

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

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INTRODUCTION and OBJECTIVE

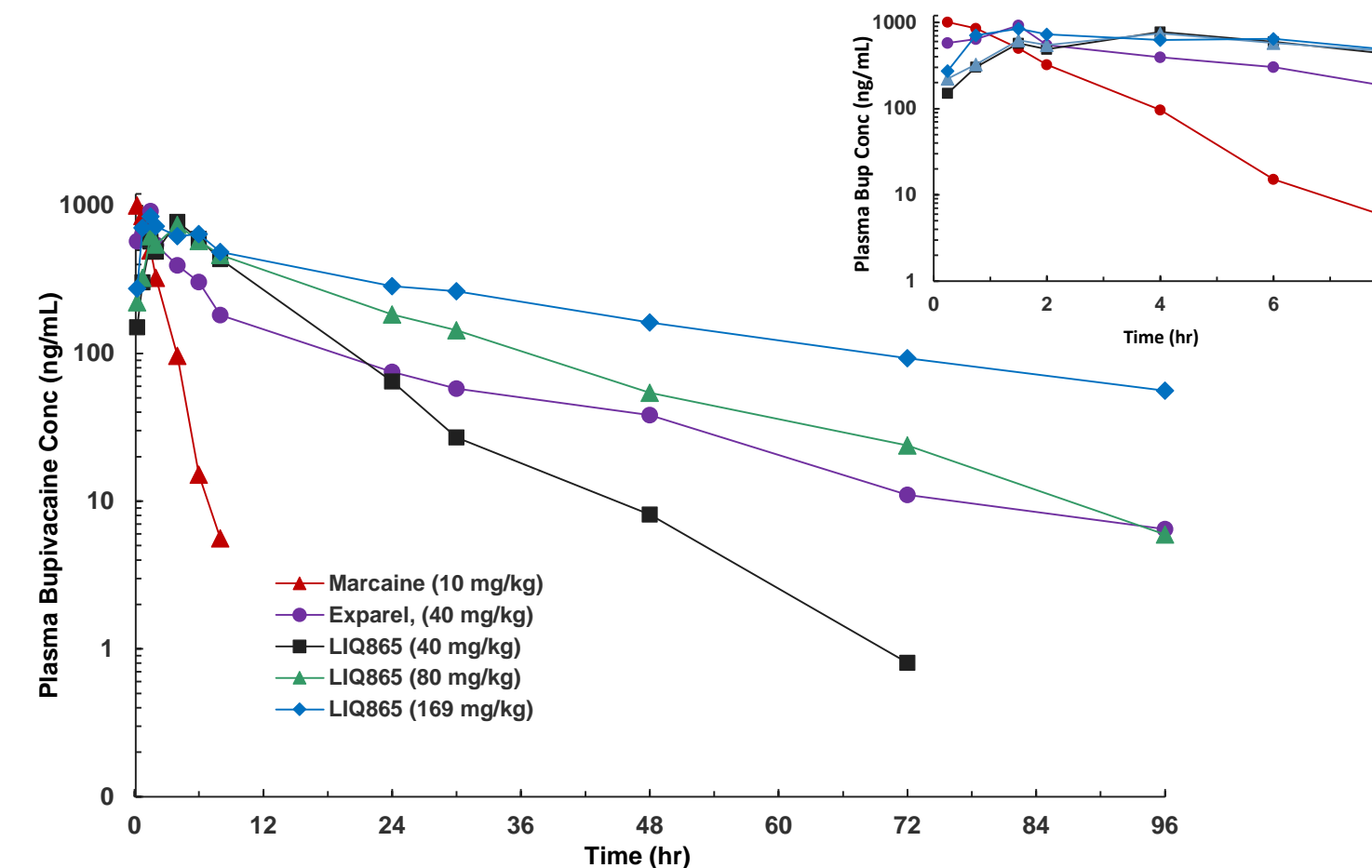
LIQ865A is a bupivacaine particle formulation developed by Liquidia Technologies, Inc. for the management of local post-operative pain. LIQ865A is manufactured using a proprietary process technology called PRINT® (Particle Replication In Non-wetting Templates) producing 25 µm hexagonal particles comprised of approximately 55% bupivacaine and 45% poly(lactic-co-glycolic) acid (PLGA). Particles are suspended in a custom vehicle for surgical site infiltration or subcutaneous (SC) administration. LIQ865A is designed to slowly release bupivacaine at the surgical site over 3 to 5 days providing a longer pain management solution as compared to the current state of the art without increasing the potential for systemic toxicity secondary to an increase in plasma concentrations of bupivacaine.

To support clinical testing, single dose bupivacaine (Bup) pharmacokinetics (PK) from subcutaneously administered LIQ865A, Marcaine™ (Bup HCl solution) and Exparel® (liposomal 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 (Rat SC PK):**
 - All rats received a single SC administration of test article (LIQ865A, Exparel, Marcaine)
 - Blood samples were collected via jugular venipuncture
 - Sparse sampling method (samples collected at 5 or 6 time points per rat)
- Miniature Swine (Yucatan):**
 - Blood samples were collected via indwelling jugular catheter.
 - Single SC Administration PK (Pig SC PK) and SC LIQ865A and Lidocaine Single SC Administration (Pig 865A/Lido PK):**
 - 3-6 SC injections along virtual 5-cm incision line
 - Lidocaine was administered 5 min prior to LIQ865A along the virtual incision line
 - Incisional Wound Model PK (Pig Wound PK):**
 - 10-cm full-thickness incisional wound on left dorsum perpendicular to midline.
 - Half of total volume administered subcutaneously on each side of the incision directly thru the open incision
 - Following dosing, incision was sutured closed and bandaged

In Rats, Plasma Bupivacaine C_{max} did not Increase with Increasing LIQ865A Dose



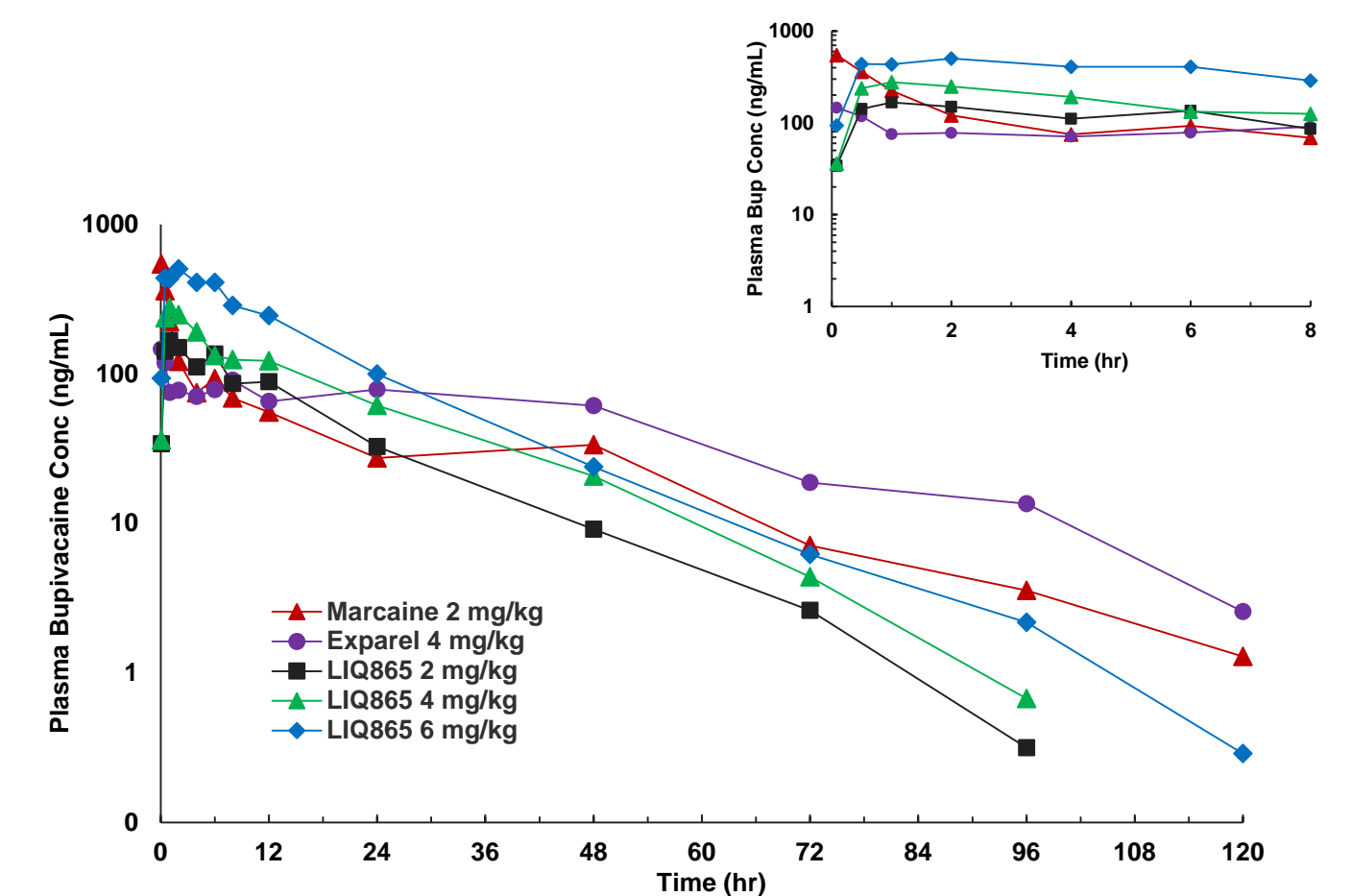
Mean Plasma Bup PK Parameters					
Treatment Group	Dose (mg/kg)	C _{max} (ng/mL)	T _{max} (hr)	t _{1/2} (hr)	AUC _{inf} (hr*ng/mL)
Marcaine	10	1004	0.3	1.0	1864
Exparel	40	919	1.5	15.3	7570
LIQ865A	40	777	4.0	7.6	9105
LIQ865A	80	743	4.0	16.1	13591
LIQ865A	169	844	1.5	28.1	23737

Summary: SC Administration In Rats

- Bup C_{max} when administered as LIQ865A, was lower than the C_{max} for Exparel or Marcaine administered at a similar or lower dose.
- Bup exposure, as measured by AUC_{inf}, increased in a less than dose proportional manner.
- Bup half-life was generally dose proportional when administered as LIQ865A.
- There were no gender differences in Bup exposure.

RESULTS

In Minipigs, LIQ865A Dosed 3 Times Higher than Marcaine Resulted in Lower Bupivacaine C_{max} Values

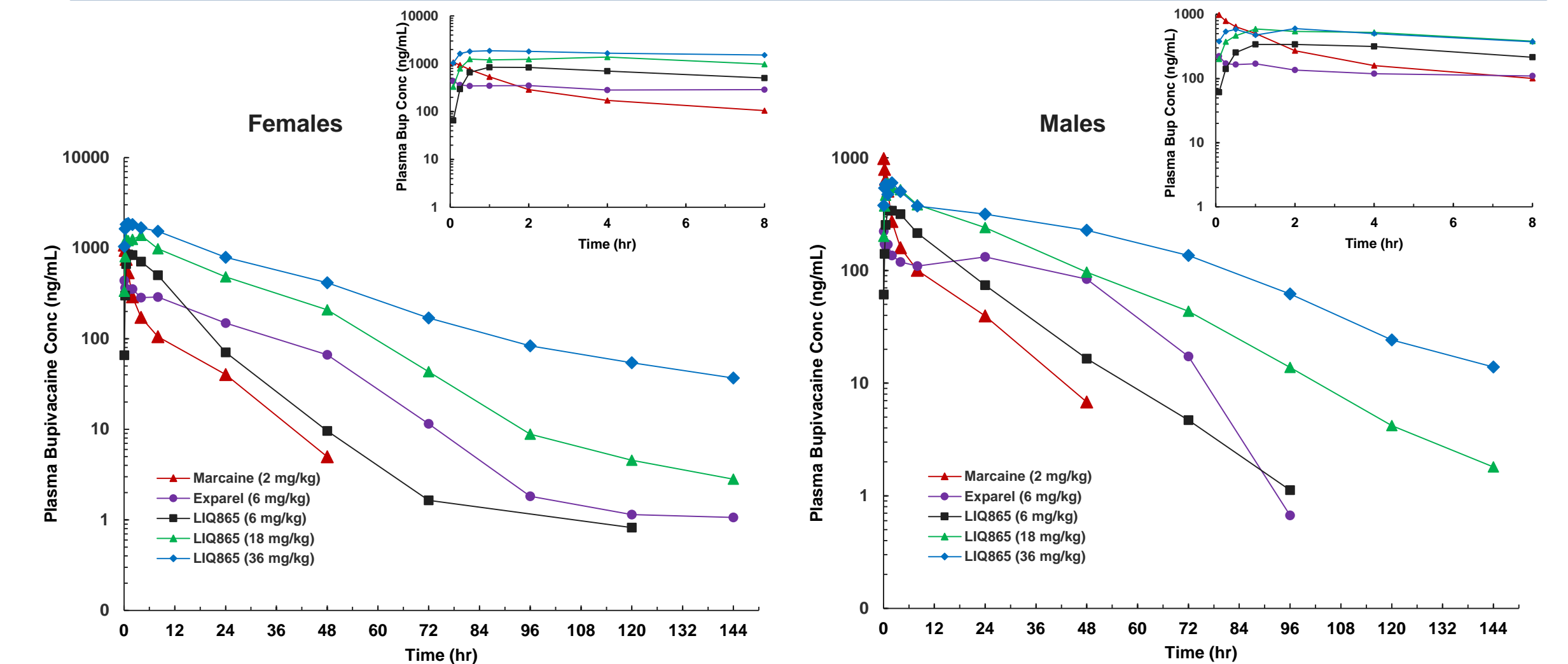


Mean Plasma Bup PK Parameters					
Treatment Group	Dose (mg/kg)	C _{max} (ng/mL)	T _{max} (hr)	t _{1/2} (hr)	AUC _{inf} (hr*ng/mL)
Marcaine	2	545	5 min	19.7	3010
LIQ865A	2	174	1.0	14.8	2780
Exparel	4	146	5 min	24.4	5050
LIQ865A	4	297	1.0	10.7	4400
LIQ865A	6	511	2.0	13.7	8320

Summary: SC Administration In Male Minipigs

- At 4 mg/kg, Exparel had the fastest absorption with a T_{max} at 5 min compared to LIQ865A at 1 hr.
- SC administration of low doses of LIQ865A resulted in dose proportional increases in Bup Exposure (C_{max}, AUC).
- Bup exposure (C_{max}, AUC) was generally dose proportional when administered as LIQ865A.
- Bup half-life did not change with increasing LIQ865A dose.

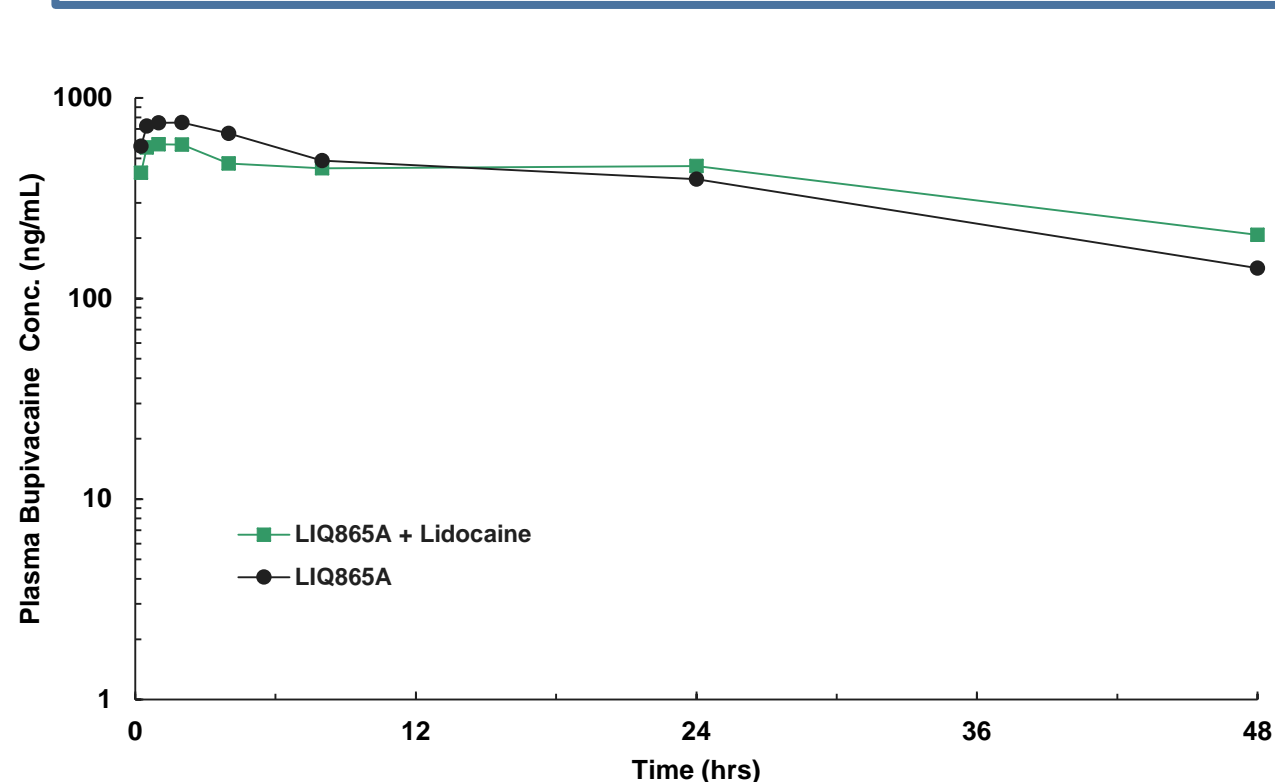
In a Mlnipig Full-Thickness Incisional Model, SC Administration of LIQ865A Over a 6-Fold Bupivacaine Dose Range Resulted in Only a 2X Increase in Bupivacaine C_{max}



Mean Plasma Bup PK Parameters							
Treatment Group	Dose (mg/kg)	Sex	C _{max} (ng/mL)	T _{max} (hr)	t _{1/2} (hr)	AUC _{last} (hr*ng/mL)	AUC _{inf} (hr*ng/mL)
Marcaine	2	M	984	5 min	9.5	3670	3780
		F	1080	5 min	8.0	3830	3930
Exparel	6	M	224	5 min	8.3	6890	7890
		F	443	5 min	19.8	9380	9980
LIQ865A	6	M	359	2.0	9.0	5940	6020
		F	865	2.0	8.3	11000	9480
LIQ865A	18	M	604	1.0	18.2	15500	15700
		F	1450	2.0	13.8	33400	33500
LIQ865A	36	M	620	2.0	20.0	24200	24600
		F	1920	1.0	32.9	59300	61100

LIQ865A Dose Proportionality							
Treatment Group	Dose (mg/kg)	Increase ^a	Male			Female	
			C _{max}	AUC _{last}	AUC _{inf}	C _{max}	AUC _{last}
LIQ865A	6	-	--	--	--	--	--
LIQ865A	18	3.0	1.7	2.6	2.6	1.7	3.0
LIQ865A	36	2.0	1.0	1.6	1.6	1.3	1.8
	overall ^b	6.0	1.7	4.1	4.1	2.2	5.4

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



Mean Plasma Bup PK Parameters				
Treatment	C _{max} (ng/mL)	T _{max} (hr)	AUC _{last} (hr*ng/mL)	AUC _{inf} (hr*ng/mL)
LIQ865A	782	1.50	22200	22400
LIQ865A + Lidocaine	613	1.50	25400	26700

Summary: SC Co-Administration of LIQ865A with Lidocaine in Mlnipigs

- No burst release of Bup when LIQ865A was dosed 5 min after Lidocaine as evidenced by a slightly lower mean C_{max} value than LIQ865A alone.
- Lidocaine did not change the Bup T_{max}.
- No gender differences were seen in Bup exposure.

Summary: SC Administration In Mlnipig Incisional Model

- At 6 mg/kg, Exparel and LIQ865A produced similar Bup AUCs and similar half-life.
- T_{max} was earliest for Exparel and Marcaine (5 min) compared to 1 to 2 hours for LIQ865A.
- Bup C_{max} was less than dose proportional while AUC was generally dose proportional
- Mean Bup C_{max} was similar at 18 and 36 mg/kg within LIQ865A genders.
- Gender differences in Bup exposure were evident for LIQ865A and Exparel.

CONCLUSION

- SC Administration of LIQ865A results in a slow controlled release of Bup without an initial burst following SC administration in rats and miniature swine:
 - Delayed T_{max} compared to Marcaine or Exparel
 - Less than dose proportional increase or no increase in C_{max} with increasing dose
 - Increased AUC with increasing LIQ865A dose
 - Prolonged t_{1/2} with increasing LIQ865A dose

Study Parameters	Rat SC PK	Pig SC PK	Pig Wound PK	Pig 865A/Lido PK
Treatment	Marcaine Exparel LIQ865A	Marcaine Exparel LIQ865A	Marcaine Exparel LIQ865A	LIQ865A LIQ865A/Lidocaine
Bup Doses (mg/kg)	10 40	2 4	2 6	18 18/4
Bup Conc. (mg/mL)	40, 80, 169 7.5	2, 4, 6 5	6, 18, 36 5	45 13.3
Dosing Volume (mL/kg)	26.7, 53.3, 113 1.35 3.0 1.5	6.7, 13.3, 20.0 0.4 0.3 0.3	15, 45, 90 0.45 0.4	45/20 0.4 0.4/0.2
No. of Animals (n/sex/group/time pt)	3 (Marcaine, males only)	3 (males only)	3	4
Blood Sampling Times (Hours Post Dose)	0.25, 0.75, 1.5, 2, 4, 6, 8, 24, 30, 48, 72, 96 hrs	0.083, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120 hrs	0, 0.083, 0.25, 0.5, 1, 2, 4, 8, 24, 48, 72, 96, 120, 144 hrs	0, 0.25, 0.5, 1, 2, 4, 8, 24, 48, 72, 96, 120 hrs

PK Analysis: Phoenix WinNonlin, ver. 6.3 or 6.4

Bioanalytical Methodology (AIT Biosciences):

- Validated Method: Solid phase extraction and LC-MS/MS instrumental analysis
- Range: 2 – 2000 ng/mL

Exparel® is a registered trademark of Pacira Pharmaceuticals, Inc. Marcaine™ is a trademark of Pfizer Inc.