in each treatment group are shown in Table 1. Postoperative resting scores after use of QP002 or bupivacaine hydrochloride were below 3, not statistically different from the injection group. Cumulative pain intensity score in the 24-hour postoperative period (NRS-R-$AUC_{0\text{-}24h}$) was significantly lower with 320 mg/9.6 mg QP002 compared to the injection group (p = 0.0342) (Table 6). Overall, post-operative pain scores were slightly higher when patients were moving than when they were at rest, but they were still relatively comfortable and not statistically different from when they were injected. NRS-A-$AUC_{0\text{-}12}$ and NRS-A-$AUC_{0\text{-}24}$ were lower in all QP002 dose groups than in the injection group, with NRS-R-$AUC_{0\text{-}24}$ significantly lower in the 320mg/9.6mg QP002 and 400mg/12mg QP002 groups (P = 0.0165 and P = 0.0435, respectively), showing some dose correlation (Table 7). For subjects using analgesics, the results of the sensitivity and NRS analyses were generally similar, with different methods of imputing missing values and analgesics having less effect

Table 5 Summary of PK Parameters of Meloxicam in Each Group After a Single Dose (PKS)

PK Parameters	80 mg/2.4 mg QP002 N = 6	160 mg/4.8 mg QP002 N = 6	240 mg/7.2 mg QP002 N = 6	320 mg/9.6 mg QP002 N = 6	400 mg/12 mg QP002 N = 6
T_{max}(h)	15.75(5.16)	15.63(3.74)	16.94(4.51)	18.50(4.42)	14.76(4.51)
C_{max}(ng/mL)	119.28(41.15)	209.67(42.77)	340.50(51.59)	376.83(120.06)	522.50(164.97)
$AUC_{0\text{-}t}$(h*ng/mL)	5324.35(2843.81)	9391.87(2682.62)	16,021.28(3670.61)	16,127.61(6318.28)	24,528.93(10,387.59)
$AUC_{0\text{-}\infty}$(h*ng/mL)	5512.47(3018.88)	10,014.95(3678.86)	16,723.13(4101.75)	16,553.27(6681.42)	25,874.32(12,597.57)
$\%AUC_{ex}$(%)	3.18(1.87)	4.50(6.27)	3.78(3.38)	2.23(1.51)	3.48(5.09)
λ_z(1/h)	0.04(0.01)	0.04(0.01)	0.03(0.01)	0.04(0.01)	0.03(0.01)
$t_{1/2}$(h)	18.54(4.94)	21.97(10.44)	22.31(6.67)	19.78(5.16)	20.60(9.09)
Vz/F(L)	16.79(14.26)	15.24(3.98)	14.14(3.32)	17.89(6.48)	14.90(5.12)
CL/F(L/h)	0.74(0.82)	0.52(0.15)	0.46(0.14)	0.65(0.22)	0.56(0.27)
$MRT_{0\text{-}t}$(h)	32.90(8.58)	37.25(6.14)	36.50(4.23)	34.34(2.80)	36.12(5.22)

Note: All values are the mean (SD).

Abbreviations: Tmax, time point corresponding to the arrival at maximum blood concentration; Cmax, maximum measured blood concentration; AUC0-t, the area under the blood concentration curve from 0 to the last measurable time point; AUC0-∞, Area under the blood concentration curve from 0 to infinity; %AUCex, percentage of residual area; λz1/h, apparent terminal elimination rate constant, obtained by taking a semi-log linear regression from the elimination phase concentration point; t1/2, apparent terminal elimination half-life; CL/F mL/h, apparent clearance rate; Vz/F mL, apparent volume of distribution of the elimination phase; MRT0-t, Mean Residence Time.

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Table 6 Summary of AUC Intergroup (Group 2-Group 1) Comparisons of Pain Intensity Scores NRS-R Under Different Time Periods After Drug Administration (PDS)

Variables	Group 1	0.25% Bupivacaine 75mg				
	Group 2	80 mg/2.4 mg QP002	160 mg/4.8 mg QP002	240 mg/7.2 mg QP002	320 mg/9.6 mg QP002	400 mg/12 mg QP002
AUC_{0-6}	Differences	0.63	−1.87	0.47	−2.2	−2.2
	P-value	0.8744	0.5397	0.9154	0.6547	0.6469
AUC_{0-8}	Differences	0.23	−2.1	1.23	−3.6	−2.6
	P-value	0.9589	0.64	0.8198	0.5378	0.6569
AUC_{0-12}	Differences	−1.13	−4.8	−1.63	−8.63	−5.3
	P-value	0.8482	0.4432	0.816	0.2536	0.4928
AUC_{0-24}	Differences	−10.28	−10.2	−13.53	−25.53	−13.2
	P-value	0.301	0.3036	0.2296	0.0342	0.2567

Notes: 1. Difference: Group 2 - Group 1 difference. 2. P-value < 0.05 (statistically different).

Table 7 Summary of AUC Intergroup (Group 2-Group 1) Comparisons of Pain Intensity Scores NRS-A Under Different Time Periods After Drug Administration (PDS)

Variables	Group 1	0.25% Bupivacaine 75 mg				
	Group 2	80 mg/2.4 mg QP002	160 mg/4.8 mg QP002	240 mg/7.2 mg QP002	320 mg/9.6 mg QP002	400 mg/12 mg QP002
AUC_{0-6}	Differences	0.1	1.18	1.6	−0.65	−2.57
	P-value	0.9812	0.7697	0.7316	0.8904	0.5876
AUC_{0-8}	Differences	−1.27	0.98	1.9	−2.18	−4.1
	P-value	0.7945	0.8379	0.739	0.6902	0.476
AUC_{0-12}	Differences	−5.27	−2.35	−0.77	−8.02	−8.93
	P-value	0.4122	0.7171	0.9201	0.2647	0.2309
AUC_{0-24}	Differences	−14.37	−9.45	−15.37	−29.37	−25.03
	P-value	0.2325	0.4296	0.241	0.0165	0.0435

Notes: 1. Difference: Group 2 - Group 1 difference. 2. P-value < 0.05 (statistically different).

on the overall trend. The majority of morphine remediation occurred within the first 12 hours, and there was no statistically significant difference in total morphine use across all time periods in any of the groups. With the exception of the 80 mg/2.4 mg QP002 group, which received morphine remedial analgesia between 24 and 48 hours, the total morphine dosage at all time points was lower in the QP002 dose groups than in the injectable group. Furthermore, no subjects in any of the groups received morphine remedial analgesia after 24 hours. The QP002 rating was "excellent" for 66.7–100% of the dose groups, spanning low to high doses, while only 40.0% of the injection groups received this rating. Notably, no subjects in any of the groups were rated as "poor" or "fair."

Discussion

Bupivacaine is an amide local anaesthetic that exerts local anaesthesia by binding to receptors on the nerve membrane, blocking sodium channels, affecting the depolarisation of the nerve cell membrane, and inhibiting action potential generation and conduction.[12] The local anaesthetic drugs most frequently employed for postoperative incisional infiltration in major clinical surgery are lidocaine, ropivacaine and bupivacaine. Bupivacaine and ropivacaine possess a more protracted duration of action in comparison to lidocaine.[13] In incisional bacteriostasis, bupivacaine demonstrated significantly superiority over ropivacaine with lidocaine.[14] The majority of currently marketed extended-release local anaesthetic drugs utilise bupivacaine as their principal active ingredient, and this agent boasts a broader range of applications. Therefore, bupivacaine has become the local anaesthetic of choice for this drug.

However, when administered in high doses, the peak concentration of bupivacaine is likely to exceed the safety threshold, resulting in central nervous system toxicity and cardiotoxicity. Therefore, the objective of this study was to determine whether lowering the peak concentration of bupivacaine could reduce CNS toxicity and cardiotoxicity.[15] The study found that QP002 had significantly lower peak concentrations at the same dose compared to the positive control (bupivacaine hydrochloride). Specifically, the peak concentration (Cmax) in the 240 mg/7.2 mg QP002 group was 250.33 ng/mL, which was similar to that of 75 mg of bupivacaine hydrochloride (Cmax) 258.40 ng/mL. This suggests that the CNS toxicity and cardiotoxicity of bupivacaine is reduced when QP002 is used, even at high doses. In the present study, QP002 was found to prolong the exposure to high plasma concentrations of bupivacaine while reducing the peak concentration. However, there was no significant difference in the type and incidence of adverse events (AEs) compared to the positive control group. This suggests that increased bupivacaine exposure time does not increase the risk of adverse events. In comparison to the biphasic pattern of liposomal bupivacaine (Exparel®) blood concentrations,[16,17] the monophasic pattern of QP002 blood concentrations is more stable and has better safety and predictability.

In clinical practice, the efficacy of local anesthetics can be diminished due to a decrease in the pH at the incision site. One approach has been to combine local anesthetics with nonsteroidal anti-inflammatory drugs (NSAIDs); however, the outcomes have not been satisfactory. In some cases, when local anesthetics were combined with diclofenac sodium, precipitation occurred, indicating that the physical and chemical properties of the drugs were altered.[18] In contrast, in this study, the metabolism of both bupivacaine and meloxicam in QP002 was stable and pharmacokinetic predictable, with little interaction between the two drugs. This was demonstrated by the linear trend of Cmax of bupivacaine in QP002 as well as the linear kinetic characteristics of AUC0-t and AUC0-∞ of both active ingredients, bupivacaine and meloxicam. Furthermore, the observed discrepancy in the occurrence of adverse events (AEs) between the various dose groups within the QP002 group did not attain statistical significance as the dosage of the pharmaceutical agent increased, thereby indicating an absence of a dose-dependent relationship in terms of AEs.

In the safety study, in addition to routine laboratory test results, vital signs and physical examination, incision partial reaction assessment and local anaesthetic systemic toxicity (LAST) assessment were also performed. The results demonstrated that there was no significant difference in the incidence of local anaesthetic systemic toxicity (LAST) assessment between the positive control group and the QP002 group, and there was no significant difference in the incisional assessment. The QP002 group not only exhibited a favourable safety profile, but also demonstrated an excellent pharmacokinetic (PK) profile, thereby further enhancing the safety of the drug. This feature reduces the need for frequent monitoring of drug concentrations during treatment and provides a safe and reliable basis for exploring higher doses in subsequent studies.

Pharmacodynamics (PD) demonstrated that there was no statistically significant difference between the NRS-AUC of the groups in the resting state at all time intervals. Given that the control group functioned as a positive control and the pain level in patients with inguinal hernia at rest was not sufficiently potent to accentuate the analgesic effect of the drug, it can be posited that the postoperative pain model could be substituted for subsequent pharmacodynamic studies. However, a statistically significant difference in the NRS-AUC was observed between the 320 mg/9.6 mg QP002 group and the 400 mg/12 mg QP002 group at the 24th postoperative hour in the exercise state. The analgesic effect of the other low-dose QP002 groups was comparable to that of the positive control group, suggesting that an increase in the starting concentration may be necessary for subsequent studies of drug efficacy.

The limitations of this study are twofold. Firstly, the study sample consisted of a majority of male patients, resulting in a lack of data representation of female cases and limiting the general applicability of the conclusions. Secondly, although phase I clinical trials can usually be conducted with small samples, the detection of rare adverse events (AEs) may be limited as a result, so the safety of QP002 needs to be further verified by larger clinical trials. The analgesic effect of QP002 groups is not directly proportional to the dose concentration, and further studies will require additional pain models.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

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Disclosure

Dr Sen Yu, Dr Yonghui Jiu, Mrs Ziteng Wu are employees of Nanjing Delova Biotech Co Ltd. Jinyu Liu is now affiliated at Department of Anesthesiology, Qionglai Hospital of Traditional Chinese Medicine, Chengdu, People's Republic of China. The authors have no other relevant conflicts of interest in this work.

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