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A randomized, controlled trial of the safety of candidate microbicide SPL7013 Gel when applied to the penis

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Abstract

Objectives—To determine the safety of the candidate vaginal microbicide SPL7013 Gel (VivaGel®) when applied to the penis.

Methods—A randomized, double blind, placebo controlled study. Thirty-six healthy men (18 circumcised, 18 uncircumcised), were randomized in a 2:1 ratio and treated with 3% SPL7013 Gel (N=24) or placebo gel (N=12), applied once daily for 7 days. Genital toxicity was determined by interview, diary, and examination.

Results—There were 10 genital adverse events (AEs) in 6 men (25%) receiving SPL7013 Gel, and 5 genital AEs in 4 men (33%) receiving the placebo that were possibly or probably related to the study product (difference of −8%, 95% CI: −40% to 23%, p=0.70). The most common genital AEs were genital pruritus and application site erythema. All genital AEs were mild (grade 1), and all but one, in the placebo group, were transient. Analysis of vital signs, non-genital AEs, and laboratory results indicated no safety or tolerability issues with SPL7013 Gel, irrespective of circumcision status. There was no detectable absorption of SPL7013 into the plasma.

Conclusions—3% SPL7013 Gel was safe and well tolerated, and comparable with placebo, when administered to the penis of both circumcised and uncircumcised men once daily for 7 days, with no evidence of systemic absorption or toxicity.

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Competing interests

Matthew Law has received research grants, consultancy fees or travel grants from: Abbott, BMS, Boehringer, Gilead, Glaxo, Janssen-Cilag, Johnson and Johnson, Merck, Pfizer and Roche. Christopher Fairley has received support from GSK and Novartis to attend the International Society of STD Research and his sister is the chief executive at StarPharma.

Author contributions

Marcus Chen, Iona Millwood, Mary Poynten, John Kaldor, Steve Wesselingh, Laura Clark, Jeremy Paull and Chrisopher Fairley were involved in the planning and design of the study. Handan Wand and Matthew Law were responsible for statistical aspects of the study: design, analysis and reporting. Iona Millward and Clare Price were responsible for data management and reporting of the study. Clare Price prepared the first draft of the manuscript. Marcus Chen, Clare Price, Iona Millwood, Handan Wand, Matthew Law, John Kaldor, Jeremy Paull and Christopher Fairley contributed to the writing and editing of the manuscript. Marcus Chen and Iona Millwood oversaw the clinical conduct of the study.

Keywords

Microbicide; HIV prevention; Phase 1 Clinical Trial; SPL7013; VivaGel™

Introduction

With the continuing global spread of HIV, new safe and effective strategies to prevent the sexual transmission of HIV are urgently required. A number of candidate vaginal microbicides are currently under development. These agents, which are applied topically to the vagina, are aimed at preventing the sexual transmission of HIV and other sexually transmitted infections (STI). They represent an attractive preventative intervention, especially for women in situations where it is difficult to negotiate the use of condoms. The ideal vaginal microbicide would be effective, safe, and affordable. It would also be highly acceptable to both women and men when used for sexual intercourse.

SPL7013 Gel (VivaGel®) (owned by Starpharma Pty Ltd) is a vaginally administered candidate topical microbicide under development for the prevention of both HIV and Herpes Simplex Virus type 2 (HSV-2) acquisition in women during sexual intercourse. The active constituent of SPL7013 Gel is SPL7013, a lysine dendrimer that has demonstrated *in vitro* and *in vivo* efficacy against both HIV and HSV. SPL7013 shows activity against HIV-1 *in vitro*^{1–2} and in colorectal and cervical explant systems.^{4,5} Protection against vaginal SHIV transmission was demonstrated in macaque monkeys at concentrations of 1%, 3% and 5% SPL7013 Gel.³ SPL7013 also shows activity against HSV 1 and HSV 2 *in vitro*^{6,7}, and against HSV-2 infection in mice and guinea pigs.⁷ The antiviral activity is thought to be due to the molecule blocking the attachment of the viruses to the cell membrane. A contraceptive effect of SPL7013 Gel has also been observed in rabbits (unpublished data).

An initial clinical study was conducted to evaluate the safety, tolerability and systemic pharmacokinetics of escalating doses of SPL7013 Gel in healthy, sexually abstinent, HIV-uninfected women. In that study, SPL7013 Gel applied once daily for seven days at concentrations of 0.5%–3%, was shown to be safe and well tolerated, with no systemic absorption.⁸

Even if vaginal microbicides are promoted so that they are used concurrently with condoms during intercourse, it is likely that there will be exposure of the penis to SPL7013 Gel. It is therefore essential that SPL7013 Gel be safe, well tolerated, and acceptable to men as well as women.

Objectives

The primary objective of this study was to determine the safety of SPL7013 Gel when applied topically to the penis in both circumcised and uncircumcised men. A second objective was to assess the systemic absorption of SPL7013 Gel.

Methodology

Study Design

This was a randomized, double-blind, placebo-controlled, phase 1 safety study of SPL7013 Gel compared with placebo gel, applied topically to the penis once daily for 7 consecutive days. Thirty-six healthy male participants were to be stratified based on circumcision status, then randomly assigned in a 2:1 ratio to either SPL7013 Gel (N=24) or placebo (N=12).

Setting

The study was conducted at the Melbourne Sexual Health Centre, Victoria, Australia.

Subjects and participants—Study participants consisted of healthy male volunteers, aged 18 or older recruited via the Melbourne Sexual Health Centre, through advertising, and via a letter of invitation to men living in local areas. Men were eligible for the study if they were HIV negative, reported vaginal intercourse within the prior 12 months, and if they agreed to abstain from any sex (oral, vaginal and anal) during the study treatment period. Masturbation was also discouraged. They were also required to avoid the application of any genital preparations other than the study products.

Men were excluded from the study using the following exclusion criteria: any STI within the previous 3 months; any current symptoms or signs of an STI or urinary tract infection; a recent history or current evidence of contact dermatitis, psoriasis, seborrheic dermatitis or eczema; current evidence of genital piercing, ulceration, tinea cruris, or other skin conditions of the genitalia or upper inner thighs; known or suspected allergy to any component of the study products; and history of significant drug reaction or allergy. Potential participants were serologically screened for HIV using enzyme linked immunosorbent assay, and for syphilis using enzyme immunoassay and the rapid plasma reagin test. In addition, screening for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* was undertaken using first-void urine and polymerase chain reaction. The first void urine specimen was also analysed using a urine leukocyte esterase test. Men were excluded from the study if any of these tests were positive. Also excluded were men with grade 2 or higher haematological or biochemical abnormalities at screening.

Intervention—Potential participants were provided with a participant information and consent form and written consent was obtained prior to study screening. Those who consented attended a screening visit where they were assessed in relation to the study inclusion and exclusion criteria and where the screening tests referred to above were undertaken. Men were asked to report their ethnicity according to pre-specified categories.

At the baseline visit, men who met the inclusion criteria were stratified according to circumcision status, and randomly assigned to receive either SPL7013 Gel or placebo in a 2:1 ratio. Randomization codes were prepared by the study biostatistician using a computer generated randomization scheme to assign treatment to participant identification numbers in each circumcision stratum. At randomization, participants were assigned to the next consecutive participation identification number within their stratum. The study was fully blinded such that none of the study participants, research nurses or investigators were aware of which identification numbers had been allocated to SPL7013 Gel or placebo groups.

The active gel contained 3% weight by weight (w/w) SPL7013 in a Carbopol®-based aqueous formulation. The placebo gel consisted of the base formulation only, without SPL7013. Both SPL7013 Gel and placebo gel were provided in identical, pre-filled, single-use applicators containing 2g of the study products. SPL7013 Gel and placebo gel were both clear, with a similar viscosity, and could not be seen through the applicator. All participants, research nurses and study investigators, including bioanalytical chemists, remained blinded to the treatment allocation until the completion of the study.

Participants were instructed to administer the study product once daily before bed for 7 consecutive days. They were instructed to spread the study product over the entire penis, including the meatus, but not the scrotum. Uncircumcised men were instructed to retract the foreskin during application to ensure coverage of the glans penis before replacing the foreskin. Participants were asked to wash the gel off with water after approximately 8 hours (range

allowed: 6–12 hours). Adherence with the dosing regimen was defined as the application of at least 6 of the 7 doses prescribed.

Participants were asked to complete a daily study diary card for the 7 day dosing period that recorded: the occurrence of solicited genital symptoms (penile burning, pain, itch, redness, rash, swelling, discharge, and dysuria); other genital and non-genital symptoms; concomitant medications; times of application and removal of gel; and any sexual activity or masturbation.

Safety was assessed at each study visit, which took place on days 0 (baseline), 3 (mid-treatment), 7 (end of treatment) and 14 (follow-up). Safety assessments included evaluation of adverse events (AEs) as reported by participants and review of laboratory results. Genital symptoms and signs were sought at each visit by interview and genital examination. This examination included review of solicited genital symptoms entered by participants into their diary card and a genital examination by investigators, who were experienced sexual health physicians. During the genital examinations, digital photographs were taken of the penis.

At days 0, 7 and 14, serum was collected and the following tests undertaken: complete blood count, clotting, liver function tests, urea and electrolytes, and analysis of plasma SPL7013 levels, and urinalysis was performed. The analysis of plasma concentrations of SPL7013 was conducted by Starpharma Pty Ltd using a capillary electrophoresis bioanalytical method employing a Micellar Electrokinetic Chromatography technique that had been developed and validated by Starpharma and which has a lower limit of quantitation for SPL7013 of 30 nM (0.5 µg/mL).

All clinical and laboratory toxicities were graded for severity according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events (December 2004). The relationship of any AE to the study product was classified by the investigator as “definitely”, “probably”, “possibly”, “unlikely” or “unrelated” to study product use, using the definitions outlined in the National Institute of Allergy and Infectious Diseases Adverse Events Reporting Requirements Standard Operating Procedures.

Safety was overseen via an expert, independent Safety Review Board who reviewed the unblinded safety data on a regular basis. Ethical approval for this study was obtained from the Ethics Committees of the Alfred Hospital, the University of Melbourne, and the University of New South Wales.

Main outcome measures

The primary outcome measures were the frequency of all genital AEs (any genital symptoms or signs) occurring during the 14 day study period. The secondary outcome measures were the frequency of non-genital AEs, laboratory abnormalities and the plasma concentrations of SPL7013.

Statistical Methods—This was a phase 1 study with determination of safety of SPL7013 Gel as the primary objective, and it was accepted that the study had limited power. In terms of AE rates, 24 treated patients gives reasonable power (>70%) of observing one or more events if the true event rate is greater than 5%, and good power (>90%) if the true event rate is greater than 10%. If no serious AEs were observed in all 24 treated patients, the upper two-sided 95% confidence interval (CI) on the event rate would be 14%. In terms of comparing randomised groups, if the rate of grade 3 or 4 AEs in placebo patients was 1%, the overall study (that is, comparing 24 treated patients with 12 placebo) would have 80% power to detect a 49% grade 3 or 4 AE rate in the treated patients (using a two-sided significance level of 5%).

Formal analyses compared the randomized treatment groups in terms of the frequency of the primary and secondary endpoints over the two week study period by randomized treatment group, both overall and separately for each stratum defined by circumcision status. Analyses were based on the intent-to-treat principle, including all randomised patients who received any study medication irrespective of whether they completed treatment or the study schedule. Proportions of patients with events were compared using Fisher's exact test.

Results

Screening procedures were performed on 65 potential participants. Twenty-eight men were ineligible, and 37 were enrolled into the study, stratified by circumcision status (18 circumcised and 19 uncircumcised). The disposition of all potential participants screened and enrolled in the study is shown in Figure 1. Twenty-five participants were randomized to receive SPL7013 Gel and 12 were randomized to receive the placebo gel.

One uncircumcised participant, who was randomized to receive SPL7013 Gel, was withdrawn from the study prior to administration of study product as a genital skin condition was detected at baseline, but only after randomization had occurred. A replacement uncircumcised participant, was randomized to the same treatment group, after the appropriate code was provided by the study biostatistician, with all other study staff remaining blinded to treatment allocation. All subsequent analyses were performed on the remaining 36 men. The baseline characteristics of men receiving SPL7013 Gel or placebo were broadly similar (Table 1).

The first participant was randomized into the study in September 2006, and the last completed the study in February 2007. All 36 men completed the 14 day study period, and all attended all five scheduled study visits except for two men, each of whom missed one of their scheduled visits.

Adherence to the study product was high, with all participants administered all 7 dose applications except for one man in the placebo group, who missed one dose. The mean duration and range of exposure to the study product was the same for both active and placebo gels: 9 hours (range 5–13 hours). Only 3 men reported masturbation during the study follow up.

A total of 49 AEs occurred in 24 (67%) out of the 36 men in the study. This consisted of 30 AEs in 15 (63%) men receiving SPL7013 Gel and 19 AEs in 9 (75%) men receiving the placebo gel. All AEs were mild or moderate in severity (grade 1 or 2). There were no serious AEs.

There was no difference in the proportion of men experiencing genital AEs when active and placebo groups were compared. Twelve genital AEs were reported by 8 men (33%) receiving SPL7013 Gel and 5 genital AEs were reported by 4 men (33%) receiving the placebo (a difference in proportions of 0%, 95% CI –33% to 33%, $p=0.99$, Fisher Exact Test). Of these, 10 genital AEs in 6 men (25%) receiving SPL7013 Gel, and all 5 genital AEs in the 4 men (33%) receiving the placebo, were considered to be either possibly or probably related to study product (a difference of –8%, 95% CI –40% to 23%, $p=0.70$, Fisher Exact Test). There was no relationship between length of exposure to the study product and AEs.

The most commonly reported genital AEs were genital pruritus (penile or genital itch) and application site erythema (penile redness or erythema) (Table 2). Genital pruritus was reported by 3 men receiving SPL7013 Gel and by one man receiving the placebo. Application site erythema occurred in one man receiving SPL7013 Gel and in 3 men receiving the placebo. All of these genital events were mild in severity (Grade 1); all but one lasted less than 24 hours (the exception being application site erythema in one man who received the placebo), and all were “possibly” or “probably” related to the study product.

Other genital events that were considered either possibly or probably related to the study product were: penile dryness, scrotal tingling, and a papular rash on the penis. Each of these was reported by only one man receiving SPL7013 Gel and all were mild in severity (Grade 1). The remaining 2 genital AEs occurred in men receiving SPL7013 Gel; however, in each case the events were considered unrelated to study product. One man had folliculitis secondary to extraction of a pubic hair, and another experienced an episode of recurrent genital herpes. Both events were mild in severity. No cases of urethral inflammation, as determined by urinary leukocyte esterase testing, occurred during the study.

Among men receiving SPL7013 Gel, the duration of 7 genital AEs considered probably or possibly related to the product, occurring in 5 men, was less than 24 hours. These consisted of 5 reports of genital pruritus (range: 0.5 minute–2 hours), one report of application site erythema (6 hours), and one report of scrotal tingling (1 minute). Of a longer duration was penile dryness in one man (7 days) and 2 reports of a papular penile rash in another man, which was still present at the final study visit.

When stratified by circumcision status, there was no significant difference in the proportion of men reporting genital AEs when comparing those in the SPL7013 Gel and placebo groups. Thirty-three percent of the circumcised men in each treatment group experienced at least one genital symptom or sign and 33% of the uncircumcised men in each treatment group experienced at least one genital symptom or sign.

A total of 32 non-genital AEs were reported by 19 of the 36 men. In the active treatment group, 18 events were reported by 12 (50%) men, and in the placebo group, 14 events were reported by 7 (58%) men. Among men receiving SPL7013 Gel, the most common non-genital AE was headache, with 4 reports by 3 men. Other non-genital events in the active group, reported once only, were acne, oral aphthous ulcers, dehydration, dental caries, diarrhoea, dry lips, nasal congestion, upper respiratory tract infection, sore throat, pustular rash, respiratory tract infection, skin lesion, vasovagal syncope and upper respiratory tract infection.

In the placebo group, the most common non-genital AEs were: headache, with 4 reports by 3 men, epistaxis, with 2 reports from one (8%) man, and rash, with 2 reports from one man. Other non-genital events in the placebo group, reported once only, were acne, increased serum creatinine, folliculitis, hiatus hernia, pharyngitis, and viral infection.

All non-genital AEs were either grade 1 or 2 in severity, and all were classified as either unrelated or unlikely to be related to study product, except for a report of a rash on the inner thighs in a man receiving placebo, which was classified as possibly related to study product. There were no clinically significant abnormalities reported with vital signs or with haematological and biochemical parameters, except for a report of increased creatinine in a man receiving placebo, who had a history of nephrectomy.

SPL7013 was not detected in any plasma samples analysed. This finding suggests that SPL7013 is not absorbed into the blood following penile administration of 3% w/w SPL7013 Gel, at least at levels above the lower limit of detection of the assay.

Discussion

In this randomized, double blind, placebo controlled study, the topical application of 3% w/w SPL7013 Gel to the penis was found to be safe and well tolerated, and comparable with placebo, in both circumcised and uncircumcised men. The genital AEs reported during the study were generally mild and transient in nature, with a similar incidence seen in both SPL7013 Gel and placebo groups. There was no evidence of systemic absorption of SPL7013 or systemic toxicity associated with its application to the penis.

This is a phase I study, and it is accepted that it has limited statistical power. Although we observed no difference between treated and placebo patients in the proportions experiencing genital AEs, the upper 95% confidence limit on this difference was 33%. This means the data in our study are consistent with the proportion of treated patients experiencing a genital AE being as much as 33% higher than placebo patients. In addition, although we observed no serious, unexpected, or grade 3 or 4 AEs in treated patients, the upper 95% confidence limit on the true rate of such events is 14%. Thus it is possible that such events could be relatively common and still not have been detected in our study. Larger studies will be needed to assess more accurately AE rates, and in particular, to exclude the chance of uncommon serious AEs.

As topical products may collect under the prepuce of uncircumcised men, and the stratified epithelium is thinner on the glans of circumcised men, SPL7013 was investigated in both circumcised and uncircumcised men. Participants were required to apply the study products to the penis and to avoid washing the product off for at least 6 hours, a period of exposure which is longer than that expected if exposure were to occur secondary to coitus. Even with this extended exposure, the incidence of both genital itch and erythema was low.

No serious AEs were seen in this study, and all non-genital AEs occurring among men receiving SPL7013 Gel were considered to be causally unrelated or unlikely to be related to use of the Gel. Furthermore, there were no clinically significant abnormalities in either vital signs or laboratory assessments among men receiving SPL7013 Gel. When considering these data with the pharmacokinetic data, which showed no measurable quantity of SPL7013 absorbed, the risk of SPL7013 Gel causing systemic toxicity appears to be low. Overall, this study demonstrated that 3% w/w SPL7013 Gel, when administered to the penis of both circumcised and uncircumcised healthy men once daily for 7 days, was safe and well tolerated.

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Figure 1.
Flowchart of disposition of study participants.

Table 1

Comparison of the baseline characteristics of men receiving SPL7013 Gel or placebo.

		3% w/w SPL7013 Gel (N=24)	Placebo gel (N=12)
Age (years)	Mean (SD)	37 (10)	36 (13)
	(Range)	(21–55)	(22–67)
Ethnicity	No. (%)		
	Caucasian	19 (79)	10 (83)
	Asian	1 (4)	2 (17)
	Aboriginal/Torres Strait Islander	0 (0)	0 (0)
	Pacific Islander	1 (4)	0 (0)
	American Indian/Alaska Native	1 (4)	0 (0)
	Other	2 (8)	0 (0)
Weight (kg)	Mean (SD)	86 (17)	82 (12)
Height (cm)	Mean (SD)	179 (60)	180 (8)
Blood Pressure (mmHg)	Mean (SD)		
	Systolic	123 (9)	117 (7)
	Diastolic	78 (8)	77 (6)
Sex partners in the prior 12 months	Mean (SD)	2 (2)	3 (2)
	(Range)	(1–10)	(1–8)
Sex partners in the prior 12 months	Mean (SD)	1 (1)	2 (1)
	(Range)	(0–4)	(1–5)

Table 2
Genital adverse events among men receiving SPL7013 Gel or placebo by relationship to the study product.*

Event type	3% w/w SPL7013 Gel (N=24)				Placebo gel (N=12)			
	Circumcised		Uncircumcised		Circumcised		Uncircumcised	
Probably related	Events	Participants	Events	Participants	Events	Participants	Events	Participants
Application site erythema								
Scrotal tingling	1	1					2	1
Penile dryness	1	1						
Genital pruritus	3	1						
Possibly related								
Application site erythema			1	1	2	2		
Genital pruritus			2	2			1	1
Papular penile rash	2	1						
Total Related Events	7	3	3	3	2	2	3	2
Unrelated Events								
Folliculitis	1	1						
Genital herpes episode								
Total All Events	8	4	4	4	2	2	3	2

* The total number of adverse events may exceed the total number of participants since a participant may have experienced more than one event.