BACKGROUND
Most surgical patients experience moderate to severe pain during the first 2-3 days after surgery, but less than half of these patients receive adequate pain relief. Appropriate post-surgical pain management contributes to improved wound recovery, faster patient mobilization, shortened hospital stay with fewer readmissions, and reduced healthcare costs. The administration of opioid analgesics is a primary modality to manage postoperative pain. However, opioids have undesirable adverse effects, including potential for opioid use disorder and opioid overdose. Local anesthetics are alternative non-opioid therapies for pain relief, but their duration is typically limited to 8-9 hours and they are associated with potential local anesthetic systemic toxicity (LAST).

Taiwan Liposome Company, Ltd. is developing TLC590, a sustained-release formulation of the local anesthetic ropivacaine with lipid nanoparticles, intended to produce extended analgesic effects and decreased toxicity in postoperative pain management following a single dose infiltration into the surgical site.

OBJECTIVES
The primary objective of this study was to evaluate the safety and tolerability of TLC590 for postoperative pain management in subjects with open inguinal hernia repair surgery.

The secondary objectives of this study were:

- To evaluate the pharmacokinetic (PK) profile and dose-exposure relationship of TLC590, as well as the bioavailability as compared with ropivacaine.
- To evaluate the analgesic efficacy of TLC590 compared with ropivacaine for postoperative pain management in subjects with inguinal hernia repair surgery.
- To evaluate the exposure-response relationship between PK parameters and pain management.

MATERIALS AND METHODS
In this first-in-human, randomized, double-blind, comparator-controlled trial, 54 adult subjects were enrolled in 4 escalating dose cohorts with TLC590 150 mg (n=10), 300 mg (n=20), 475 mg (n=25) and 570 mg (n=10). Each cohort randomized 12 subjects treated with TLC590 and 4 with ropivacaine hydrochloride 5% (ropivacaine) 150 mg (n=10) via infrascapular local administration following inguinal hernia repair surgery.

All subjects underwent a Lichtenstein inguinal hernia repair under general anesthesia (induced or spinal anesthesia was not permitted). Intravenous administration of opioids (except IV ketorolac) or any other analgesic was prohibited. Subcutaneous ropivacaine injection for 48 hours post-surgery and were followed for a total of 4 weeks; efficacy and PK were evaluated for 1 week post-surgery. Assessments included tobita, DCS,numeric rating scale (NRS), patient global assessment (PGA), and surgical site assessment. During the study, subjects could only receive postoperative rescue medications as needed, which consisted of oral acetaminophen (no more than 4000 mg per day), oral tramadol (no more than 400 mg per day) and/or oral/diloxane (no more than 300 mg per day) or celecoxib (no more than 500 mg per day).

Consent was obtained from all participants enrolled in the study. The protocol was approved by the local Institutional Review Board and the study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The study was registered at ClinicalTrials.gov (NCT04029919).

RESULTS & DISCUSSION
64 subjects were randomized into 4 cohorts. No serious AEs or LAST events were observed in the study. TEAEs were mild to moderate in severity and resolved without sequelae (Table 1). Overall, safety and tolerability in all 4 TLC590 dose groups were similar to ropivacaine 150 mg group.

Table 1: Summary of TEAEs (Safety Population)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Any TEAE (%)</th>
<th>Any ropivacaine TEAE (%)</th>
<th>Any serious TEAE (%)</th>
<th>Any TEAE of special interest (%)</th>
<th>Any TEAE leading to withdrawal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC590 150</td>
<td>11 (9.1)</td>
<td>2 (1.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TLC590 300</td>
<td>11 (9.1)</td>
<td>2 (1.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TLC590 475</td>
<td>11 (9.1)</td>
<td>2 (1.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TLC590 570</td>
<td>11 (9.1)</td>
<td>2 (1.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

MATERIALS AND METHODS

The most frequently reported TEAE was nausea (TLC590 group: 27.1%; ropivacaine group: 63.8%) followed by constipation (TLC590 group: 34.8%; ropivacaine group: 50.0%), and vomiting (TLC590 group: 23.1%; ropivacaine group: 18.8%). The incidence of these problems opioid-related events in lower than in TLC590 dose group than in the ropivacaine group.

CONCLUSION
TLC590 showed similar safety and tolerability as ropivacaine with no LAST events observed in the study. Subjective pain reduction, opioid-sparing, and reduced opioid use were observed. The results showed preliminary efficacy and safety of TLC590 for use in the clinic. TLC590 is being developed for the potential treatment of neuropathic pain.