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

Vaughn TA1, Kjær Jensen E2, Bøgevig S3, Springborg AD2, Werner MU2

1Liquidia Technologies, Raleigh, NC, USA; 2Multidisciplinary Pain Center, Neuroscience Center, Copenhagen University Hospitals, DENMARK; 3Department of Clinical Pharmacology, Copenhagen University Hospitals, DENMARK

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) 1, 2, 3, 4, and 5. Pharmacodynamics were analyzed by Quantitative Sensory Testing (QST) assessing mechanical and thermal stimulation modalities, and maintained through 72h - 120h for bupivacaine doses greater >225 mg and dose levels of both formulations. Hypoesthesia and hypoalgesia were demonstrated for all mechanical and thermal stimulation modalities, and maintained through 72h - 120h for bupivacaine doses greater >225 mg and dose levels of both formulations. Hypoesthesia and hypoalgesia were demonstrated for all mechanical and thermal stimulation modalities, and maintained through 72h - 120h for bupivacaine doses greater >225 mg and dose levels of both formulations. Hypoesthesia and hypoalgesia were demonstrated for all mechanical and thermal stimulation modalities, and maintained through 72h - 120h for bupivacaine doses greater >225 mg and dose levels of both formulations. Hypoesthesia and hypoalgesia were demonstrated for all mechanical and thermal stimulation modalities, and maintained through 72h - 120h for bupivacaine doses greater >225 mg and dose levels of both formulations.

Pharmacokinetics: Mean (SE) dose-dependent PK-profiles from 0-120h are illustrated in FIG. 2. The highest individual plasma bupivacaine concentration (Cmax) 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 1 time point for all stimulation modalities and dose levels of both formulations. Hypoesthesia and hypalgesia were demonstrated for all mechanical and thermal stimulation modalities, and maintained through 72h - 120h for bupivacaine doses greater >225 mg compared to the controls (diluent alone). Mean dose-dependent PD-profiles from 0-120h for Mechanical Detection Threshold (MDT) and Thermal Thresholds (CDT) are illustrated in FIG. 3, compared to controls (diluent).

Safety/Tolerability: Overall, administration of LIQ865A (n = 16) and LIQ865B (n = 12) were 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 LIQ865 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.

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Conclusions: These preliminary QST results indicate a duration of hypoesthesia and hypalgesia 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.

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 needle was evenly distributed in the red rectangle representing the sensory testing area (2.5 x 5.0 cm²).

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

FIG. 3. Cool Detection Threshold (CDT) profiles and Mechanical Detection Threshold (MDT) profiles for LIQ865A and LIQ865B from 0-120 h, compared to controls.