

**Lipocine's Lip'ral™ Technology
Platform for the Optimal
Absorption of Poorly Water
Soluble Drugs**

Typical Problems with Poorly Water Soluble Drugs

- **Poor bioavailability leading to high dose and/or multiple dosage units per dose**
- **Highly variable pharmacokinetics leading to inadequate therapy and/or safety concerns**
- **Significant food effects on bioavailability leading to dosing restrictions in labeling and consequent patient compliance problems**

Conventional Approaches Nanoparticle technology

- **Nanoparticle technology**
 - **Primarily increase surface area for dissolution**
 - **Addresses only the dissolution rate aspect of the problem with delivery of poorly soluble drugs**
 - **Introduces manufacturing complexity**
- **Nanoparticle technology does not address**
 - **transport challenges across the aqueous boundary layer**
 - **effect of physiological factors – food, pH effects**
 - **precipitation/re-dissolution issues**

Conventional Approaches Solid Dispersion Technology

- **Solid dispersion technology**
 - Stabilizes a more rapidly dissolving “amorphous state” of the drug in a solid matrix
 - Addresses only the dissolution rate aspect of the problem with delivery of poorly soluble drugs
 - Introduces significant physical stability concerns and manufacturing complexity
- **Solid dispersion technology does not address**
 - transport challenges across the aqueous boundary layer
 - effect of physiological factors – food, pH effects
 - precipitation/re-dissolution issues

Basis of Food Effects on Absorption of Poorly Soluble Drugs

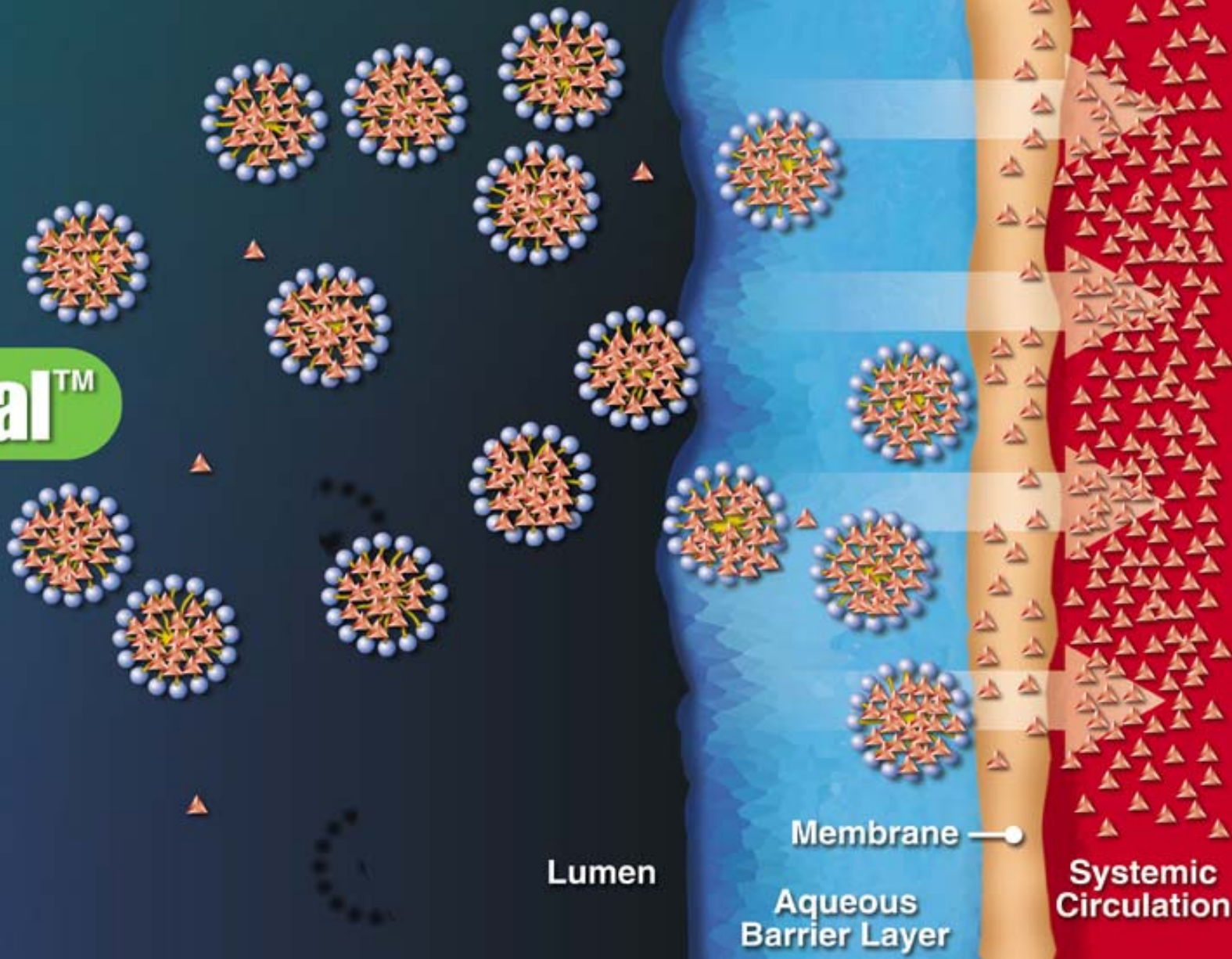
- **Mono and di-glycerides generated from digestion of meal fat**
- **Bile salts secreted following ingestion of meal**
- **Mono/di-glycerides and bile salts form mixed micelles that solubilize the drug and transport it to the absorption site, thus improving absorption**

Lip'ral™ Technology

- **Lip'ral technology is based on lipidic compositions that form the optimal dispersed phase for absorption of poorly water soluble drugs**
- **Lip'ral technology greatly improves upon the mechanism by which food increases absorption of poorly water soluble drugs**

Lip'ral™ in the GI Tract

Lip'ral™



Lip'ral™ Technology Platform

- Proprietary compositions of **bioacceptable** lipid excipients with high drug loading capacity
- Robust to dilution - spontaneous formation of micellar phase over a range of aqueous dilutions
- Drug stays solubilized upon dilution
- Conventional scale-up and manufacturing process
- Protected by several issued and pending patents, world-wide

Lip'ral™ Solubility of Hydrophobic Drugs

<u>Active</u>	<u>Aq. Solubility</u>	<u>Lip'ral Sol. (Enhancement)</u>
simvastatin	~3 µg/ml	60 mg/ml (20,000)
carvedilol	~30 µg/ml	90 mg/ml (3000)
cyclosporine	~6 µg/ml	150 mg/ml (25,000)
rapamycin	~6 µg/ml	10 mg/ml (1,600)
fenofibrate	~0.1 µg/ml	100 mg/ml (1,000,000)
isotretinoin (acid)	~5 µg/ml	40 mg/ml (8,000)
itraconazole (basic)	<0.1 µg/ml	40 mg/ml (400,000)
progesterone	~6 µg/ml	50 mg/ml (8,000)

**EXTENT OF SOLUBILITY ENHANCEMENT
ACHIEVED BY LIP'RAL FAR SUPERIOR TO
CONVENTIONAL TECHNOLOGIES**

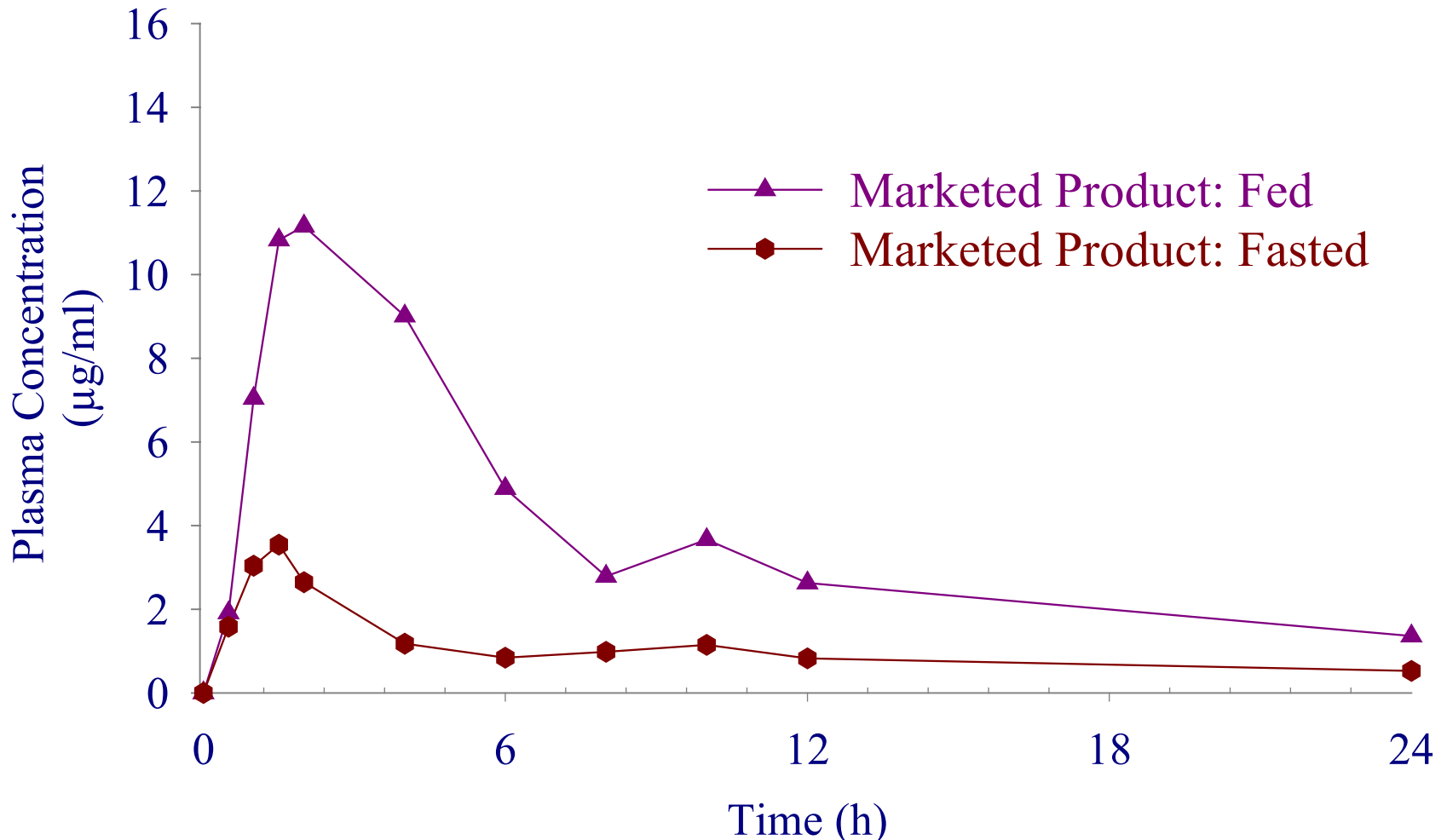
CASE STUDY 1

Model Compound LPCN 1001

- **Non-Ionizable Hydrophobic Drug**
- **Very Low Aqueous Solubility of $\sim 0.1 \mu\text{g/ml}$**

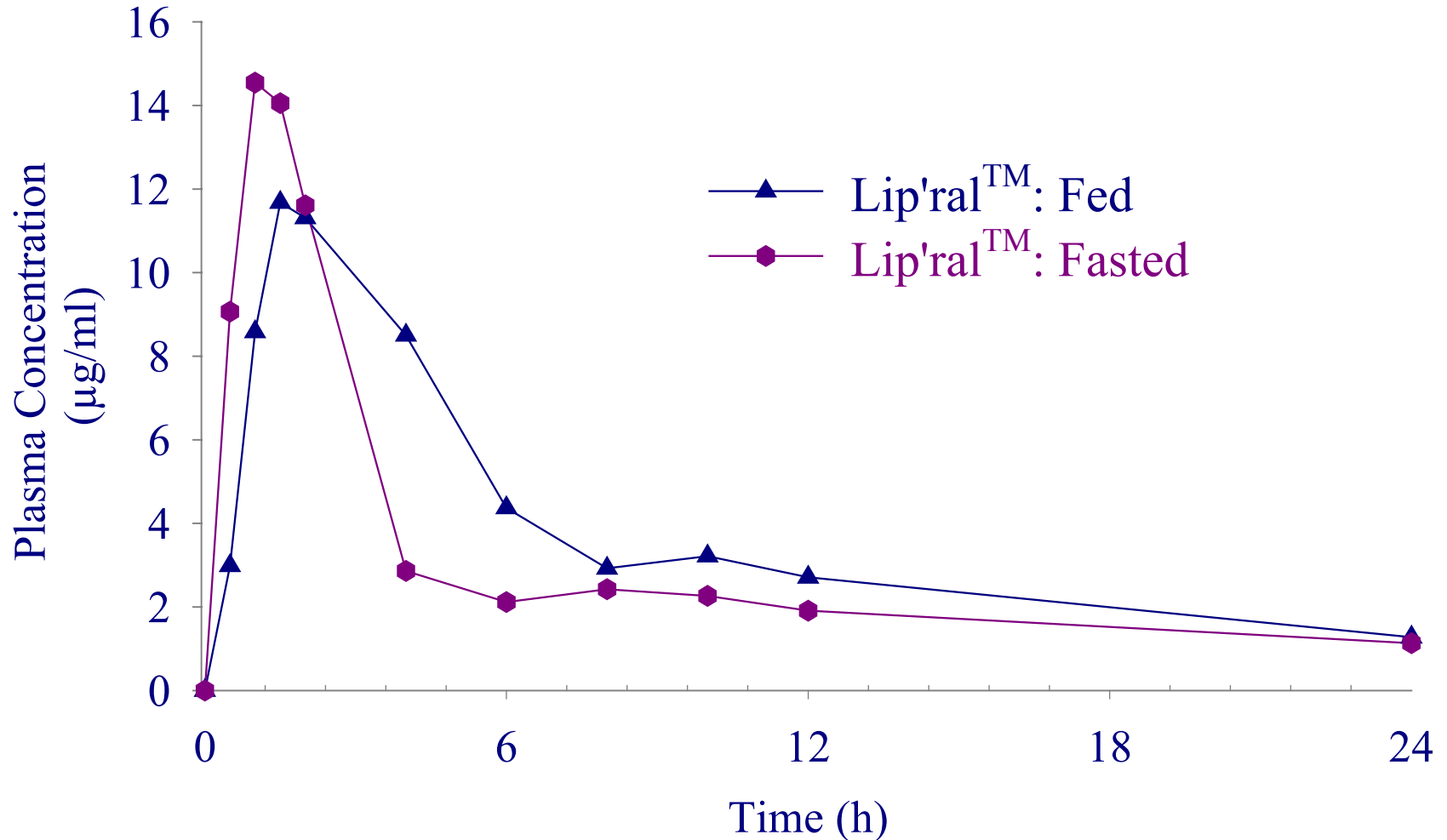
**Marketed Product Must be Taken
With Food to be Efficacious**

Marketed Product Fed vs. Fasted In Dogs



*Absorption 4-fold lower under fasting
condition with marketed product*

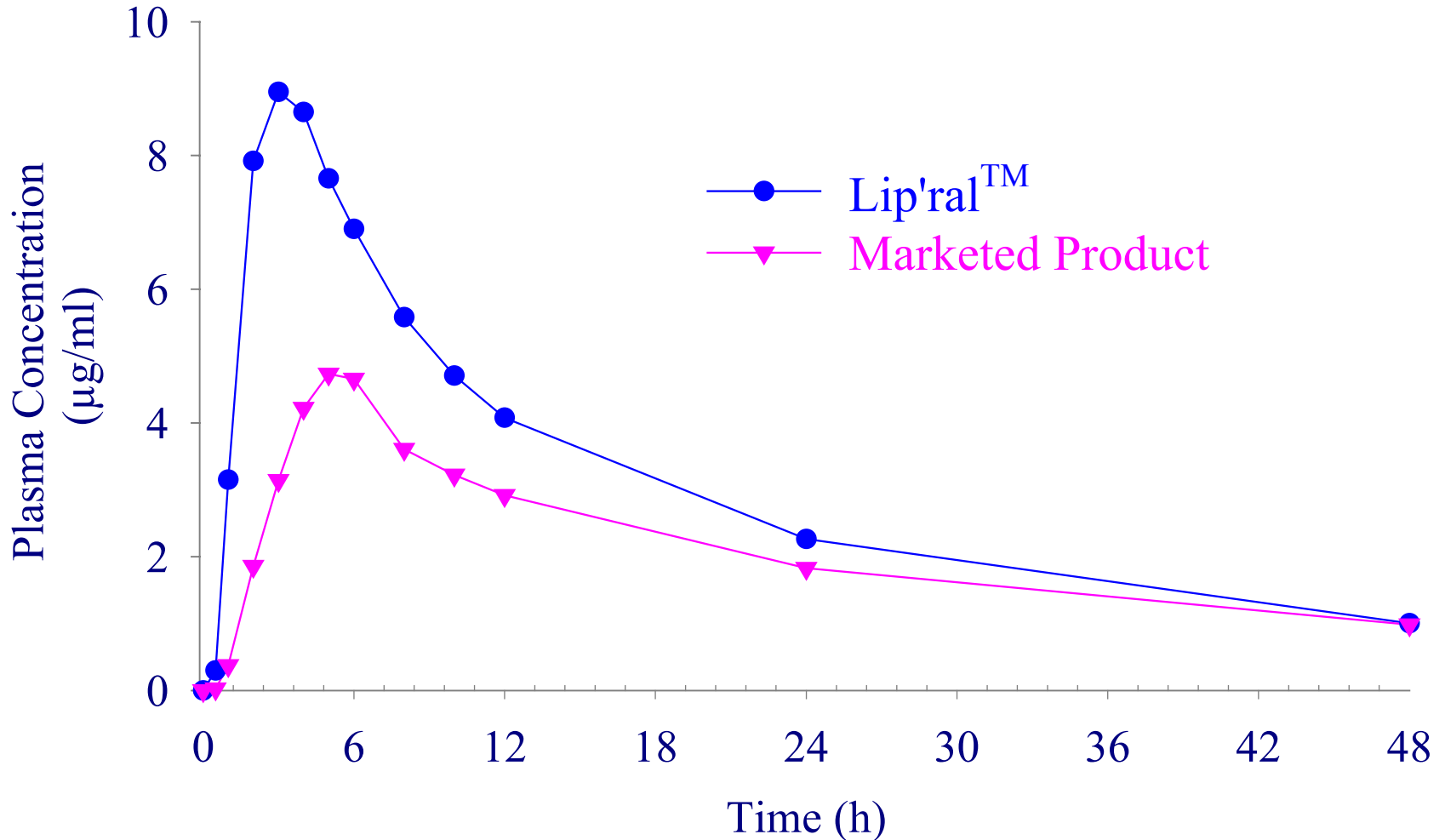
Lip'ral™ Capsule Fed vs. Fasted in Dogs



*Equivalent absorption under fed and
fasted conditions with Lip'ral™*

Lip'ral™ vs. Marketed Product

Protocol 1001-02-001, n=11 healthy volunteers



*Significantly reduced efficacious dose
with Lip'ral™*



CASE STUDY 2

Model Compound

LPCN 1002

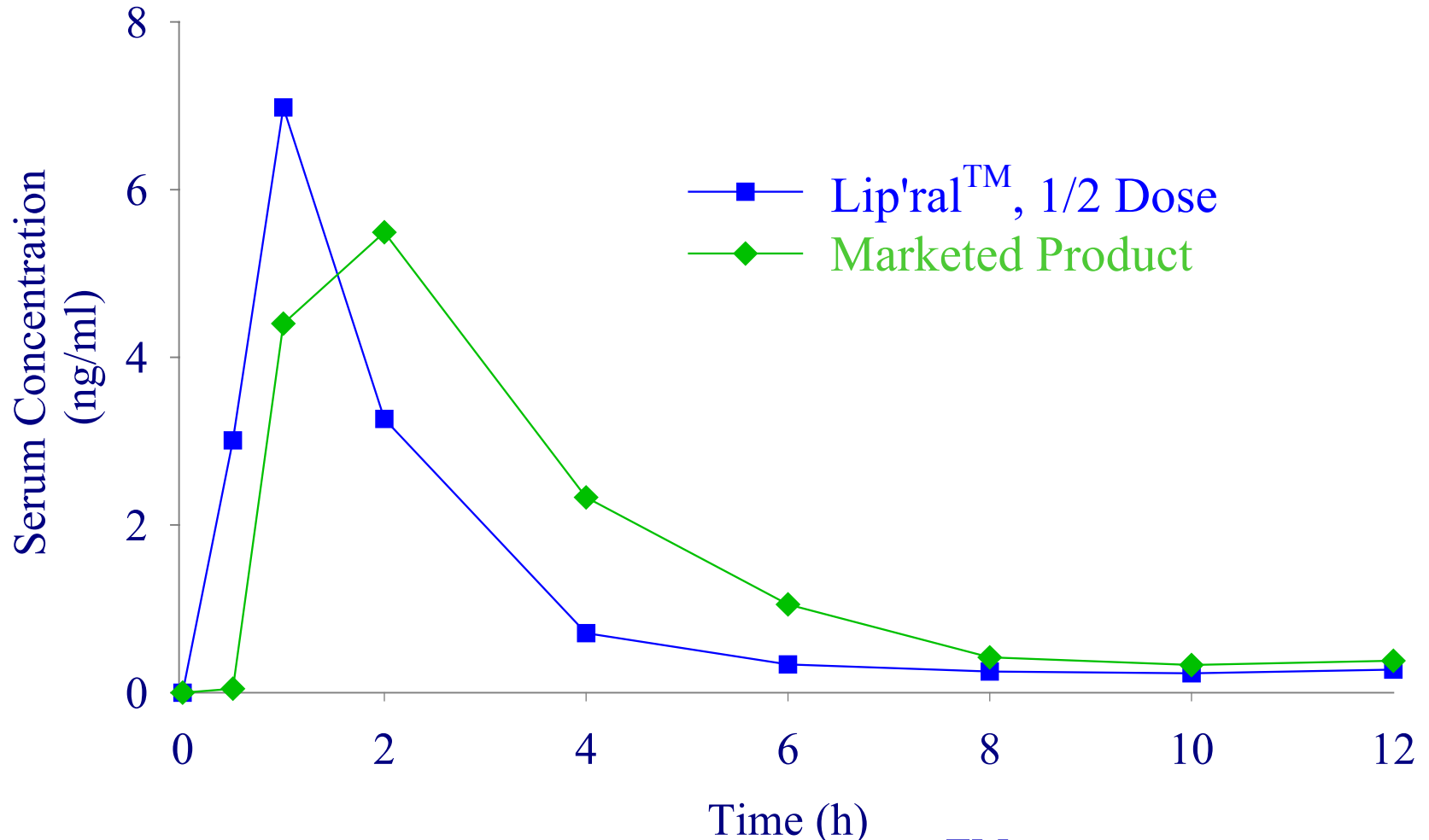
- Non-Ionizable Hydrophobic
- Very Low Aqueous Solubility of $\sim 5 \mu\text{g/ml}$

Marketed product is

- Poorly absorbed
- Highly variable AUC and C_{max}

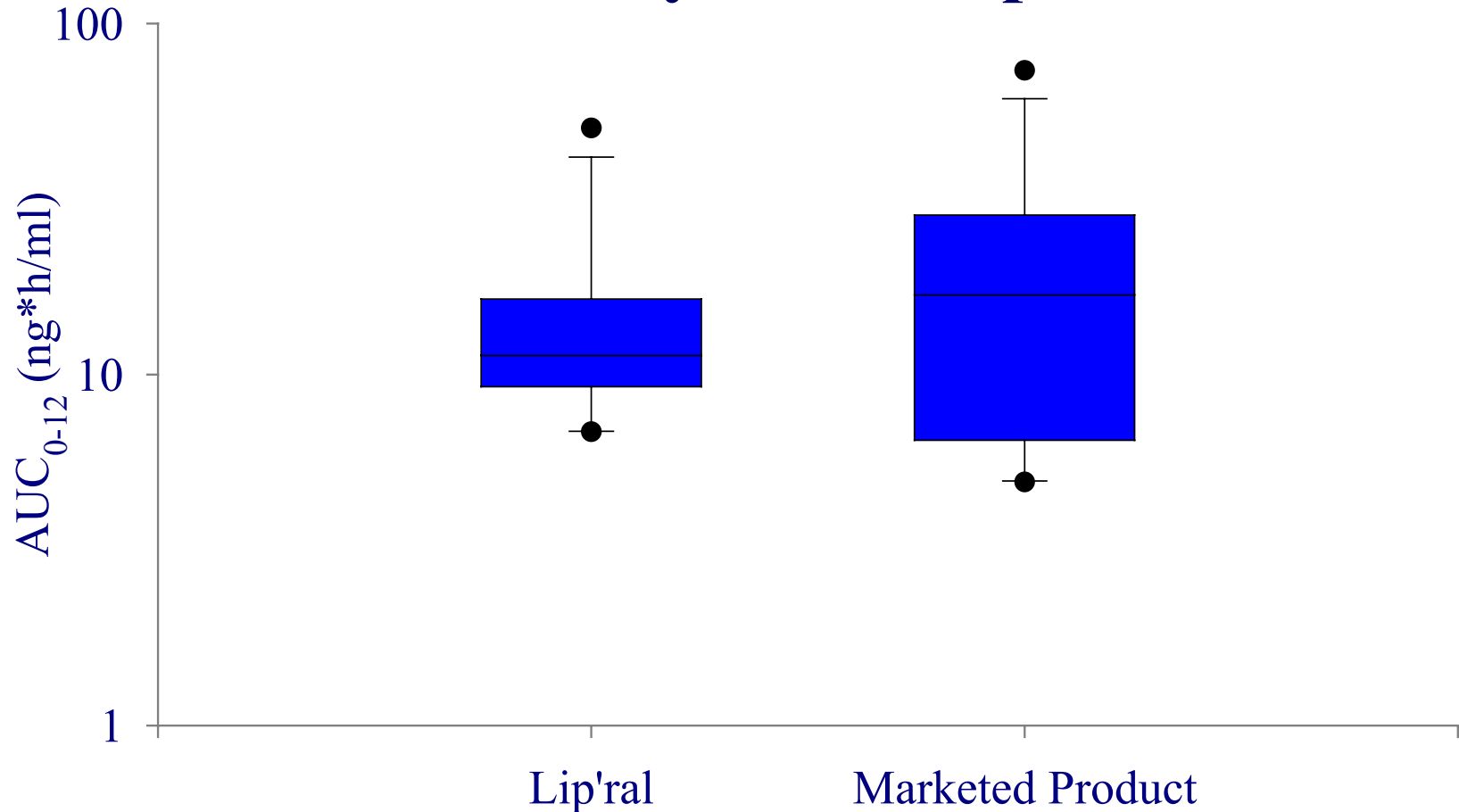
Lip'ral™ vs. Marketed Product

Protocol 1002-01-01, n=12 healthy volunteers



*Comparable absorption with Lip'ral™
at half the dose*

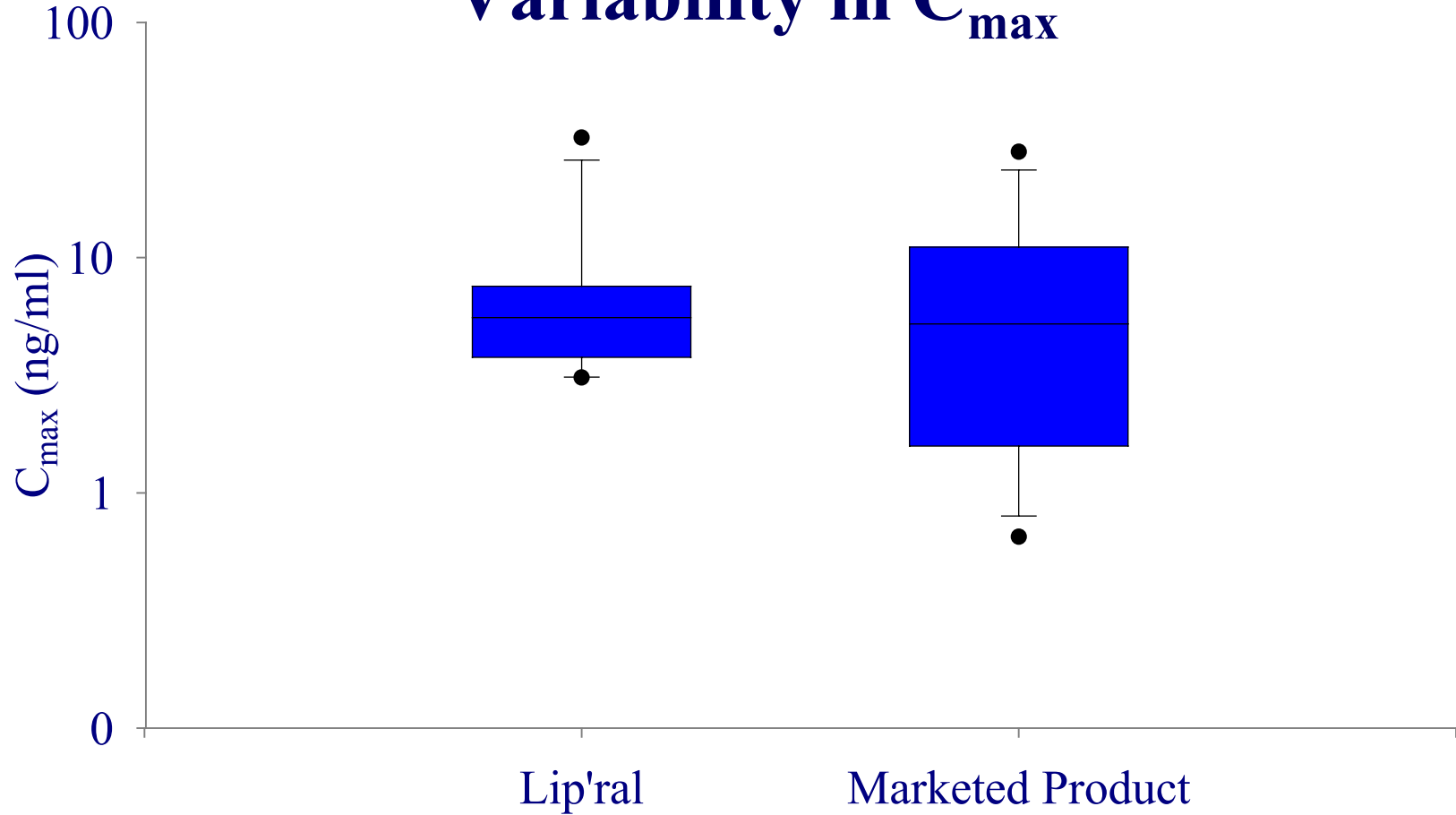
Lip'ral™ vs. Marketed Product Variability in Absorption



Lip'ral™ reduced variability in AUC

Lip'ral™ vs. Marketed Product

Variability in C_{max}



Lip'ral™ reduced variability in C_{max}

CASE STUDY 3

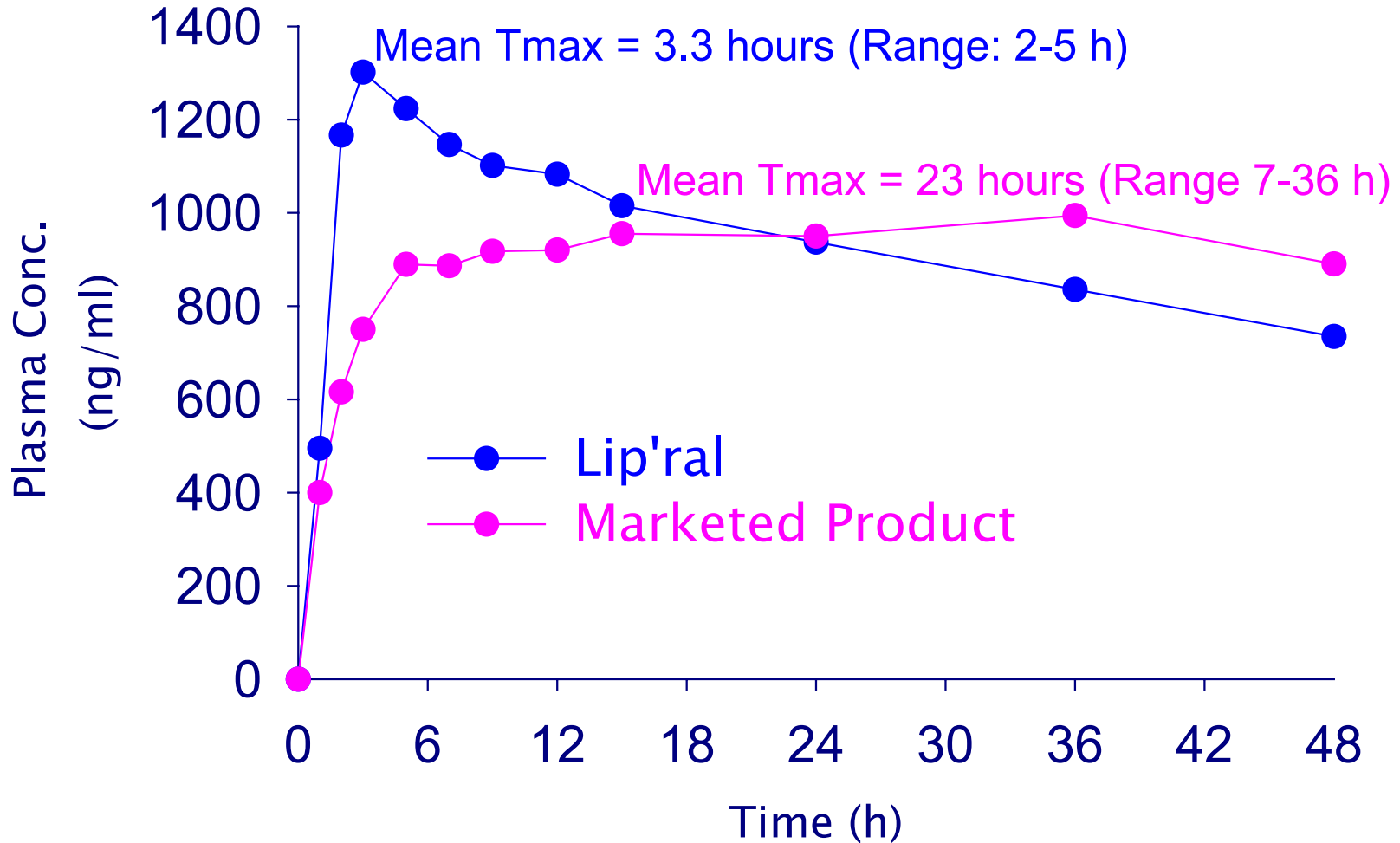
Model Compound

LPCN 1015

- Non-Ionizable Hydrophobic
- Very Low Aqueous Solubility of $\sim 3 \mu\text{g/ml}$
- **Very slow absorption, $T_{\text{max}} > 24 \text{ h}$**
- **Target - *faster, more consistent absorption***

Clinical Study Results

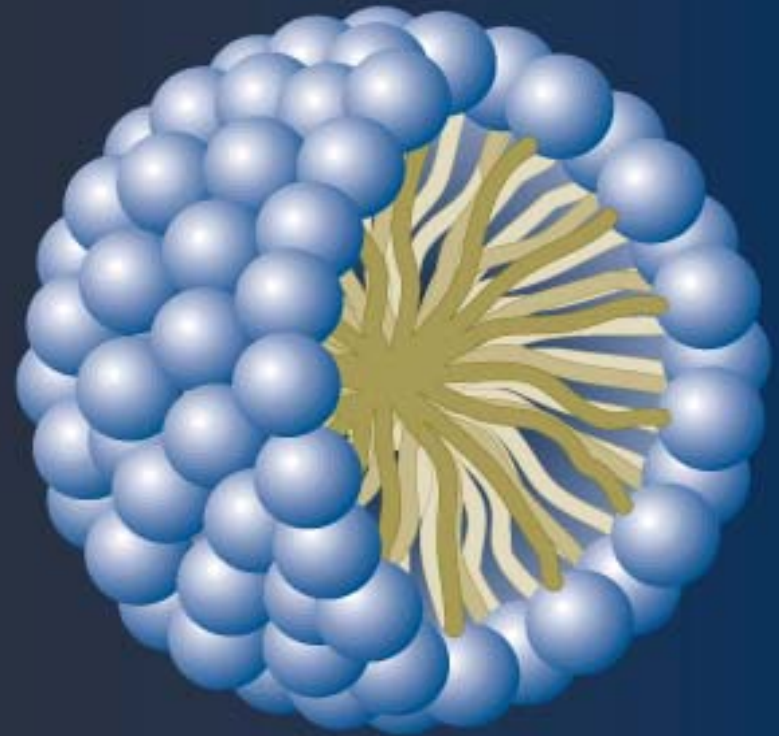
Potocol 1015-05-001, n=12 healthy volunteers



T_{max} reduced by 20 h with Lip'ral

Lip'ral™ Technology Benefits

- Increased Bioavailability
- Faster Onset of Action
- Faster Apparent Elimination
- Refractory To Food Effects
- pH Independent Drug Solubilization
- More Consistent Product Performance



Uniqueness of Lipocine Technology

- **Very Strong Proprietary Position**
 - **Technology Platform Patents**
 - **Product Specific Patents**
 - **Additional Firewall Patents**
- **Breakthrough Technologies**
 - **Clinically Validated**
 - **Superior to Competing Technologies**
 - **Conventional Manufacturing Techniques**
 - **“Bioacceptable” Excipients**

What Lipocine Can Do For You

- **Develop Proprietary Products with Improved Safety/Efficacy/Compliance**
- **Enable Product/Brand Life Cycle Management Beyond Compound Patent**
- **Discovery/Development Support for NCE –Identify “Winners” and Shelve “Losers”**