LIQ865A Produces a Slow Controlled Release of Bupivacaine after Subcutaneous Dosing in Rats and Minipigs

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LIQ865A is a bupivacaine particle formulation developed by Liquidia Technologies, Inc. for the management of local post-operative pain. LIQ865A is manufactured using a proprietary process technology called PRIENT® (Particle Replication In Non-Wetting Templates) producing 25 μm hexagonal particles comprised of approximately 55% bupivacaine and 45% polylactic-co-glycolic acid (PLGA). Particles are suspended in a custom solution with Exparel® (liposomal bupivacaine) were studied in Sprague Dawley rats and Yucatan miniature swine.

To support clinical testing, single dose bupivacaine (Bup) pharmacokinetics (PK) from subcutaneously administered LIQ865A, Marcaine™ (Marcaine) and Exparel® (ispoma bupivacaine) were studied in Sprague Dawley rats and Yucatan miniature swine.

**STUDY DESIGN AND METHODS**

- LIQ865A formulations were prepared just prior to administration.
- Single SC Administration PK in Sprague Dawley Rats (SC PK). All rats received single subcutaneous (SC) injection of a single dose dose of LIQ865A, Marcaine or Exparel. Blood samples were collected at necropsy
- Blood samples were collected via jugular catheter
- Sparse sampling method (samples collected at 24 time points per rat)

**Summary: SC Administration In Rats**

- **Bup Cmax** when administered as LIQ865A, was lower than the Cmax for Expere or Marcaine administered at a similar or lesser dose.
- Bup exposure, as measured by AUC(0-24h) increased in a less than dose proportional manner when administered as LIQ865A.
- Bup half-life was generally dose proportional when administered as LIQ865A.
- There were no gender differences in Bup exposure.

**IN RATS. Plasma Bupivacaine Cmax did not increase with Increasing LIQ865A Dose**

**RESULTS**

**In Minipigs, LIQ865A Dosed 3 Times Higher than Marcaine Resulted in Lower Bupivacaine Cmax Values**

**SC Administration of Lidocaine to Minipigs 5 min prior to LIQ865A Did Not Result in a Burst Release of Bupivacaine**

**CONCLUSION**

- SC Administration of LIQ865A resulted in a slow release of Bupivacaine following SC administration in rats and minipigs: 
  - Delayed Tmax resulted compared to Marcaine or Exparel
  - Less than dose proportional increase in Cmax with increasing dose
  - Increased AUC with increasing LIQ865A dose
  - Prolonged t1/2 with increasing LIQ865A dose

**LIQ865A Produces a Slow Controlled Release of Bupivacaine after Subcutaneous Dosing in Rats and Minipigs #1600**

Marcaine™ is a trademark of Pfizer Inc.
LIQ865A is a slow release microparticle formulation of bupivacaine, is well-tolerated and does not interfere with wound healing after subcutaneous dosing in rats and minipigs.

### INTRODUCTION AND OBJECTIVE

LIQ865A is a bupivacaine (Bup) formulation developed by LiquiDynamics, Inc. for the management of local post-operative pain using a proprietary process technology called PRINT® (Particle Replication In Non-wetting Templates). The core process involves four basic steps: 1) Create a film of the desired composition on a delivery sheet. 2) Laminate the film with a mold template where the material is shaped into a predefined form. 3) Remove particles from the mold template. 4) Collect particles to create a particle suspension or dry powder.

During PRINT manufacturing, the components are formed into the desired shape and size using a molding process that produces a bulk powder consisting of particles of uniform size, shape, and composition. Several variables can be varied to produce a wide range of shapes, sizes, and compositions. The core process involves four basic steps:

1. Create a film of the desired composition on a delivery sheet.
2. Laminate the film with a mold template where the material is shaped into a predefined form.
3. Remove particles from the mold template.
4. Collect particles to create a particle suspension or dry powder.

### PRINT® Fabrication Process

**Step 1**: Create a film of the desired composition on a delivery sheet.
**Step 2**: Laminate the film with a mold template where the material is shaped into a predefined form.
**Step 3**: Remove particles from the mold template.
**Step 4**: Collect particles to create a particle suspension or dry powder.

### STUDY DESIGN AND METHODS

**Single SC Administration Toxicity Study In Rats**

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<tr>
<th>Treatment</th>
<th>Bup (mg/kg)</th>
<th>Particle Conc. (mg/mL)</th>
<th>Total Conc. (mg/mL)</th>
<th>No. of Animals/Sex/Cohort</th>
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<td>168</td>
<td>6.0</td>
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**Single SC Administration Toxicity Study in Minipig**

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**In Rats and Minipigs, LIQ865A Administration over a 4 to 6 fold Bup Dose Range Resulted in <2X InCREASE In Bup Cmax**

**In Minipigs, LIQ865A was Well-Tolerated with No Effect on Wound Healing**

**CONCLUSION**

In both rats and minipigs, the local changes associated with LIQ865A were consistent with a degradable foreign body response and what is reported for Bupivacaine. No novel findings or safety concerns were identified. The high dose level was considered the NOAEL in both studies.