



## **SPL7013 Gel (VivaGel®),**

*a topical microbicide for prevention of HIV and genital herpes:  
relationship with the concept of rectal microbicides.*

**Jeremy Paull, PhD**  
**Starpharma Pty Ltd**

*Presentation to the International Rectal Microbicide Working Group*

**October 2007**



## Company Overview

- World leader in developing dendrimer products for pharmaceutical and life-sciences
- Lead product VivaGel® is being developed under IND as a topical microbicide to prevent HIV and Genital Herpes
- Deep pipeline of programs - drug delivery, siRNA delivery and drug optimisation
- Wholly-owned US subsidiary – DNT Dendritic Nanotechnologies Inc. – a leader in the development of advanced dendrimers for life science and industrial applications

### Starpharma Holdings Limited (5/9/07)

ASX Code	SPL
Level 1 ADR (OTCQX)	SPHRY
Share Price SPL AUD	37c
12 Month High/Low AUD	64c / 29c
Shares on Issue	179.7M
Market Capitalisation USD	~ \$55M*
Average Mthly Volume: ASX	4M shares
Average Mthly Volume: OTCQX	2M shares#
Cash on Hand (June07) AUD	\$10.1M^

\* \$1 AUD = 0.8224 USD

# 1SPHRY=10 shares

^ pre-August 2007 financing

Starpharma is a world leader in the development of dendrimer products for pharmaceutical, life-science and other applications



## Company Structure

**Starpharma Holdings Limited**  
ASX:SPL  
OTCQX:SPHRY

100%

### **Starpharma Pty Ltd**

- 35 employees based in Melbourne, Australia
- Leading developer of dendrimers as pharmaceuticals
- Lead development product, VivaGel™ is a vaginal microbicide for the prevention of genital herpes and HIV
- Broad portfolio of other dendrimer projects including drug delivery, cancer and targeted diagnostics

100%

### **Dendritic Nanotechnologies Inc. (DNT)**

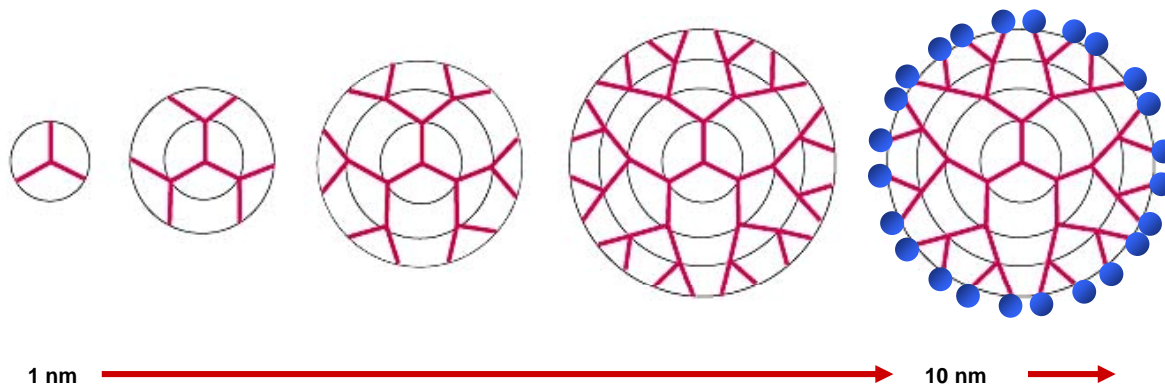
- Wholly owned subsidiary based in Michigan, USA (16 employees)
- Leading developer and provider of advanced dendrimers for life science & industrial/materials applications
- Existing licensing agreements with established revenue streams for dendrimer technology

## Technology Overview

### Unique Characteristics of Dendrimers:

- Precisely defined, synthetic macromolecules (1-10nm)
- Can be designed to precisely define surface topology, optimize potency, pharmacokinetics and localization; heat stable or biodegradable
- High multivalent binding affinity - ability to disrupt protein-protein interactions

*Dendrimer as a drug  
e.g. VivaGel® active SPL7013*



**Starpharma's existing commercial agreements for dendrimers**

**Stratus CS®** : Cardiac marker diagnostic licensed to Dade Behring

**DADE BEHRING**

**SuperFect®** : Gene transfection technology licensed to Qiagen



**STARBURST®** dendrimers commercially available via Sigma Aldrich

**ALDRICH**

**Prioject®** siRNA & DNA transfection reagents

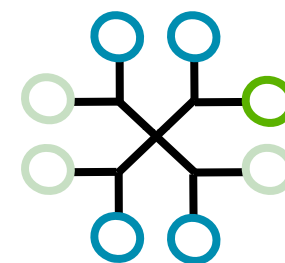


## Technology Overview (continued)


### Advantages of Dendrimers:

- Key enabling nano-scale technology
- Highly versatile technology:
  - drugs e.g. VivaGel® active SPL7013
  - drug delivery
  - RNAi/DNA delivery
  - diagnostics & materials applications
- Scalable chemical manufacturing process
- can tailor features for tissue targeting
- competitive COGs
- Well tolerated

*Example: dendrimer as a drug delivery vehicle*



 Solubilising/PK

 Small molecule drug or protein therapeutic

 Targeting agent



Pipeline				
Pharmaceutical & Medical Products	Proof of Concept	Lead	Clinical Trials	Sales
<b>VivaGel®</b> <ul style="list-style-type: none"> <li>▪ HSV-2 prevention</li> <li>▪ HIV prevention</li> <li>▪ Condom coating &amp; other line extensions</li> </ul>				
<b>ADME Engineering™</b> <ul style="list-style-type: none"> <li>▪ Therapeutic protein PK optimization</li> </ul>				
<b>Drug Delivery – Small Molecules</b> <ul style="list-style-type: none"> <li>▪ Cancer therapeutic</li> </ul>				
<b>Drug Optimization</b> <ul style="list-style-type: none"> <li>▪ Enhanced solubilisation</li> </ul>				
<b>In-vivo and in vitro Diagnostics</b> <ul style="list-style-type: none"> <li>▪ Stratus CS® (Cardiac Diagnostic)</li> <li>▪ MRI imaging (Ovarian cancer &amp; cardiovascular disease)</li> </ul>				
Life-science Products	Proof of Concept	Prototype	Pre-launch	Sales
<b>Gene Transfection Reagents</b> <ul style="list-style-type: none"> <li>▪ SuperFect®</li> </ul>				
<b>siRNA/DNA Transfection Reagents</b> <ul style="list-style-type: none"> <li>▪ PrioFect™</li> </ul>				



## VivaGel® – Lead Product for Prevention of Sexually Transmitted Infections (STIs)





## VivaGel® – Lead Product for Prevention of Sexually Transmitted Infections (STIs)

- VivaGel® is a topical vaginal microbicide being developed to prevent STIs in women
- Being developed under two INDs for the prevention of HIV and genital herpes (HSV-2) in women
- Gel-based formulation with a nanotech dendrimer active (SPL7013), delivered via a vaginal applicator
- Dendrimer inactivates HIV and HSV-2 by binding to the virus preventing it attaching to the host
- Significant and growing recognition that microbicides offer the best alternative for prevention
- Potent contraceptive activity in animal models



### HIV

- Major health burden in both developed and developing countries
- 39 million people living with HIV; every day 7,000 women are newly infected
- No cure - more than 50 HIV vaccines have failed and estimates are that an effective vaccine is many years away

### Genital Herpes

- Recurrent, lifelong viral infection
- Estimated to infect between 15-25% of adults in developed countries, growing to between 40-50% women in the US by 2025
- Existing prevention methods have proven ineffective and developmental vaccines disappointing



## Commercial Opportunity for Microbicides

- **Large, addressable markets**
  - HIV more common in developing countries
  - HSV-2 common in both developing and developed countries
  
- **Increasing market support for products**
  - US government committed to development of safe and effective microbicides
  - US opinion leaders now calling for National Herpes control Program
  
- **Several industry surveys have confirmed strong consumer demand**
  - 30-40% female US college students would buy a microbicide - 70% with contraceptive properties
  - Over 20 million women in US would use a microbicide
  - Microbicide market estimates > \$1.5-3 Billion

### Estimated Market for microbicides in Developed Countries

Market Penetration	Average Frequency of Use Per Annum		
	25x US\$M	50x US\$M	100x US\$M
2.5%	365	730	1,460
5.0%	725	1,450	2,900
10.0%	1,450	2,900	5,800

#### Key assumptions

- 291m women of reproductive age (15-49) in developed countries
- Unit sale price circa US\$2
- Usage rates according to published data



## VivaGel® – Product Features and Performance

### VivaGel® Offers Several Key Advantages

- Market research indicates significant (international) user and payor demand for microbicide gels
- VivaGel® : “first in class” for Herpes
- Compelling HSV-2 & HIV efficacy and potent contraceptive activity in animal models
- Significant NIH support for development
- Viruses appear not to develop resistance to VivaGel®

### Excellent Results in Human and Animal trials

- Successfully trialled in both men and women under IND
- VivaGel® is currently in expanded safety human studies in USA & Africa
- VivaGel® shows excellent activity in relevant HIV & HSV-2 strains in very stringent animal models
- Well tolerated in male and female subjects

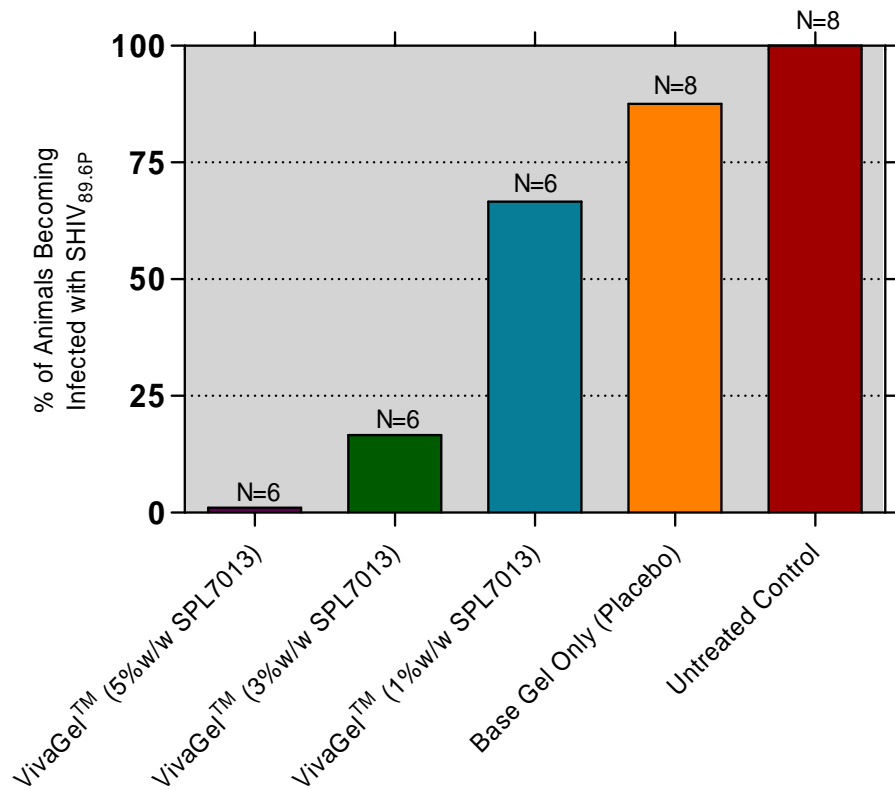
### Excellent Drug Characteristics

- Lower development risk : Topical gel, external to body
- Full development package; well defined chemical entity, scalable
- Affordable – Low manufacturing cost
- Excellent IP position

## VivaGel®: Animal Efficacy results

### SHIV/HIV Protection

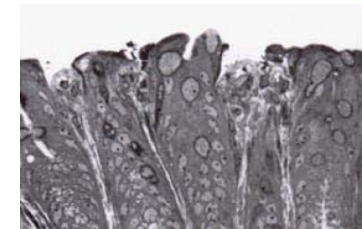
% Animals Infected with SHIV<sub>89.6P</sub> Following No Treatment or Pre-Treatment with VivaGel™ (0 to 5% w/w SPL7013)



**Advantage: VivaGel® is NOT a surfactant**  
 Surfactants damage epithelial cells INCREASING the chance of HIV transmission. VivaGel® is NOT a surfactant .



Normal



After surfactant

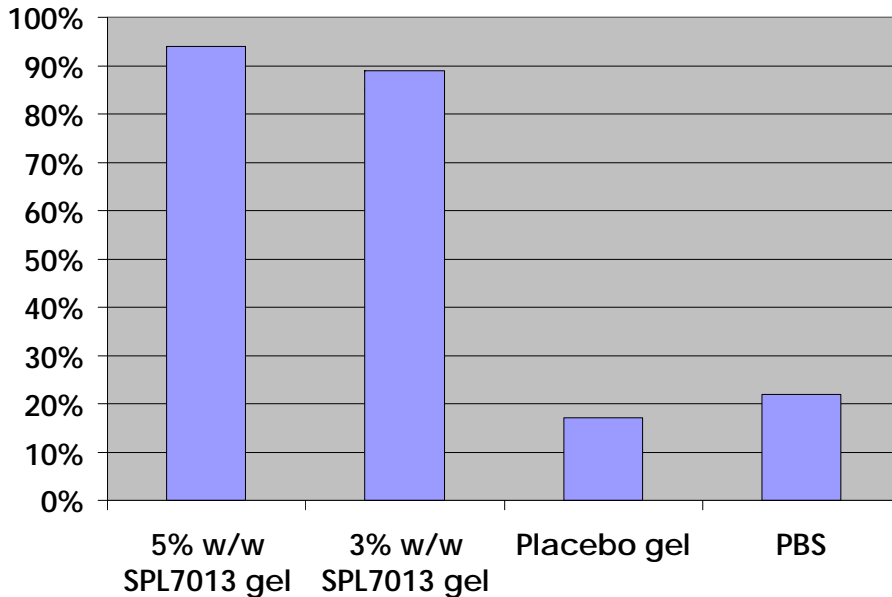
*Contraception 1998;57:341-348*



## VivaGel®: Animal Efficacy results (continued)

### HSV Protection

VivaGel™: animals protected from HSV-2



**Approximately 45 million Americans (26% of women and 18% of men) are infected with HSV-2, the causative agent of genital herpes.**

Epidemiology of HSV in Developed Countries, HERPES, 11 Supplement 1, 2004

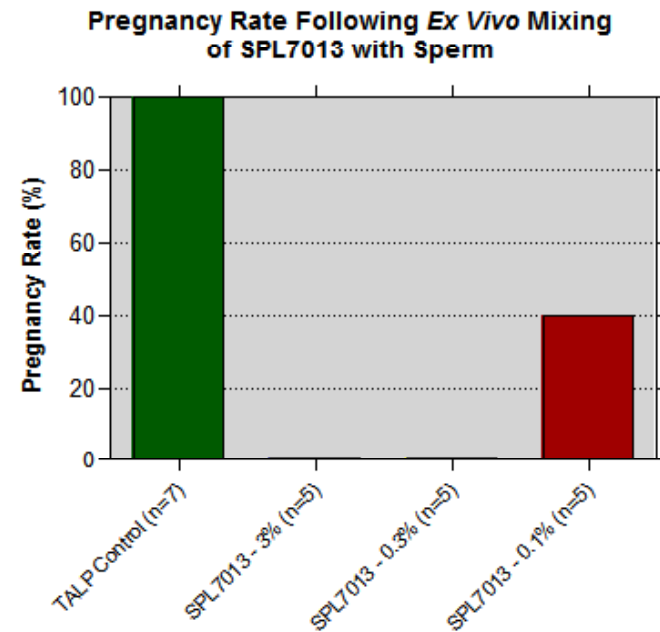
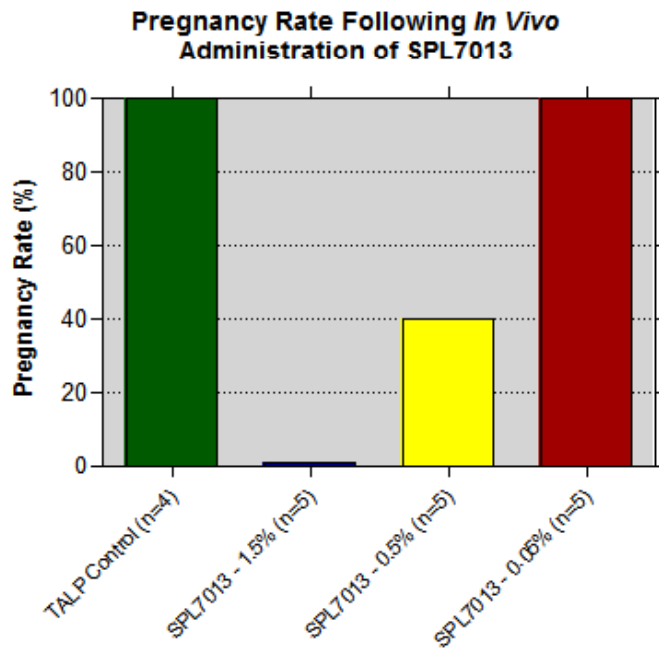
**“Women in the United States also need HIV prevention tools like microbicides. AIDS is now the number 1 cause of death among African-American women between the ages of 25 and 34.”**

“The Microbicide Development Act,” in the Senate of the United States, 2005

## VivaGel® : Potent Contraceptive Activity *In Vitro* and in Rabbits

- SPL7013 (VivaGel® active ingredient) potent inhibitor of enzymatic processes and sperm mobility
- SPL7013 exhibits potent contraceptive effect in rabbits (in independent studies undertaken at Johns Hopkins University and CONRAD)
- If contraceptive activity is confirmed in humans, contraception is an additional claim
- Findings relevant to both the stand-alone gel and condom coating opportunities

- **VivaGel® active ingredient a potent contraceptive in animals**





## VivaGel® - Clinical Trial Status

Study	No. Participants	Site(s)	IND Application	Status
Safety, tolerability and pharmacokinetic study of escalating doses of VivaGel in healthy women when administered vaginally, once daily for 7 days	37	Adelaide, Australia	Prevention of HIV	Complete
Safety and acceptability study of VivaGel when administered to the penis of healthy male volunteers once daily for 7 days	37	Melbourne, Australia	Prevention of HIV	Complete
Expanded safety and tolerability study of VivaGel in healthy young, sexually abstinent women when administered twice daily for 14 days	60	San Francisco, USA and Kisumu, Kenya	Prevention of genital herpes	Ongoing
Expanded safety and acceptability study of VivaGel in healthy young, sexually active women when administered twice daily for 14 days	40	Tampa, USA and San Juan, Puerto Rico	Prevention of HIV	Ongoing



## VivaGel™ - Development stage and plan

### PRODUCT TYPE



## VivaGel™ today



## VivaGel® and the Rectal Microbicide Concept

- Rectal Microbicide could encompass:
  - A vaginal microbicide used 'off-label' rectally
    - As seen with other products (e.g. N-9)
  - A microbicide designed and developed specifically for rectal use
    - Significant market need and potential
- Key issues to consider for a rectally applied product:
  - Formulation, delivery, activity/coverage, compatibility of a vaginal product with the rectal mucosa
  - People will use a vaginal product rectally
- Anticipate that rectal safety assessment of a microbicide intended for vaginal use will be a regulatory recommendation, if not requirement prior to registration/marketing

## VivaGel® and the Rectal Microbicide Concept

- Assessment of a vaginal microbicide used rectally 'off-label' (e.g. VivaGel®)
  - Vaginal safety studies
  - Nonclinical, GLP toxicology studies (subchronic rectal administration)
    - Rat and rabbit, or dog, up to 14 days
    - Full histopathology
  - Phase 1 clinical safety study: once daily application in males and females, 7-14 days
- Assessment of a microbicide designed / developed specifically for rectal use
  - Formulation development / optimisation
  - Delivery method development / optimisation
  - Nonclinical safety and efficacy
  - Clinical safety and efficacy

## VivaGel® and the Rectal Microbicide Concept

- Implications of safety issues for a vaginal product:
  - Physiological and anatomical differences of rectum vs. vagina may lead to different safety profile rectally vs. vaginally
  - Positive safety profile – no product warning
  - Negative safety profile – product warning against rectal use
  - No safety profile – potential regulatory hurdle, product warning against rectal use (not tested)

## VivaGel® and the Rectal Microbicide Concept

- Rectal Safety Data for VivaGel®:
  - Non-GLP study in male and female macaques
  - No deleterious effects of 3 daily rectal applications of 2.5mL of 3% SPL7013 Gel (VivaGel®), as assessed by
    - determination of rectal microflora status
    - pH change
    - evaluation of rectal lavage for evidence of cellular debris, epithelial desquamation and stroma and/or blood associated with epithelial sheets.

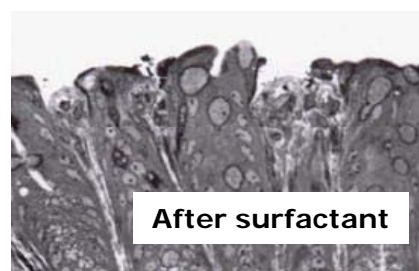
## VivaGel® – The Condom Coating Opportunity

### The Reason for the Opportunity

- Condom manufacturers have long recognised a demand for premium condoms with added protection
- Historically N9 (a surfactant) has been used
- N9 is no longer considered appropriate as it has been shown to increase risk of HIV and HPV
- N9 is thought to disrupt the vaginal wall, allowing entry to these viruses.
- Condom manufacturers and regulators are actively seeking an N9 replacement
- VivaGel® may be the replacement of choice given it is not cytotoxic and its activity: antiviral (HSV-2/HIV) and contraceptive

### VivaGel™ is NOT a detergent (surfactant)

#### Illustration of surfactant action (not VivaGel™)

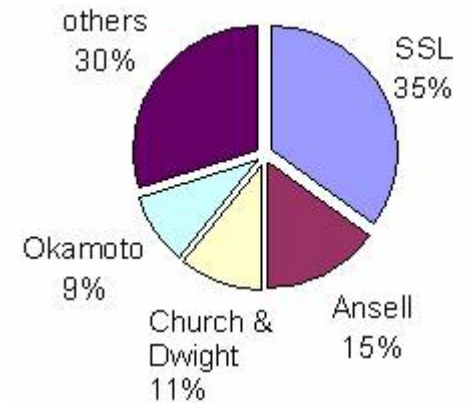


*Contraception* 1998;57:341-348

### Condom Market at a Glance

Total Sales: US\$3.26B (2006)  
 Top 4 sales: 70% of total  
 Sales Growth: 4-5% annually

**Chief Factor in growth:  
 awareness of AIDS and STIs**



source: "Condoms - a global strategic business report 2005"

**Condoms represent a US\$3.26B market in which VivaGel® offers a potential premium product**



## VivaGel® – Development and Commercial Strategy

### VivaGel®

- One of the most advanced 2<sup>nd</sup> generation microbicides
- First in class for HSV-2
- Significant non-dilutive NIH support; strong ongoing support for microbicides
- Broad application; chronic-use product
- Partnering/commercial strategies likely to differ between developed (OTC/Pharma) markets and developing (NGO/Govt.) countries

**Status:** Expanded Safety human trials in US, Australia and Kenya

### VivaGel® Condom Coating opportunity

- Possible replacement to common spermicidal coatings e.g. nonxynol-9 (N-9)
- Likely less onerous regulatory path for VivaGel® as a condom coating - offering a line-extension with shorter path to market.

**Status:** Regional deal announced July 2007  
In discussions with further potential commercial partners



## Starpharma Pty Limited

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