

SPL7013 Gel (VivaGel™),

a topical microbicide in development for prevention of HIV and genital herpes, shown to be well tolerated and comparable with placebo after 7 days administration in healthy males.

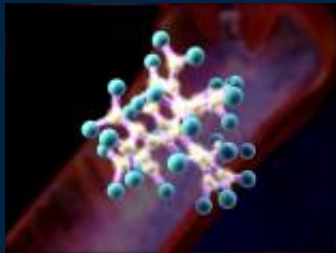
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TUAC1 - Female-Initiated HIV Prevention Technology
Late Breaker

Introduction

- SPL7013 Gel (VivaGel™)
 - In development as a topical vaginal microbicide for prevention of sexually transmitted HIV and HSV
 - HIV Epidemic
 - HSV Epidemic
 - Link between HIV and HSV
 - API is dendrimer, SPL7013
 - Prevention of HIV *in vitro* and in macaque
 - Prevention of HSV *in vitro* and in guinea pig
 - Contraceptive effect in rabbits, inhibition of sperm function *in vitro*



SPL7013




Microbicide Applicators

Introduction

- 2 completed clinical trials
 - SPL7013-001 – Female volunteers
 - SPL7013-002 – Male volunteers
- Currently under clinical investigation in 2 ongoing clinical trials:
 - STI-CTG (DMID/NIAID, NIH)
 - DMID 05-0121 (SPL7013-004) – Sexually abstinent females
 - Microbicide Trials Network (MTN) (DAIDS/NIAID & NICHD, NIH)
 - MTN-004 (SPL7013-006) – Sexually active females
- Further trials planned

Rationale

- Promising clinical and nonclinical safety profile
- Topical microbicides require:
 - Favourable risk/benefit profile – local (topical) and systemic toxicity / efficacy
 - Tolerability
 - Acceptability
- Incidental exposure in men, or eventual product for use by men:
 - Assess safety, tolerability and acceptability in men  **SPL7013-002**
- Assessing safety and tolerability in men:
 - Stratified epithelium thinner on glans of uncircumcised penis
 - Topical products may collect under the prepuce of uncircumcised penis

 **Stratify for circumcision status**

Objectives

- Primary Objective
 - Assess safety of 3% SPL7013 Gel compared with placebo when applied topically to penile epithelium and urethral mucosa
- Secondary Objectives
 - Assess systemic safety of 3% SPL7013 Gel
 - Assess systemic absorption of SPL7013
 - Assess acceptability of study products

Endpoints

- Primary Endpoints
 - Participant reports of genital pain / burning; penile itching / rash / ulceration; other genital symptoms
 - Observation of erythema, vesiculation, bullous reaction, ulceration or other genital findings of the penile shaft, foreskin, glans or meatus
- Secondary Endpoints
 - All other AEs, Lab abnormalities
 - Plasma concentrations of SPL7013
 - Expectations and experiences of the study products

Participant Criteria

- Informed Consent
- Healthy males 18 years +
- Negative for HIV, syphilis, gonorrhoea, and Chlamydia
- No STI within 3 months of screening
- Able to comply with procedures / restrictions
- No history of allergy / drug reactions / dermatological conditions
- No genital pain, piercing, or significant conditions

Design

- 2g of 3% SPL7013 Gel, topically, *qd* for 7 days
- Double-blind
- Placebo-controlled: Base gel without active
- Randomised: 2:1, active to placebo
- Stratified: circumcision status
- Single-centre: Melbourne Sexual Health Centre

Protocol

Design	Healthy male volunteers, aged at least 18 years of age	3% SPL7013 Gel (N = 24) 1 x daily for 7 days		Follow-Up	
		Day 0	Day 6	Day 7	Day 14
		Placebo Gel (N = 12) 1 x daily for 7 days		Follow-Up	
Visits	Screening Day -14 to -3	Baseline Day 0	Mid-Treatment Day 3 (2-4)	End-of-Treatment Day 7	Follow-Up Day 14
	Assessments	Medical History Physical Exam Vital signs Genital Exam HIV Test STI Status Clinical Labs	Physical Exam* Vital Signs Genital Exam STI Status** Clinical Labs Con Meds PK Sample Sexual History	Physical Exam* Genital Exam AE Review Con Meds Adherence / Use	Physical Exam* Vital Signs Genital Exam STI Status** AE Review Clinical Labs Con Meds PK Sample Adherence / Use

* Symptom directed; ** If indicated

Results - Demographics

- SPL7013 Gel / Placebo, well matched demographics / baseline characteristics

	3% SPL7013 Gel	Placebo Gel
Age: mean (range)	37 (21-55)	36 (22-67)
Race / Ethnicity: n (%)		
<i>Caucasian</i>	19 (79)	10 (83)
<i>Asian</i>	1 (4)	2 (17)
<i>Aboriginal/Torres Strait Islander</i>	0 (0)	0 (0)
<i>Pacific Islander</i>	1 (4)	0 (0)
<i>American Indian/Alaska Native</i>	1 (4)	0 (0)
<i>Other</i>	2 (8)	0 (0)

Results – Adherence / Exposure

- All subjects “adherent” to dosing regimen (≥ 6 doses)
- Mean daily duration of exposure to product similar between groups

	3% SPL7013 Gel	Placebo Gel
Duration of Daily Exposure: mean (range)	8'52" (5'45" – 13'45")	9'9" (5'55" – 13'0")

Results – Genital Events

- Occurrence
 - 12 (33%) participants reported to have at least 1 genital AE
 - 17 genital AEs reported in total
 - All Grade 1 (Mild)
 - SPL7013 Gel – 12 genital AEs in 8 (33%) participants
 - Placebo Gel – 5 genital AEs in 4 (33%) participants
- Relatedness
 - 15 genital AEs had potential causal relationship to study product (“possibly” or “probably” related)
 - SPL7013 Gel – 10 genital AEs in 6 (25%) participants
 - Placebo Gel – 5 genital AEs in 4 (33%) participants
- Onset / Duration
 - Majority commenced during 7 days of treatment
 - Majority had duration < 24 hours

Results – Genital Events

- Most Commonly Occurring
 - Genital Pruritis (penile or genital itching)
 - SPL7013 Gel – 5 reports in 3 (12%) participants
 - Placebo Gel – 1 report in 1 (8%) participant
 - Application site erythema (penile redness)
 - SPL7013 Gel – 1 report in 1 (4%) participant
 - Placebo Gel – 4 reports in 3 (25%) participants
- Circumcised vs. Uncircumcised
 - No apparent difference in genital AE profile between circumcised / uncircumcised

Results – Secondary Endpoints

- Non-genital AEs
 - 32 non-genital AEs reported in 19 participants
 - All Grade 1 or 2 (Mild or Moderate)
 - All Grade 2 non-genital AEs considered potentially related to treatment were in the placebo group
 - No SAEs, no Grade 3 or 4 AEs
- Lab Abnormalities
 - 1 reported as AE, “unlikely”, in placebo group
- Plasma concentrations of SPL7013
 - Not detected in samples after 7 days dosing
- Expectations and experiences
 - Acceptable to men, if proven to be effective at preventing STIs

Summary and Conclusions

- 3% SPL7013 Gel (VivaGel™)
 - Was safe and well tolerated
 - Did not result in systemic absorption of API, SPL7013
- following administration to the penile epithelium once daily for 7 days in 36 circumcised and uncircumcised healthy male volunteers.
- 3% SPL7013 Gel (VivaGel™) warrants further development and investigation as a topical microbicide

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