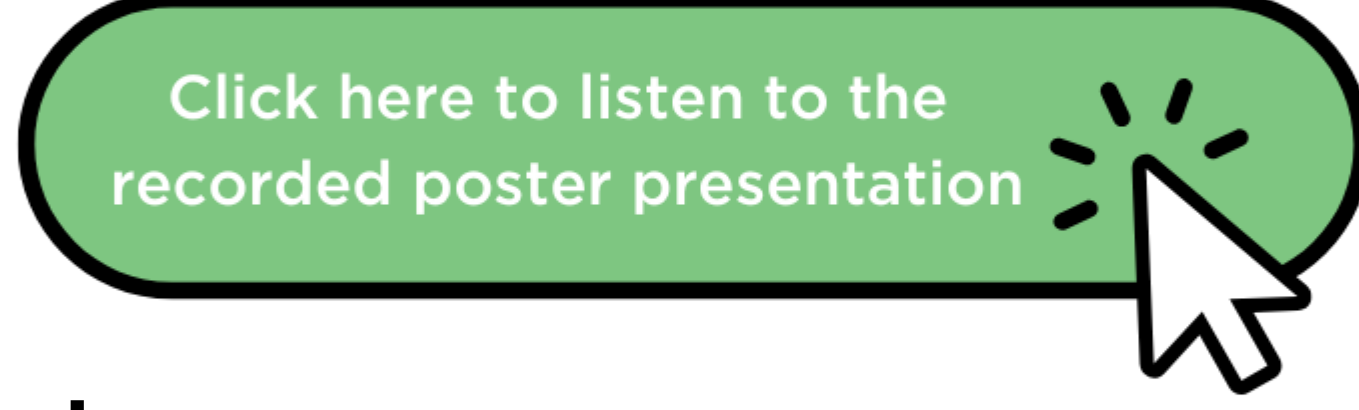


# Pharmacokinetic Study of a Long-Acting Transdermal Buprenorphine in Four Strains of Miniature Swine

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## INTRODUCTION

- Buprenorphine is a semisynthetic, partial  $\mu$ -opioid receptor agonist, widely used for analgesia in laboratory animals.
- Long-acting buprenorphine injectable formulations are available that provide prolonged analgesia.
- Disadvantages of injectable formulations in swine:
  - No approved product for swine.
  - Available pharmaceutical-grade product requires large volumes for swine and is costly.
  - Other products are non-pharmaceutical, compounded, and difficult to obtain due to availability.
- A new transdermal long-acting buprenorphine, Zorbium®, is approved to provide up to 4 days of analgesia in cats.
- Advantages of long-acting transdermal formulation of buprenorphine in swine:
  - No injection stress
  - Cost-effective
  - Pharmaceutical grade
  - Ease of administration
  - Readily Available
  - Prolonged analgesia
- Hypothesis:** Topical Zorbium® would result in therapeutic levels of at least 0.1 ng/ml for up to 96 hours in four strains of minipigs, comparable to a long-acting injectable formulation.

## METHODS

- Detailed clinical observations:
  - 6-8 hours post dose
  - Daily for 3 days post dose
- Modified draize scores:
  - 1-2 hours post dose
  - Daily for 3 days post dose
- Blood collected pre-dose, 0.5, 1, 2, 4, 8, 12, 24-, 48-, 72-, and 96-hours post-dose.
- Buprenorphine was analyzed in K2EDTA plasma samples by liquid-liquid extraction and LC-MS/MS (analytical range is 10-4000 pg/ml).
- Non-compartmental analysis of plasma concentration conducted on individual concentration data using validated Phoenix® WinNonlin® version 8.0.

Table 1: Experimental Design

Group	Test Material	Dosing Phase Day	Dose Level (mg/kg)	Dose Route	Animals <sup>b</sup>
1	Bup ER	1	0.24	SC	Yucatan (n=2/sex)
2	Zorbium®	1	1	Topical <sup>a</sup>	Yucatan Hanford Göttingen
		15	2.5		Sinclair Nanopig (n=2/sex/strain)
3	Zorbium®	1	2.5	Topical <sup>a</sup>	Göttingen Sinclair Nanopig (n=3/sex/strain)

<sup>a</sup>Topical administration was performed on the dorsal surface where the pinna joins the head and there is minimal interference with hair. For animals dosed at 2.5 mg/kg, the amount was split evenly between both ears to accommodate larger volumes.  
<sup>b</sup>Animals ranged from 5-21 months of age & 19.4-62.7 kg based on availability.

## RESULTS

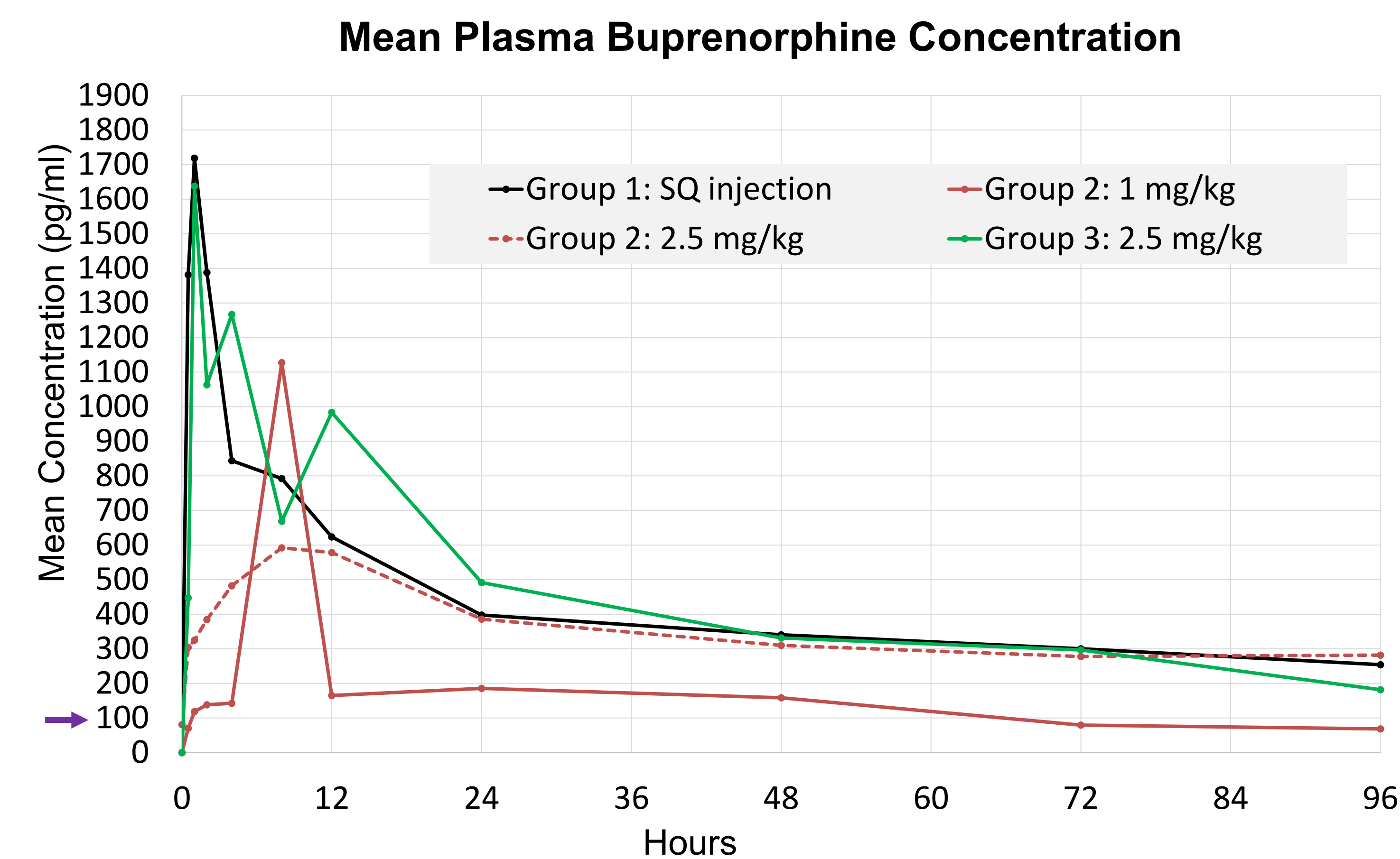


Figure 1: Mean plasma buprenorphine concentration per group and dose level. Arrow = target therapeutic level.

Note: Group 2 was dosed on Day 15 at 2.5 mg/kg following a wash-out period from the initial dose administered on Day 1 (1 mg/kg). Predose concentrations were not below the limit of quantitation following the wash-out period.  $T_{1/2}$ , CL/F, and Vz/F were not reportable due to the lack of a distinct elimination phase.

Table 3: Clinical Signs Summary

Group	Clinical Sign	Animals Affected
1	Swelling at dose site	4 of 4 Yucatan
	Vomitus	1 (f) Yucatan
2	Vomitus	1 (m) Gottingen (2.5 mg/kg)
3	Mild decreased food consumption	2 (m) and 1 (f) Gottingen

Table 4: Cost Comparison Between Common Long-Acting Buprenorphine Formulations

	Zorbium® (20 mg/ml)	Bup-ER (10 mg/ml)	Ethiq® (1.3 mg/ml)
Price/ml	\$16.54	\$114.00	\$138.33
Dose Level	2.5 mg/kg	0.24 mg/kg	0.24 mg/kg
Dose for 30 kg pig	3.8 ml	0.7 ml	5.5 ml
Price for one dose	\$62.03	\$82.08	\$766.15

## CONCLUSIONS

- Animals receiving SC Buprenorphine ER and topical Zorbium® at 2.5 mg/kg had sustained buprenorphine concentrations at or above therapeutic range for at least 96 hours post dose.
- Sex-related differences in mean  $C_{max}$  and  $AUC_{0-96}$  values were less than 2-fold following either SC or topical administration of Zorbium®.
- Exposure to buprenorphine, in terms of  $C_{max}$  and  $AUC_{0-96}$ , was generally similar between minipig strains (< 2-fold difference) when Hanford, Sinclair, and Göttingen miniature swine were compared to Yucatan miniature swine.
- Zorbium® at 2.5 mg/kg offers comparable plasma concentration levels as the SC formulation with minimal clinical signs and cost savings. As such, it has become part of our standard analgesia regimen in swine.

Table 2: Summary of Plasma Pharmacokinetic Parameters

Group	Level (mg/kg)	Strain	Sex	$T_{max}$ (h)	$C_{max}$ (pg/ml)	$C_{last}$ (h)	$AUC_{0-96}$ (h*pg/ml)
1	0.24	Yucatan	F	0.750	1580	253	37100
			M	4.50	2110	255	43600
2	1	Yucatan	F	28.0	1480	95.1	17500
			M	10.0	1040	49.8	10000
			F	4.25	922	423	44900
			M	12.0	643	198	24300
	2.5	Hanford	F	8.00	1060	89.5	20500
			M	28.0	1360	96.6	15500
			F	4.25	1350	298	37100
			M	6.00	764	343	37300
	1	Sinclair	F	12.5	715	56.7	20100
			M	12.0	343	61.7	9210
			F	4.25	788	263	34500
			M	8.00	541	205	25700
2.5	Göttingen	F	8.00	241	54.6	8940	
		M	28.0	630	43.8	18300	
		F	12.0	586	325	36200	
		M	2.25	663	202	31100	
3	2.5	Sinclair	F	4.00	1190	158	43500
			M	12.0	2590	170	51000
		Göttingen	F	4.00	1600	227	41900
			M	4.00	5790	174	38000