



## **Clinical Study Shows STARPHARMA's VivaGel™ is Safe**

**Melbourne (Australia), 16 December 2004:** Starpharma Holdings Limited (ASX:SPL) today released full human clinical trial results indicating that VivaGel™ (SPL7013 gel) has a suitable safety profile to be developed as a vaginal microbicide for the prevention of HIV.

The unblinded data confirm and extend the findings of Starpharma's preliminary announcement issued on November 17, 2004 that initial results of the Phase 1 study were positive. VivaGel™ caused no irritation, inflammation or other significant adverse effect. In pharmaceutical industry terminology, VivaGel™ was considered "safe and well-tolerated."

The Phase 1 study compared 36 women who received either various intra-vaginal doses of VivaGel™ or a placebo gel daily for one week. The trial was double blinded so that the volunteers, principal investigator and Starpharma did not know who was receiving placebo or VivaGel™. Study participants were assessed by a gynaecologist for possible irritant effects of the gel. Additionally, the women were assessed for any possible effect upon vaginal microflora (natural micro-organisms in the vagina) or absorption into the blood of the active ingredient of VivaGel™.

"Based upon our thorough review of the complete data, VivaGel™ appears to be a very safe and gentle product for intravaginal use by women," stated the Principal Investigator on the study, Dr John O'Loughlin of the Royal Adelaide Hospital. "There is no evidence to indicate that VivaGel™ caused any irritation or inflammation whatsoever."

VivaGel™ is being developed as a topical microbicide that has the potential to prevent the transmission of HIV and other STDs when applied to the vagina prior to sexual intercourse. In earlier studies performed in monkeys, VivaGel™ was found to be highly effective in preventing HIV transmission.

Dr John Raff, CEO of Starpharma, said: "We are delighted to receive this very positive data supporting the safety of VivaGel™ in humans. Combined with our earlier animal studies demonstrating the effectiveness of VivaGel™ as an HIV preventative agent, we believe that this data supports future larger-scale efficacy and safety clinical trials of the product. VivaGel™ is shaping up to become an important weapon in the battle against the HIV/AIDS epidemic."

The clinical trial was conducted at CMAX, a Division of IDT Australia Ltd, in Adelaide under an effective "Investigational New Drug" application filed with the US Food and Drug Administration (FDA). Starpharma's VivaGel™ is the first drug product in the world based upon nanoscale molecules called dendrimers to enter human trials under FDA Regulations.

An expanded summary of the clinical trial results is included in the Appendix to this announcement.

This announcement has been prepared in compliance with the draft ASX and AusBiotech Code of Best Practice for Reporting by Biotechnology, Medical Device and other Life Sciences Companies.

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**About Starpharma:**

Starpharma Holdings Limited (ASX:SPL) is focused on the development and application of dendrimer nanotechnologies as drugs against major diseases. VivaGel™ is a topical microbicide gel product that has been developed for women as a preventative against the sexual transmission of HIV. It is also active in animal studies for the prevention of other sexually transmitted diseases including genital herpes and Chlamydia. SPL also has an equity interest in a US based company – Dendritic Nanotechnologies, Inc. (DNT) – established with the US pioneer of dendrimer nanotechnology Dr Donald A. Tomalia.

**Microbicides**

A microbicide inactivates, kills or destroys microbes. Microbicides may be formulated as gels, creams, sponges, suppositories or films with the purpose of reducing significantly the incidence of STDs. There are currently no vaginal microbicides on the market. They are intended for vaginal or rectal use to afford protection for varying periods, from several hours up to days. Microbicides may also be designed to have a contraceptive function by inhibiting sperm.

**Dendrimers**

Dendrimers are a type of nanoparticle. They are man-made chemicals that form tiny balls made up of a dense network of branches. Dendrimers have applications in the medical, electronics, chemicals and materials industries.

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## APPENDIX – SPL7013-001/CM4402 PHASE 1 CLINICAL TRIAL RESULTS

This appendix contains a summary of the final analysis of the results of the first clinical trial assessing the safety of VivaGel™ (SPL7013 gel), which was conducted in Australia under US Food and Drug Administration (FDA) Investigational New Drug Application (IND) No. 62,482.

### Study Title

A Controlled Study of the Safety, Tolerability and Pharmacokinetics of Escalating Intravaginal Doses of SPL7013 Microbicide Gel in Healthy Female Volunteers When Administered Once Daily for 7 Days.

### Study Phase

The objective of this Phase 1 trial was to determine the safety and tolerability of VivaGel™ (SPL7013 gel) at a concentration up to 3% w/w of SPL7013. This was the first study of the product in humans and was carried out in sexually abstinent, healthy female volunteers who were confined to a Phase 1 clinic during the drug administration period. The effectiveness of the drug in preventing HIV was not studied.

The study was conducted in compliance with international Good Clinical Practice (GCP) guidelines and regulations, including ICH-GCP and applicable US FDA regulations, 21CFR Parts 50, 54, 56 and 312.

### Blinding Status

The trial was double blinded so that the trial volunteers, the principal investigator/trial site and Starpharma did not know if a volunteer was receiving placebo or gel containing SPL7013.

### Treatment Method, Route of Administration, Frequency and Level of Dose, and Number of Trial Subjects

The study was a randomized, blinded, placebo controlled, repeat dose, dose-escalation study.

The starting dose was 0.5% w/w SPL7013 gel applied intravaginally once daily for seven days and increased to 1% and 3% w/w SPL7013 gel in subsequent dose groups. Progress to the next step was based on a blinded assessment (*i.e.* continuing to not know which women were receiving placebo or active gel) of vital signs, physical examination, colposcopy, laboratory parameters and the results of direct questioning of volunteers regarding adverse events.

The table below describes the number of trial subjects in each of the three groups who received placebo and active gel. Subjects were allowed to participate in one group only.

Group	Dose Level SPL7013 gel (% w/w SPL7013)	Number of Subjects	Treatment Allocation
1	0.5	12	8 subjects SPL7013 gel 4 subjects placebo gel
2	1.0	12	8 subjects SPL7013 gel 4 subjects placebo gel
3	3.0	12	8 subjects SPL7013 gel 4 subjects placebo gel
3, withdrawn	3.0	1	1 subject SPL7013 gel

## Subject Withdrawal or Dropout

One trial participant was withdrawn from the study based on the results of a laboratory test indicating a vaginal condition that was present prior to dosing commencing. The finding was therefore deemed to be unrelated to the study treatment and the trial participant was replaced in the study. No other subjects were withdrawn or dropped out of the trial.

## Subject Selection Criteria

Subjects were required to be healthy females, aged 18 to 45 years with a regular menstrual cycle length of 25-35 days. In practice, the age of trial participants spanned 18-43 years.

## Primary Endpoints and Results

The primary endpoints of this study were the safety and tolerability of SPL7013 gels and the extent to which SPL7013 is absorbed into the blood following intravaginal administration. The methods of assessment and the results for these primary endpoints are described below.

### 1. Safety and Tolerability

This assessment considered both the local effects of the gel at the site of administration (*i.e.* the vagina, cervix and external genitalia), and systemic effects.

#### (a) Local Effects Assessed by Colposcopy

**Background:** At time points around the first, fourth and seventh doses, and also during the follow-up assessment on Day 14 of the study, the principal investigator evaluated each volunteer for clinically significant changes, such as inflammation or irritation, to the epithelium, or lining, of the vagina and cervix using the standard gynaecological technique of colposcopy.

**Result:** Based on the principal investigator's experience and international guidelines for these assessments in microbicide clinical research, there were no clinically significant findings or changes in the vagina, cervix or external genitalia of any of the women receiving either the placebo or active gels, as determined by colposcopic examination.

#### (b) Local Effects Assessed by Measurement of Vaginal Microflora

**Background:** The vagina has a natural balance of microflora (micro-organisms) that contributes to a woman's reproductive health. Imbalances in the microbiology of the vagina can be caused by a reduction in the normally predominant and beneficial lactobacillus and can result in an environment dominated by an overgrowth of other organisms (anaerobes) that result in the condition known as bacterial vaginosis (BV). BV is relevant to microbicide development because HIV acquisition has been shown to be increased in women with BV.

Therefore, it was important to determine the effect of vaginal administration of the placebo, 0.5%, 1% and 3% w/w SPL7013 gels on the balance of vaginal micro-organisms in healthy women. A vaginal swab was taken at most colposcopic examinations and cultured to determine the presence and measure the levels of different micro-organisms. A useful measure of the relative balance of vaginal flora is the Nugent score, which is based on a method called Gram staining. Scoring is based on the ratio of lactobacilli (Gram-positive rod) to other micro-organisms, or anaerobes (*e.g.* Gram-negative to Gram-variable bacilli) detected in the swabs.

**Results:** Lower concentrations of normal lactobacillary flora commonly occurred during gel use in both the placebo and active groups and there was no statistically significant difference in the reduction between the placebo and active groups. In the subjects receiving active gels, this decrease in beneficial lactobacilli concentration was accompanied by a proportional decrease in potentially harmful anaerobic bacteria. The vaginal flora had generally returned to pre-gel levels when assessed again seven days after the end of dosing. Importantly, the

balance of lactobacilli and anaerobes, as measured by the Nugent score, did not change significantly during gel use, and no subject obtained a Nugent score indicating development of bacterial vaginosis.

**(c) Systemic Effects and Adverse Events**

**Background:** At set times throughout the clinical trial, the vital signs (e.g. temperature, pulse rate and blood pressure) for each volunteer were recorded, blood was drawn for laboratory measurements (e.g. haematology, coagulation and clinical chemistry) and adverse events (AEs) were recorded according to MedDRA (Medical Dictionary for Regulatory Activities) standardized AE terms. An AE can be any untoward medical occurrence in a clinical trial subject and does not necessarily have any causal relationship to the treatment administered.

**Results:** All measurements of vital signs and assessment of laboratory tests were deemed to be acceptable by the Principal Investigator.

There were no serious adverse events (SAEs) in any of the subjects during this study.

One volunteer in the placebo group experienced an isolated adverse event (AE) of a tension headache classified as severe in intensity. An AE of moderate intensity (skin rash) and deemed possibly related to study medication at the time of being recorded (*i.e.* before the trial staff knew what study treatment the volunteer was receiving) also occurred in a volunteer receiving the placebo gel.

All other AEs deemed to be possibly related to study treatment were of mild intensity. These were all solicited clinical symptoms of abdominal discomfort or pain in five subjects (4 receiving active gel, 1 receiving placebo), dysuria (painful urination) in one subject (active), and genital pruritus (itching) in one subject (placebo). These AEs were deemed not clinically significant by the Principal Investigator. Common AEs deemed unlikely to be or not related to study treatment included headache, metrorrhagia (breakthrough menstrual bleeding), and venepuncture site bruise.

**2. Level of SPL7013 in the Blood Following Intravaginal Administration of SPL7013 Gel (Plasma Pharmacokinetics).**

**Background:** The active ingredient of SPL7013 gels, the dendrimer SPL7013, exerts its activity in the vagina during the initial stages of exposure to and infection with HIV or other sexually transmitted infections during heterosexual intercourse. The effectiveness as well as the safety profile of the product will be benefited if there is minimal or no loss of SPL7013 from the vagina through absorption from the gel into the blood system. If SPL7013 is absorbed into the blood, there may be systemic effects due to systemic exposure. The pharmacokinetics of SPL7013 absorption, if any, were determined in the current trial by analysing plasma samples collected from the participants at time points around the first, third, fifth and seventh dose. In several nonclinical animal studies conducted prior to the clinical trial, SPL7013 was not detected in any plasma samples taken from the animals after intravaginal administration of SPL7013 gels.

**Results:** No SPL7013 was detected in any plasma sample at or above the lower limit of quantitation of the validated bioanalytical assay method used. This finding in humans adds to the body of nonclinical evidence, and suggests that SPL7013 is not absorbed into the blood following intravaginal administration of SPL7013 gel. This finding is promising from both a safety and efficacy viewpoint, because it means that exposure to the drug is localised to the place of administration and site of action in women, without local irritation or systemic effects.

## **Safety and Tolerability**

As described above, the study showed that VivaGel™ (SPL7013 gel) is safe and well tolerated in healthy females at dose levels of 0.5% to 3% w/w SPL7013 when applied intravaginally once daily for seven consecutive days.