



"Delivering more"

**Phosphagenics Limited**  
**Delivering Pain Drugs Topically and**  
**Systemically**

**Fred Banti, SVP & Chief Business Officer**

**Pain Therapeutics Summit**

**October 6<sup>th</sup> - 7<sup>th</sup> 2008**

**New Brunswick, New Jersey**



*This presentation contains forward-looking statements based on current expectations of future events. If underlying assumptions prove inaccurate or unknown risks or uncertainties materialise, actual results could vary materially from the Phosphagenics' expectations and projections. Risks and uncertainties include general industry conditions and competition; economic conditions, such as interest rate and currency exchange rate fluctuations; technological advances and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approvals; domestic and foreign health care reforms and governmental laws and regulations.*



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## ➤ **Phosphagenics Corporate Summary**

Phosphagenics Delivery Technology

Non-Systemic Localized Delivery

Systemic Transdermal Delivery

Pipeline and Patents



*Melbourne based, global biotechnology company, with an office in New Jersey, focused on the discovery of new and cost effective ways to enhance the delivery of proven products.*

## Public listed company

- Australian Stock Exchange (POH)
- London Stock Exchange - Alternative Investment Market (PSG)
- US Level 1 ADR - OTCQX (PPGNY)



## Management

- Harry Rosen, President & CEO
- Dr Esra Ogru, Exec. Vice President, R&D
- Fred Banti, SVP & Chief Business Officer
- Alister Hodges, Chief Financial Officer
- Mary McSwiggan, Investor Relations Manager

## Research & development

- Significant personnel expansion in:
  - Pre-clinical & clinical
  - Development & manufacturing
- Experts in their respective fields
- 24 scientists including 14 PhD's



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# Phosphorylated tocopherol

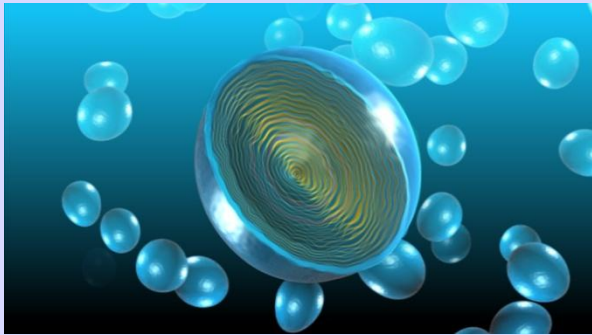
## Effect of phosphorylating tocopherol

- Phosphorylation enhances:
  - the absorption of tocopherol through the skin
- Phosphagenics discovered in 2002 that tocopheryl phosphate can also be used to carry other drugs through the skin
- Tocopheryl phosphate exists naturally in biological tissues and common foods
- This discovery led to the development of Phosphagenics' transdermal delivery platform

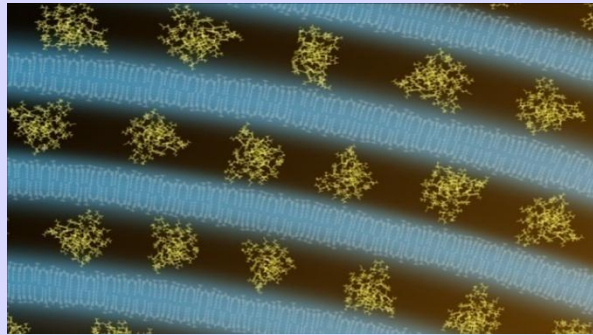
## Transdermal delivery platform

- TPM is either an association based micro-emulsion system or a vesicular delivery system

# Drug delivery platform: vesicular encapsulation



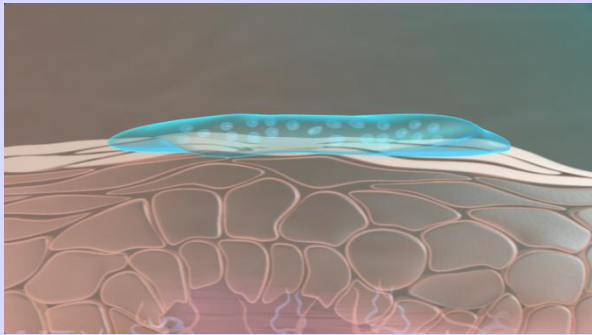
**Figure a)** Close-up of a TPM vesicles showing its multi-layered interior.



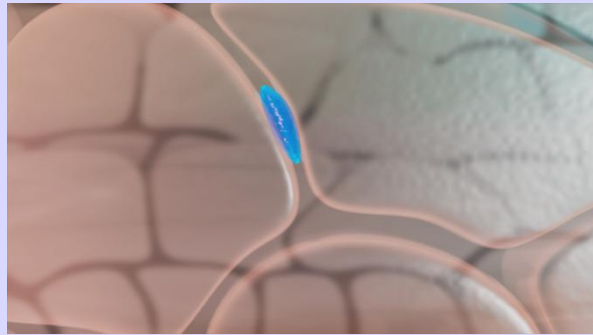
**Figure b)** Inside view of the TPM vesicle, showing how the drug to be delivered (“the active”) may be positioned within the layers of the vesicle.



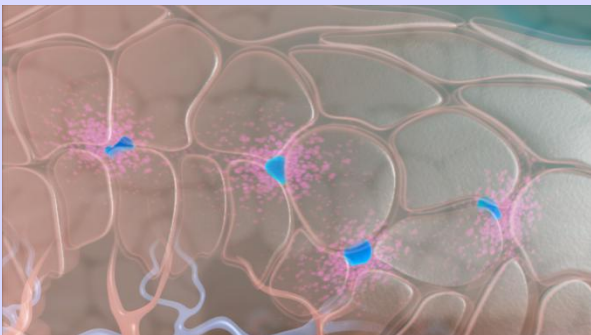
**Figure c)** An example of where and how the TPM/active gel may be applied to the skin.



**Figure d)** Close-up of the TPM/active gel, showing the vesicles in suspension.



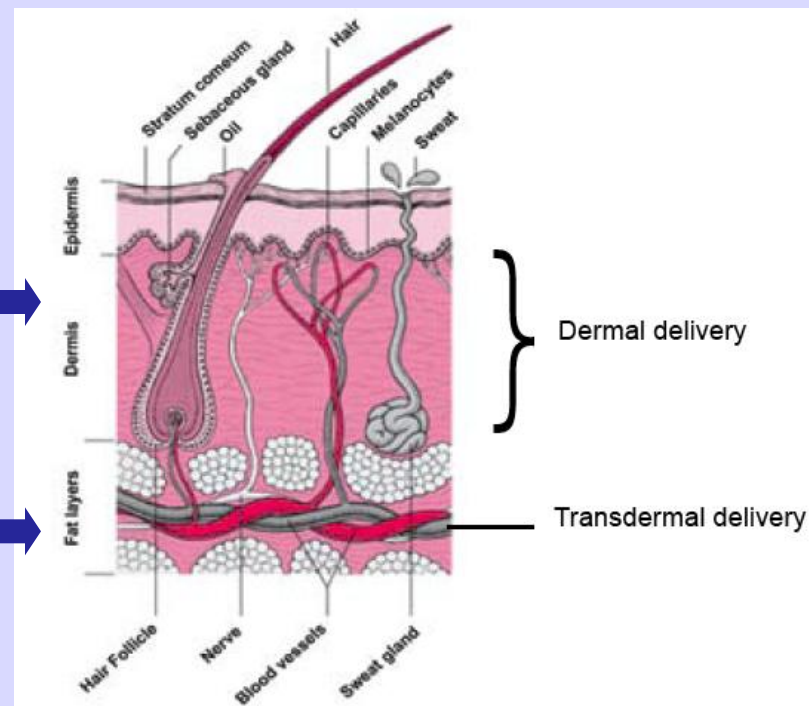
**Figure e)** Close-up showing how the TPM/active vesicles’ flexibility allows them to squeeze between the skins cells and travel towards the more vascular, deeper layers of the skin.



**Figure f)** A representation of TPM vesicles delivering the active to the site of action, in this case the deeper layers of the skin.

Versatile technology that is uniquely applicable to large and small molecules for:

- Non-systemic (localized) Delivery →
- Systemic (transdermal) Delivery →

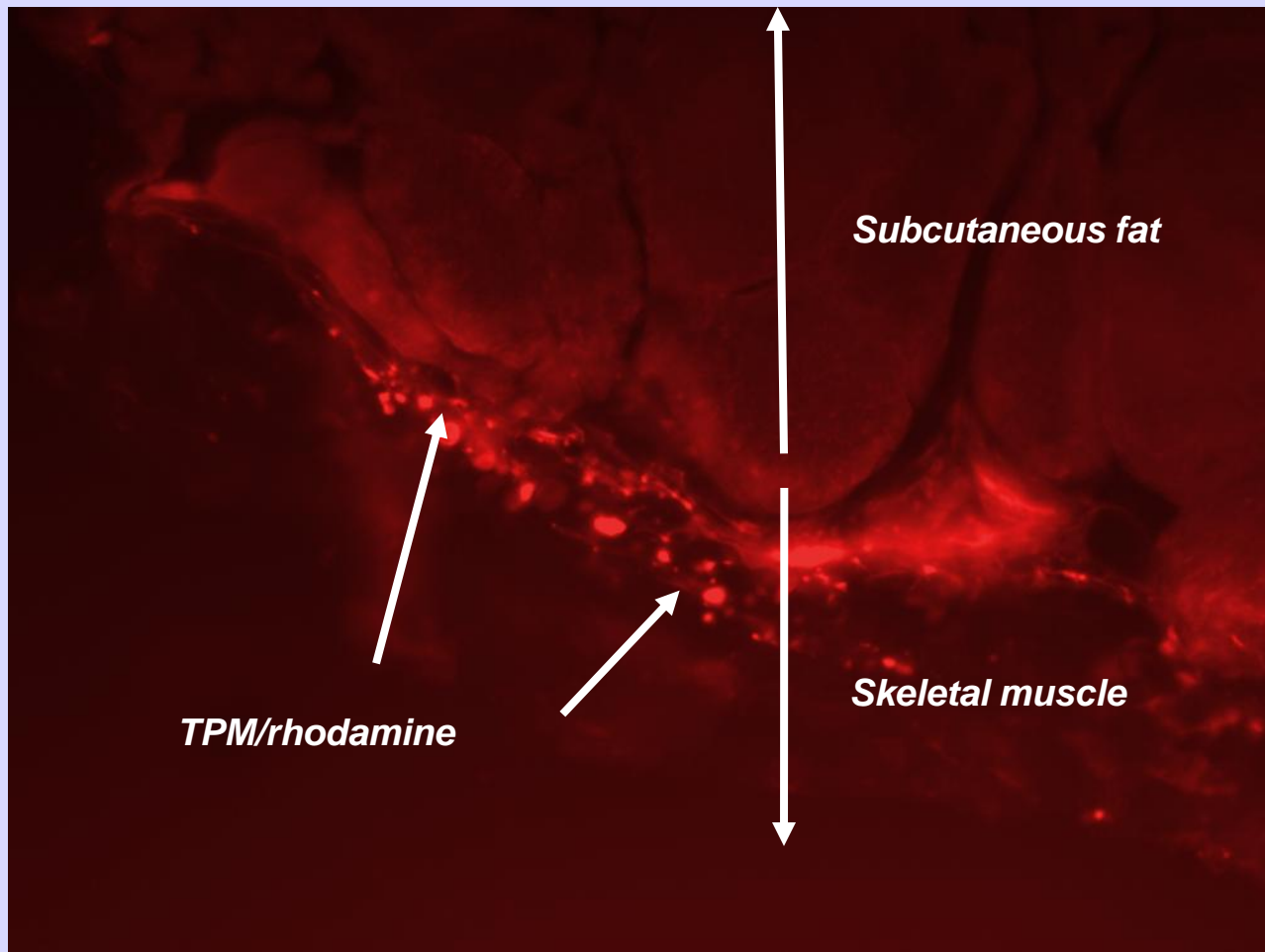


# TPM vesicles: *in-vivo* cross section data



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Fluorescence image – TPM/rhodamine fluorescence in skeletal muscle, deep below the skin surface





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## Competitive positioning

The platform offers opportunities to:

- Provide a more effective topical product
- Reduce systemic exposure of the active
- Provide a variety of dosage forms including gels, foams and sprays without comprising the effectiveness of the product
- Reduce intolerance and dermal reactions caused by many topical therapies

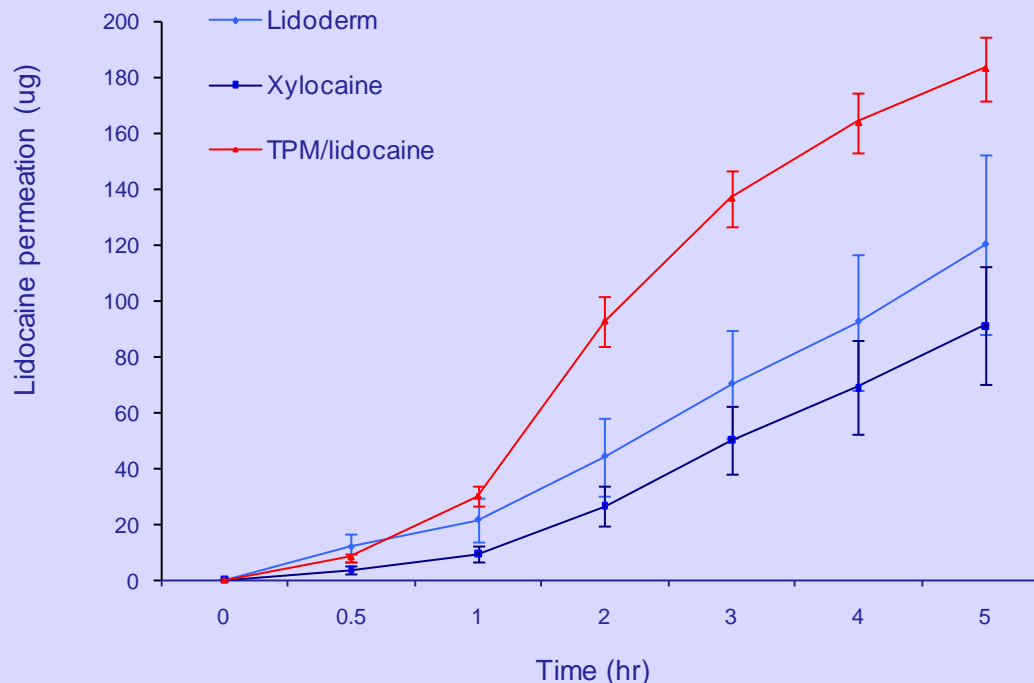
## Pre-clinical success

*In-vivo* animal studies have shown that the platform has the ability to:

- Enhance the delivery of topically applied compounds compared with other approved topical products
- Minimize systemic exposure
- Minimize dermal irritation

## Pre-clinical – Lidocaine permeation *in-vitro* through excised rat skin

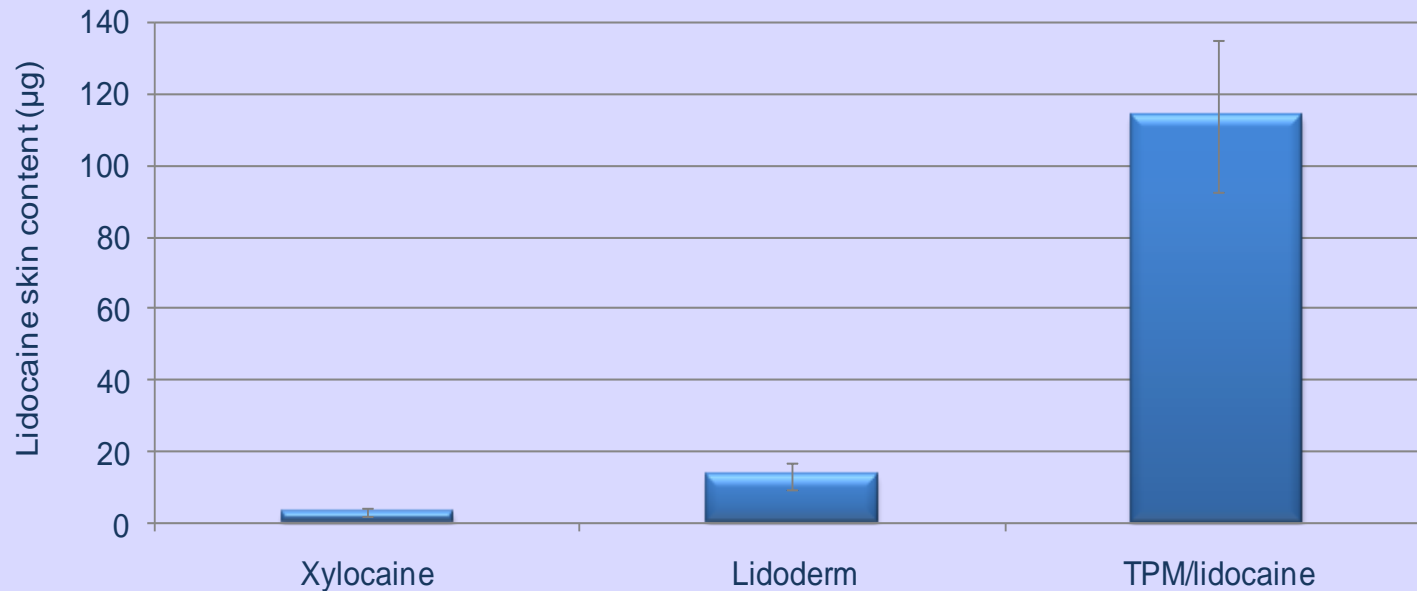
- Equivalent dose of Xylocaine 5% ointment, Lidoderm and TPM/lidocaine
- N = 6 diffusion cells, bars represent SEM. Finite dosing conditions with non-occlusion



TPM/lidocaine increases transdermal delivery *in-vitro* compared to both Xylocaine and Lidoderm ( $p < 0.05$ )

## Pre-clinical – Dermal absorption of lidocaine after topical application *in-vivo*

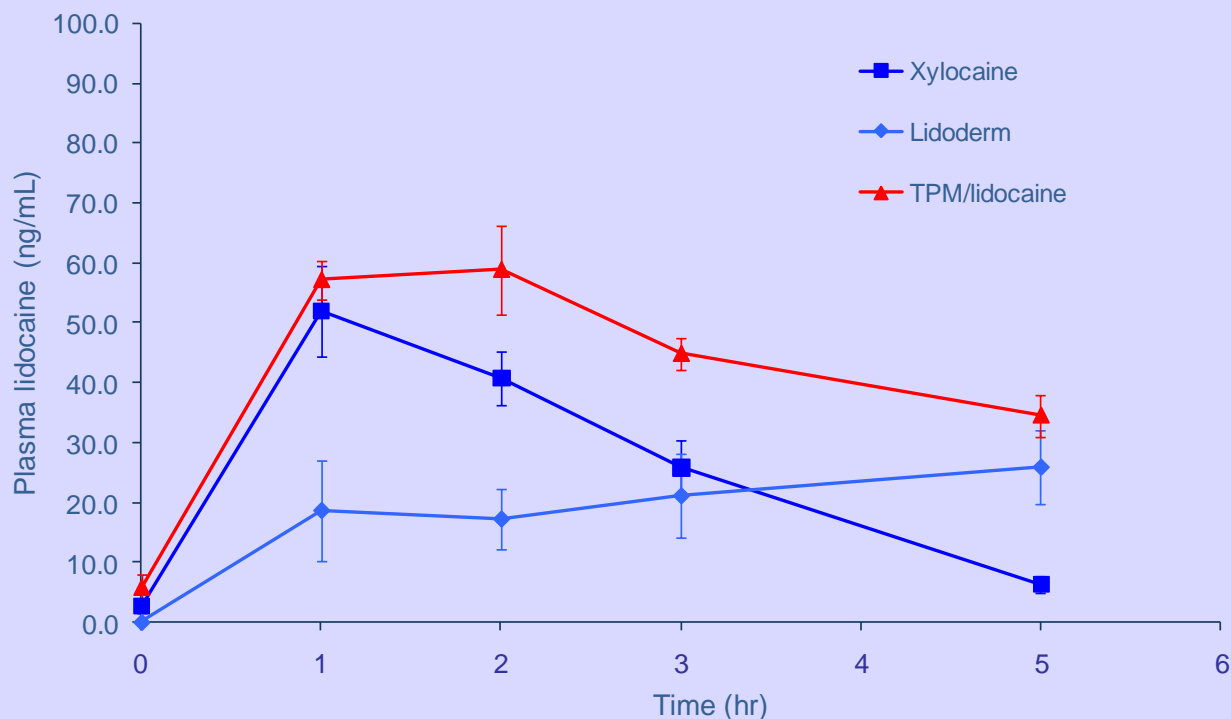
- Equivalent dose of Xylocaine 5% ointment, Lidoderm and TPM/lidocaine
- N = 10 Sprague Dawley rats, bars represent SEM



TPM/lidocaine shows increased dermal absorption *in-vivo* compared to both Xylocaine and Lidoderm ( $p < 0.001$ )

## Pre-clinical - systemic absorption of lidocaine after topical application *in-vivo*

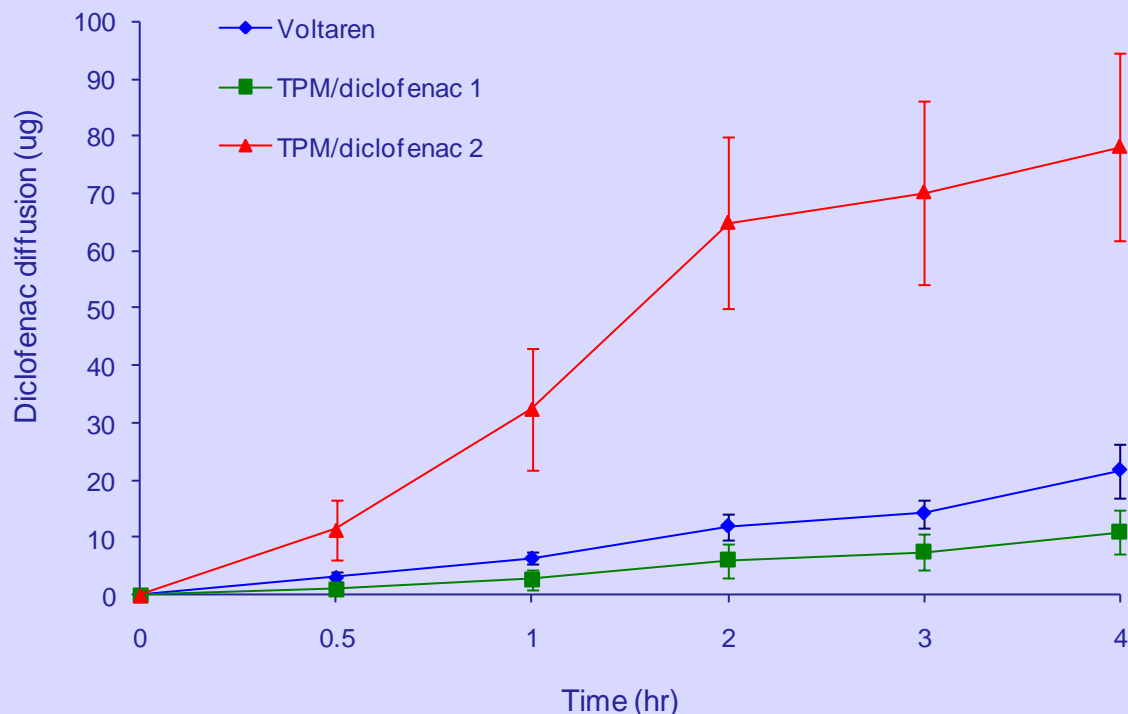
- Equivalent dose of Xylocaine 5% ointment, Lidoderm and TPM/lidocaine
- N = 10 Sprague Dawley rats, bars represent SEM



TPM/lidocaine does not exceed plasma concentration levels of Xylocaine, despite significantly increasing the amount delivered to the skin

## Pre-clinical – Diclofenac permeation *in-vitro* through excised rat skin

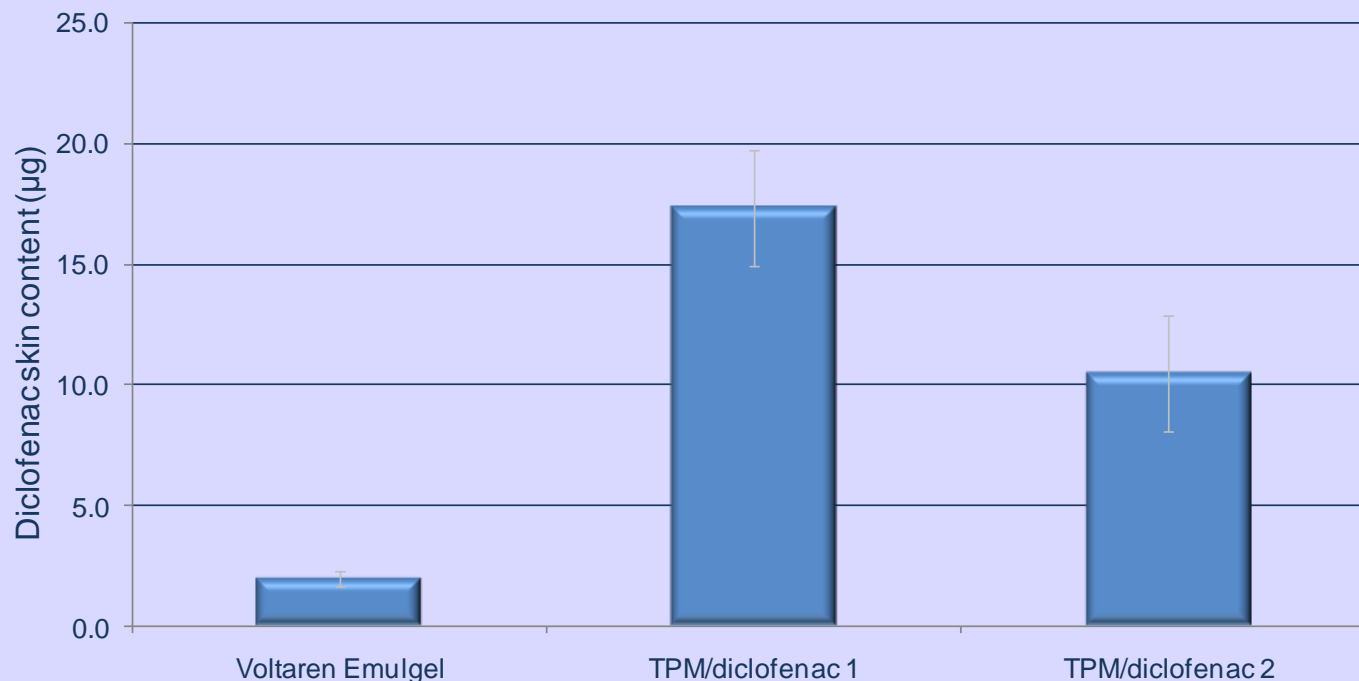
- Equivalent dose of Voltaren Emulgel, TPM/diclofenac 1 and TPM/diclofenac 2
- N = 6 diffusion cells, bars represent SEM. Finite dosing conditions with non-occlusion



TPM/diclofenac 2 increases transdermal delivery *in-vitro* compared to Voltaren and TPM/diclofenac 1 ( $p < 0.001$ )

## Pre-clinical - Dermal absorption of diclofenac after topical application *in-vivo*

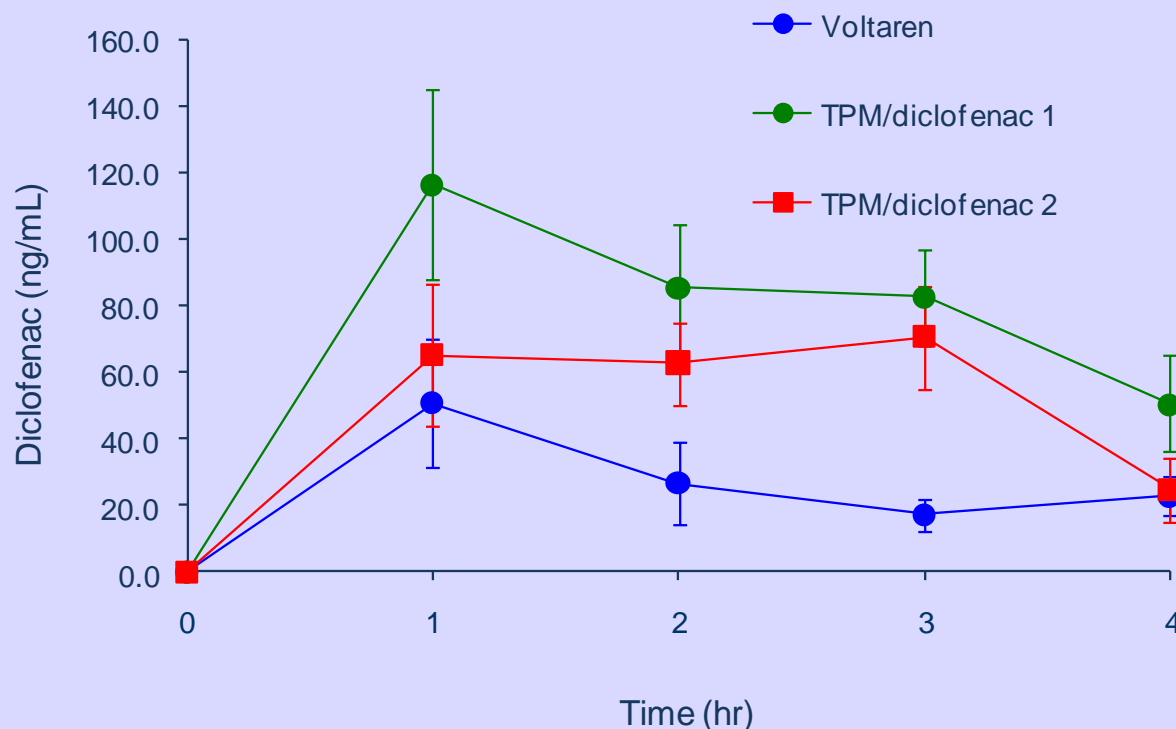
- Equivalent dose of Voltaren Emulgel, TPM/diclofenac 1 and TPM/diclofenac 2
- N = 10 Sprague Dawley rats, bars represent SEM



TPM/diclofenac 1 and 2 increase dermal absorption *in-vivo* over Voltaren ( $p < 0.02$ )

## Pre-clinical - Plasma diclofenac levels after topical application *in-vivo*

- Equivalent dose of Voltaren Emulgel, TPM/diclofenac 1 and TPM/diclofenac 2
- N = 10 Sprague Dawley rats, bars represent SEM



TPM/diclofenac formulations show increased average diclofenac plasma levels than Voltaren although the difference is not significant

## Lidocaine

- Human proof of concept pk trial to begin in Q3 2008
- Based on positive results of phase I, phase II efficacy trial to begin in Q3/Q4 2009

## Diclofenac

- Human proof of concept pk trial to begin in Q4 2008
- Based on positive results of phase I, phase II efficacy trial to begin in Q3/Q4 2009



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## Market size

- Sales of narcotic analgesics ~ \$US 7.7 B globally per annum
- Oxycodone is a leading pain-management drug with worldwide annual sales exceeding \$US 1 B

## Market opportunity

- Transdermal administration of analgesics can offer the benefit of sustained delivery of morphine or oxycodone for chronic pain sufferers and may lessen “breakthrough pain”
- Potential for decreasing side-effects by preventing dose spiking observed with oral doses

## Market positioning

- No other transdermal morphine or oxycodone are available

# Transdermal morphine

## TPM/morphine - phase I results

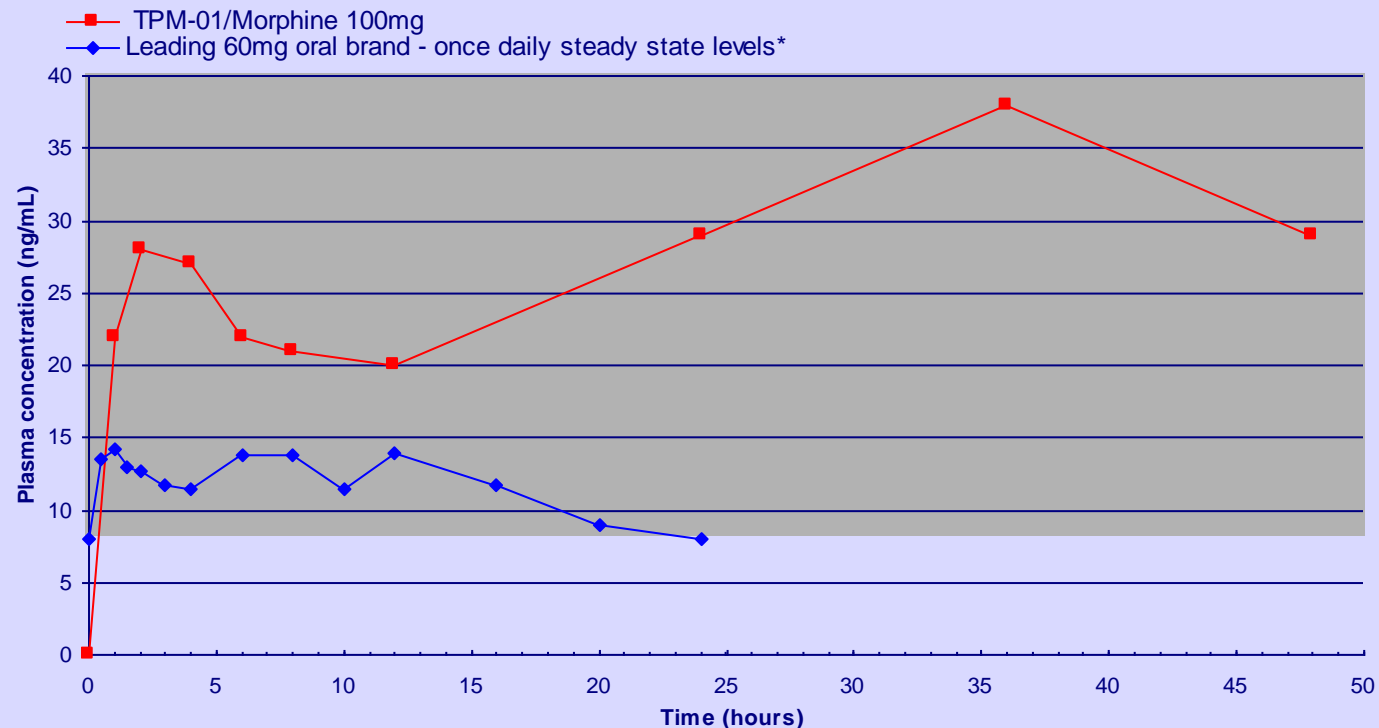


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Mean plasma morphine concentrations reached therapeutic levels (>8ng/mL) within ~2 hours

Therapeutic levels maintained for at least 48 hours following a single administration

Mean plasma morphine concentrations following a single dose



\*Steady state plasma levels of morphine are achieved 2 to 3 days after initiation of once daily administration (Source: Published health professional information).

**Shading denotes therapeutic blood levels.**

# Transdermal oxycodone

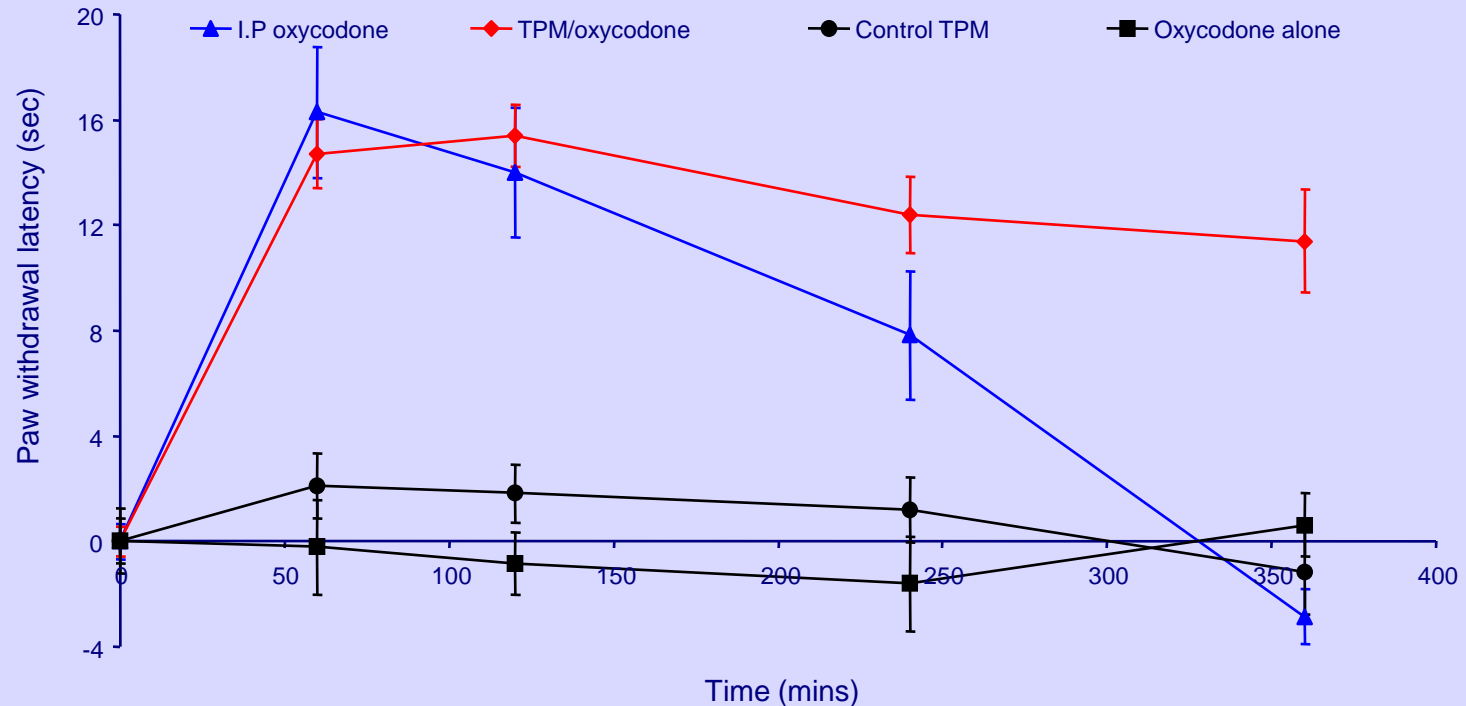
## TPM/oxycodone - animal study



### Key findings in animal proof of concept study

- Rapid onset of activity
- Prolonged effect

Average paw withdrawal latency in rats using plantar analgesiometer following treatment with Transdermal & Intra-Peritoneal (I.P.) Oxycodone (+/- SEM)



## Morphine & oxycodone formulated with TPM

- Resists physical dissolution (cannot be dissolved in alcohol and acidic beverages)
- Thick-high viscosity prevents injection
- Stickiness prevents snorting
- Novel formulation prevents thermal extraction

**Sustained release of morphine or oxycodone = No EUPHORIA**



## Regulatory filings

- Drug Master Files (CMC) TPM/morphine submitted to the FDA
- FDA IND packages for TPM/morphine and TPM/oxycodone underway

## Toxicology

- Robust safety package available – acute dermal, 28 day oral, skin sensitization, 28 day chronic dermal toxicity study

## Clinical

- TPM/morphine phase IIa pharmacodynamic study to be completed
- TPM/oxycodone phase I safety and tolerability study – completed
- Patch and gel technology in development

## Manufacturing

- GMP documentation
- GMP produced TPM available



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# Current product pipeline



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	Discovery & Research	Pre-clinical	Phase I	Phase II	Target Application
<b>Drug Delivery – Systemic/Transdermal</b>					
Insulin	[Progress bar]				Diabetes
Morphine	[Progress bar]				Pain Management
Oxycodone	[Progress bar]				Pain Management
<b>Drug Delivery - Non-systemic/Localised</b>					
Tretinoin (Dermatology)	[Progress bar]				Acne
Lidocaine	[Progress bar]				Pain Management
Diclofenac	[Progress bar]				Pain Management
<b>Oral</b>					
Phospha E® (Nutra)	[Progress bar]				Metabolic Syndrome

## Transdermal delivery patents

### Title

- Improved process for phosphorylation
- Formulation containing phosphate derivatives of electron transfer agents
- Carrier
- Alkaloid formulation
- Carrier Comprising One or More Di and or Mono (Electron Transfer Agents) Phosphate Derivatives or Complexes Thereof

### PCT

- PCT AU 2000/00452
- PCT AU 2001/01475
- PCT AU 2003/00998
- PCT AU 2005/000307
- PCT AU 2006/000839

## Other intellectual property

- Know how

# Summary of the TPM delivery system



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FEATURE		BENEFITS	
<b>1</b>	<b>Can transport both small and large molecules</b>	→	<i>Technology applicable to a wide range of drugs</i>
<b>2</b>	<b>TP found as an endogenous molecule in biology (tocopherol converts to TP)</b>	→	<i>Natural and Safe</i>
<b>3</b>	<b>Powerful penetration enhancer that does not disrupt or irritate the dermis</b>	→	<i>No skin irritation Maintains skin integrity</i>
<b>4</b>	<b>Allows for a sustained release of compounds from just one application</b>	→	<i>Flexible dosage regimens Longer therapeutic levels maintained</i>
<b>5</b>	<b>Rapidly penetrates the dermis (less than 1 hour)</b>	→	<i>Permits normal daily activities (e.g. showers, swimming)</i>
<b>6</b>	<b>Cost-effective to produce</b>	→	<i>Significant value add opportunity</i>
<b>7</b>	<b>Other routes of administration beyond transdermal under investigation</b>	→	<i>Can be produced in a wide range of presentations (powder, liquid, gel, sprays etc)</i>

## Clinical and development

- Continue with human pk “Proof of Concept” trials for lidocaine and diclofenac
- Advance oxycodone from animals studies into human pk trials
- Explore different topical delivery applications (i.e. sprays, roll on applicator, foams, etc.)

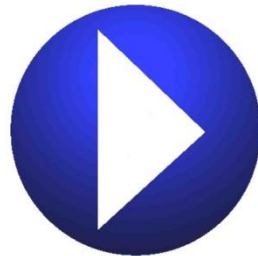
## Commercial

- Seek a worldwide collaboration on the Pain Portfolio – individually or collectively
- Seek to formulate partners proprietary compounds with our TPM technology



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To learn more go to  
[www.phosphagenics.com](http://www.phosphagenics.com)  
or email Fred Banti  
[fbanti@phosphagenics.com](mailto:fbanti@phosphagenics.com)



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