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Dermal Cumulative Irritation Assay

TESTAGEN™ PLACEBO

Document type:	Clinical Study Report **Summary TESTAGEN™ PLACEBO**
Development phase:	Pre-Phase 1
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AMENDMENTS:

1.	2.	3.	4.

Signature page for Investigator

Clinical Study Report -TESTAGEN™ PLACEBO

I have read this report and agree this trial was conducted in accordance with all stipulations of the protocol and the Guidance for Good Laboratory Practice (FDA Clinical Trials Regulations) and in accordance with the Declaration of Helsinki.

Principal Investigator

Howard Maibach, M.D.

signature _____ Date 3/20/13

Name of Test Product	**TESTAGEN™ PLACEBO**
Title of the Study	Dermal Cumulative Irritation Assay – TESTAGEN™ PLACEBO
Report Number **Clinical Phase**	**TESTAGEN™ PLACEBO** **Pre-phase 1**
Principal Investigator	Howard Maibach, M.D.
Study Site	Dermatology Research Laboratory 2435 Ocean avenue San Francisco, CA
Rationale	A new formulation (TESTAGEN™ PLACEBO) of TDS® drug delivery system (TransDermal Solutions Corp, Florida, USA) which is a novel, proprietary transdermal technology, developed for use in pharmaceutical, cosmetic and over-the-counter products. Transdermal administration combines a rapid onset of action with a convenient and patient-friendly method of administration, which, it is believed, will provide an attractive alternative to the traditional administration of Chemical and Biological Agents.
Objectives	The aim of this hypothesis generating study is to investigate the Cumulative Skin Irritation potential of a new transdermal delivery vehicle composed of ethanol, propylene glycol and other excipients.
Design:	A single center, controlled, repeat test study that evaluates the empty delivery system application in open and under occlusion.
Duration of treatment:	The duration of treatment was 21 days.
Study Population:	Healthy volunteers aged between 21 and 70 years old (about 53,4 years old in average) were recruited for the study.

Main Criteria for Inclusion	1. Male and female Caucasian subjects were 18 years of age or older, inclusive. 2. The subject was willing and able to read, understand and provide written informed consent. The subject was in otherwise good health as determined by medical history. 3. The subject was willing and able to comply with all testing and requirements defined in the protocol.
Main Criteria for Exclusion:	1. Dermatologic disease that might interfere with the evaluation of test site reaction. 2. The subject had had a clinically significant illness within 30 days preceding entry into this study. 3. The subject had a history of significant neurological, hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, or metabolic disease. 4. The subject had a known allergy or history of hypersensitivity to any of the TESTAGEN™ PLACEBO drug delivery system components. 5. The subject had used any prescription medication within 7 days or over-the-counter (OTC) medication or alcohol within 48 hours or intended to use any prescription or OTC medication during the study that might interfere with the evaluation of study product (excluding oral contraceptive). 6. Alcohol consumption greater than community norms (i.e. more than 21 standard drinks per week). 7. Subjects who had received an investigational drug or had used an investigational device in the 30 days prior to study entry. 8. Concerns of Volunteer's participation in the study were raised by their General Practitioner.
Concomitant Medication Restrictions	The intake of any medications (OTC or prescription) was vigorously discouraged.
Total number of subjects	A total of 36 subjects were pre-selected on the screening day. Four of them were withdrawn form the study before Day 1. They were immediately replaced on Day 1 by four other ones. A total of 32 subjects (17 female and 15 men) completed the study.

Criteria for evaluation:	The end point of the study was scoring of skin reactions performed by a trained observer at each evaluation, using an appropriate scale. Dermal reactions were scored on a scale that describes the amount of erythema, edema, and other features indicative of irritations. **Safety and Tolerability** Adverse Events were recorded throughout the study, at all visits and during any telephone calls. Details on medical history and concomitant illnesses were recorded on the day of screening by conducting a medical interview of subject or subject relative(s) and/or review of the subject's medical records. Any changes observed or reported during the study were recorded. A brief physical examination of the arm skin was performed at Screening Visit.
Study Material	The investigational product is the "TESTAGEN™ PLACEBO"; which does not contain a *primary chemical or biological agent.* The system is therefore inert.
Dermal Challenge	The investigational product was applied according to the following modalities in each subject: - a one (1) mL dose of the TESTAGEN™ PLACEBO drug delivery system was applied in open to a cutaneous area delimited on the right or left forearm (according to randomization). Applications were done once in 23 hours (± I hour) Monday to Friday, continuing on weekends for 21 days to the same skin site. - a 200 µL dose of the TESTAGEN™ PLACEBO drug delivery system to the right or left arm (according to randomization), under an occlusive patch (Hilltop 25 mm chamber®). Applications were done once in 23 hours (± I hour) Monday to Friday (patch remaining onto the skin during weekends) for 21 days to the same skin site. Each day, each site was evaluated by the research team for reaction and the delivery system reapplied.

Results

<u>Open application to the forearm skin:</u>

Dermal Response (grading scale in 8 points - 0 to 7)	
Cumulative Daily mean score	0
Cumulative Total score	0

The repeated open application of the product designated as "**TESTAGEN™ PLACEBO**", to the forearm skin, at the dose of 1 mL daily, for 21 consecutive days, in 32 healthy Caucasian subjects aged from 21 to 70 years old, did not lead to any noticeable cutaneous reaction.

Moreover, no subjects reported any discomfort linked to the product application to the forearm throughout the study duration.

These results show an excellent cutaneous acceptability of **TESTAGEN™ PLACEBO when applied under the normal conditions of use.**

<u>Application under occlusion to the arm skin:</u>

Dermal Response (grading scale in 8 points - 0 to 7)	
Cumulative Daily mean score	0.154
Cumulative Total Score	5

The repeated application of the product designated as "**TESTAGEN™ PLACEBO**", to the arm skin, at the dose of 0.2 mL daily, under occlusion (Hilltop 25 mm chamber®), for 21 consecutive days, in 32 healthy Caucasian subjects aged from 21 to 70 years old, did not lead to any clinically significant cutaneous reaction.

Results (continue)	For 4 subjects, the investigators reported transient very slight erythema (barely perceptible: grade 1) on the application site, occurring on D7, D14/15 or D21. For 3 of these subjects, the reaction disappeared within the following 24h hours and for the other one within the following 48 hours. One of these subjects had reported associated discomfort (transient itching sensation of mild intensity the day before). Three other subjects reported transient itching or stinging sensations of mild intensity, to the application site one to 3 times during the study. These results show a good cutaneous compatibility of **TESTAGEN™ PLACEBO when applied under occlusion.**