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A Phase 1 Randomized, Controlled, Double-Blind, Single Ascending Dose Safety and Pharmacokinetic/Pharmacodynamic Study in Healthy Adult Males after LIQ865 Injection

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Introduction: An exploratory ascending dose safety study was conducted at a Phase 1 facility in Copenhagen, Denmark, under DKMA/IEC approval to assess the tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of LIQ865A and LIQ865B, two free-base bupivacaine formulations designed to produce a long-acting local anesthetic relief for 3 to 5 days after injection. Both formulations are made using PRINT® (Particle Replication In Non-wetting Templates) Technology, a proprietary particle engineering technology that allows precise control over particle features such as size, shape, and chemical composition.

Methods: Ascending bupivacaine doses from 150 mg to 600 mg were injected subcutaneously in the medial calf using a fixed volume of 10 mL with 6 passes (3/opposite corner) within a rectangular test area using a 21G 2" needle (**FIG. 1**). Each subject received randomized either injectable suspension of bupivacaine/poly(D,L-lactic-co-glycolic acid) [PLGA] PRINT® particles (**LIQ865A**) or bupivacaine free base PRINT® particles (**LIQ865B**), in one test area, and diluent alone in the contralateral test area. Up to six subjects were enrolled in each cohort with dose escalation occurring after evaluating safety. Pharmacokinetics were analyzed by measurements of plasma concentrations of bupivacaine at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12 and 24 hours, and on days (D) 2, 3, 4, and 5. Pharmacodynamics were analyzed by Quantitative Sensory Testing (QST) assessing mechanical and thermal sensitivity in the injection test areas. Mechanical Detection Threshold (MDT) and Mechanical Pain Threshold (MPT) were assessed using calibrated polyamide monofilaments (Stoelting-Europe) and pin-prick stimulators (MRC Systems), respectively. Warmth Detection Threshold (WDT), Cool Detection Threshold (CDT), Heat Pain Threshold (HPT) and perception of a SupraThreshold Heat Stimulus (STHS; 47°C, 5 s) were assessed with a computerized thermode (active surface: 2.5 x 5.0 cm^2; MSA, Somedic AB). Pharmacodynamic evaluations in the test sites were performed by blinded examiners and completed over 5 days (testing at 1, 2, 4, 6, 8, 12, and 24h, and once daily on D2 – D5. Values were compared to baseline and to the contralateral control leg.

Safety/Tolerability: Overall, administration of LIQ865A (n = 16) and LIQ865B (n = 12) was generally well-tolerated at all dose levels in the study. Most AEs were local at the sites of injection mainly resulting from the extensive needling procedure (**FIG. 1**). Bruising at the injection site occurred in all treatment/dosing groups regardless of whether the leg was the active or control diluent side. Slightly more bruising was noted in the leg site that received bupivacaine compared to the control site. There were 5 cases of subcutaneous induration at the injection site, LIQ865A (n = 4) and LIQ865B (n = 1), with 4 mild and 1 moderate in the 450 mg dose groups and none in any of the other groups. The induration was transient and resolved by 30 to 60 days except for one subject who reported resolution just past the 60-day point.

Pharmacokinetics: Mean (SE) dose-dependent PK-profiles from 0-120h are illustrated in **FIG. 2**. The highest individual plasma bupivacaine concentration (C_{max}) obtained was 728 ng/mL. Bupivacaine clearance in both formulations exhibited "flip-flop" kinetics where the rate of clearance was driven by the rate of drug absorption from the extended release formulation.

Pharmacodynamics: QST-testing demonstrated an onset of action at the 1h time point for all stimulation modalities and dose levels of both formulations. Hypoesthesia and hypoalgesia were demonstrated for all mechanical and thermal stimulation modalities, and maintained through the 72h (120h) time point for bupivacaine doses greater >225 mg compared to the controls (diluent alone). Mean (SE) dose-dependent PD-profiles from 0-120h for Mechanical Thresholds (MDT) and Thermal Thresholds (CDT) are illustrated in **FIG. 3** compared to controls (diluent).

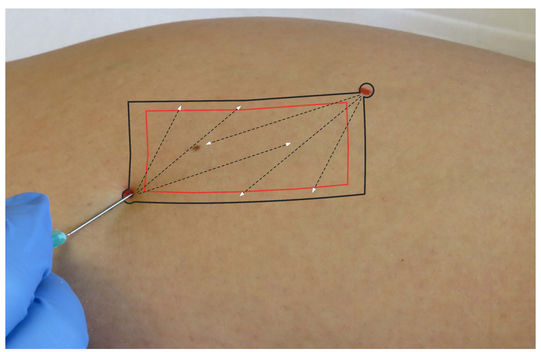

FIG. 1. The injection site on the medial calf. Three passes with the needle (indicated by dashed arrows) were made in each of two opposite corners. The injectate was evenly distributed in the red rectangle representing the sensory testing area (2.5 x 5.0 cm^2).

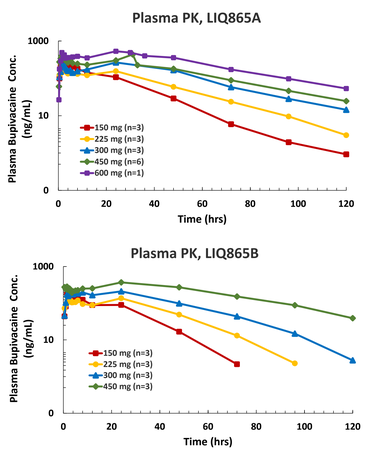

FIG. 2. Pharmacokinetic profiles of LIQ865A and LIQ865B from 0-120 h.

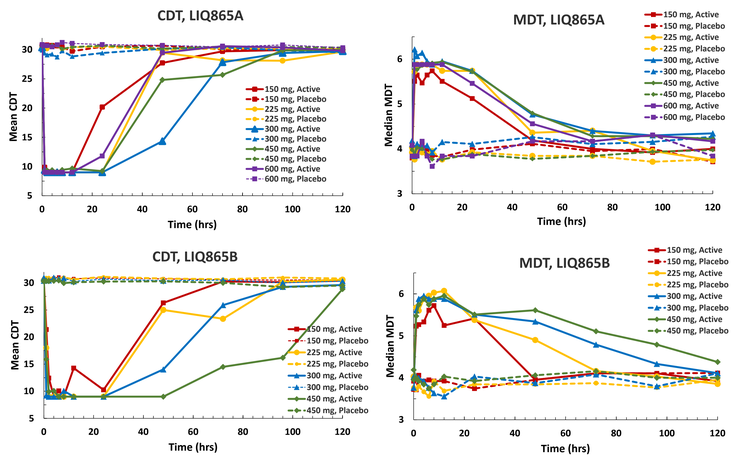

FIG. 3. Cold Detection Threshold profiles and Mechanical Detection Threshold profiles for LIQ865A and LIQ865B from 0-120 h, compared to controls.

Conclusions: These preliminary QST results indicate a duration of hypoesthesia and hypoalgesia up to 3-5 days, depending upon stimulation modality, particularly at doses of 300 mg and higher. These results warrant additional studies to examine the clinical utility and safety of LIQ865 when injected into the surgical site to produce long lasting postoperative analgesia.