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Proprietary Drug Name: AndroGel [®]	Generic Drug Name: testosterone gel 1%	Condition: Type 2 diabetes/ Hypogonadism
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Name of Sponsor/Company:
Solvay Pharmaceuticals

Title of Study:
A Double-Blind, Randomized, Placebo-Controlled, Parallel Study to Evaluate the Efficacy and Safety of AndroGel[®], as an Adjunct to Hypoglycemic Therapy, in the Treatment of Hypogonadal and Low Testosterone Men with Type 2 Diabetes
Protocol No.: S176.2.101

Investigator(s):
46 Investigators.

Study Center(s):
This study was initiated at 71 sites in the United States. Of these, 46 sites randomized subjects.

Publication (Reference):
Not applicable.

Study Period: 05 NOV 2004 (First Subject First Visit) 01 JUN 2007 (Last Subject Last Visit)	Phase of Development: Phase II
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Objectives:
The primary objective of this proof-of-concept Phase II study was to evaluate the efficacy of AndroGel[®] (testosterone gel 1%) versus Placebo Gel in the glyceic control (mean change in glycosylated hemoglobin [A1C] from Baseline to Week 26) of hypogonadal or low testosterone type 2 diabetic males who have had moderate control (A1C, 7.0% to 9.5%) on a stable dosing regimen (eight to 12 weeks prior to screening) of oral hypoglycemic agents alone or in combination with insulin.

Secondary Objectives:

- To evaluate the mean change in glyceic control (A1C) from Baseline to other individual visits throughout the study.
- To evaluate the mean change from Baseline in lean body mass.
- To evaluate the mean change from Baseline in FBG.

Tertiary Objective:

- To evaluate the mean change from Baseline in Homeostasis Model Assessment of Insulin Resistance (HOMA IR): $\text{insulin resistance} = \frac{\text{fasting serum insulin } (\mu\text{U/mL}) \times \text{fasting plasma glucose (mmol/L)}}{22.5}$.

Safety assessments included an evaluation of adverse events (AEs), hypoglycemic episodes, laboratory evaluations, vital signs, physical examination, assessment of the prostate gland (digital rectal examination [DRE], prostate-specific antigen [PSA] and electrocardiograms

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(ECGs).

Methodology:

This was a Phase II, multicenter, double-blind, randomized, placebo-controlled, parallel group study designed to evaluate the efficacy and safety of AndroGel[®] (testosterone gel 1%) versus Placebo Gel in the glycemic control of hypogonadal and low testosterone type 2 diabetic males. Males with moderate glycemic control on a stable dosing regimen of oral hypoglycemic agents alone or in combination with insulin were enrolled.

Subjects were required to have an average serum total testosterone concentration of ≤ 400 ng/dL during the Pre-screen visit. In addition, to establish that these subjects had achieved mild to moderate glycemic control, they were required to have an A1C value from 7.0% to 9.5% at the Pre-screen visit (Week -1) while on a stable dosing regimen of oral hypoglycemic agents (alone or in combination with insulin). Subjects who satisfied the inclusion and exclusion criteria in the Screening period were then randomized to AndroGel[®] or Placebo. The 26-week double-blind treatment period was divided into an initial dosing (Week 0 to Week 2), dose-titration (Week 3 to Week 6), and dose maintenance phase (Week 7 to Week 26). Subjects started treatment at 7.5 g/day and were uptitrated every two weeks with an increase in dose by 2.5 g until a maximum dose of 15.0 g or until the target range of 600 to 1000ng/dL was reached (whichever occurred first).

While testosterone levels in the low normal range (>400 to <600 ng/dL) are able to maintain aspects of sexual function, it was hypothesized that high normal range (≥ 600 to 1000 ng/dL) would be required to improve glycemic control in Type 2 diabetic subjects.

Number of Subjects (Planned, Consented, Randomized and Analyzed):

There were 180 subjects planned, 1152 consented, and 183 randomized. Three subjects, all in the AndroGel[®] treatment group, did not take study drug and were therefore excluded from the Safety sample. Therefore, there were 180 subjects included in the Safety sample (AndroGel[®], 93 subjects; Placebo, 87 subjects). There were 157 subjects in the Full Analysis sample (FAS) (AndroGel[®], 82 subjects; Placebo, 75 subjects) and 116 subjects in the Per Protocol sample (PPS) (AndroGel[®], 56 subjects; Placebo, 60 subjects).

Diagnosis and Main Criteria for Inclusion:

The subjects enrolled in this study were hypogonadal or low testosterone type 2 diabetic males.

- A1C (%) in the range 7.0% to 9.5% at Pre-screen.
- Hypogonadism and low testosterone defined as an average serum total testosterone concentration ≤ 300 ng/dL and >300 to ≤ 400 ng/dL, respectively.
- Currently being treated for type 2 diabetes with oral hypoglycemic agents alone or in

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combination with insulin.

Test Product, Dose and Mode of Administration:

AndroGel® is a clear, colorless hydroalcoholic gel containing 1% testosterone. AndroGel® is applied topically once daily (QD). AndroGel® is given as a 7.5 g initial dose and thereafter adjusted by 2.5 g every 2 weeks, as needed, with a minimum dose of 5.0 g and a maximum dose of 15.0 g.

Duration of Treatment:

26 weeks

Reference Therapy, Dose and Mode of Administration:

Matching placebo gel, applied topically

Criteria for Evaluation:

Efficacy:

The primary efficacy variable was the mean change from Baseline to Week 26 for A1C.

Safety:

Safety assessments included AEs, laboratory evaluations and assessment of the prostate gland.

Statistical Methods:

The Safety sample was used for the analysis of the safety and tolerance data. The efficacy analyses were performed on the Full Analysis Sample (FAS) and the Per Protocol Sample (PPS), with the FAS being the primary sample.

The Safety sample consisted of all subjects who had been allocated to treatment and who had at least one dose of study drug administration. The FAS consisted of all subjects who were included in the safety sample; had data for at least one Post-baseline assessment of any efficacy measurement; had a baseline total testosterone value ≤ 400 ng/dL and had a baseline A1C with the range of 6.9% to 9.6. The PPS consisted of all subjects who were included in the FAS, had a Post-baseline A1C measurement, were on an assigned treatment dose after their Week 6 visit, and did not have any major protocol deviations.

For the primary efficacy variable, the last observation carried forward (LOCF) method was used for the mean change from Baseline to Week 26 in A1C. The null hypothesis was that there was no difference between the two treatment groups, with the alternative hypothesis that there was a difference.

Three planned, unblinded interim analyses were performed for this study. An interim analysis was conducted when approximately the first 25%, 50% and 75% of the total number of subjects to be randomized either withdrew from the study or completed 26 weeks of treatment. The interim analyses were conducted to evaluate efficacy (A1C and fructosamine). Each interim analysis was performed for administrative purposes only and was intended for the purpose of designing subsequent studies. A penalty of $\alpha = 0.0001$ was paid for each interim analysis,

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leaving the significance level at $\alpha = 0.0497$ for the final analysis of A1C and fructosamine.

Statistical tests were two-sided and performed at the significance level of $\alpha=0.0497$. The comparison between treatment groups for change in A1C was conducted using an analysis of covariance (ANCOVA) model with terms for Baseline A1C, treatment, and pooled center (main model).

For AEs, medical history and concomitant medications, the denominator for the percentage calculation was the number of subjects at risk for the particular treatment arm. A subject was considered at risk if the subject was in the safety sample and entered the respective study period.

Summary

Efficacy Results:

Efficacy was evaluated in the FAS population (AndroGel[®], 82 subjects; Placebo, 75 subjects) and in the PPS population (AndroGel[®], 56 subjects; Placebo, 60 subjects). As evaluated in the FAS, the majority of subjects in both treatment groups were treated for >14 weeks (AndroGel[®], 79.3%; Placebo, 90.6%).

- There was no significant difference between the AndroGel[®] and Placebo treatment groups in the primary efficacy variable, mean change in A1C from Baseline to Endpoint.
- The majority of subjects in the AndroGel[®] treatment group (52 subjects of 79 subjects, 65.8%) did not achieve testosterone levels in the target range of ≥ 600 to 1000 ng/dL at Endpoint (last non-missing value during treatment), despite dose titration every 2 weeks by increments of 2.5 g/day up to a maximum daily dose of 15.0 g of AndroGel[®].
- In the subjects with AndroGel[®] who achieved target total testosterone levels of 600 to 1000 mg/dL between week 6 and Endpoint (N=27), the mean decrease in the primary efficacy variable was 0.10%. This is in contrast to the mean increase (+0.13%) seen in the subjects who did not achieve the target total testosterone levels (N=15).
- The decrease in HOMA IR was greater in the AndroGel[®] treatment group (-0.533 $\mu\text{U}/\text{mL} \times \text{mmol}/\text{L}$) than in the Placebo treatment group (-0.177 $\mu\text{U}/\text{mL} \times \text{mmol}/\text{L}$). This difference was not statistically significant.
- At Endpoint, lean body mass increased by 1.40 kg in the AndroGel[®] treatment group, but decreased in the Placebo treatment group (-0.62 kg). The difference was statistically significant ($p < 0.001$).

Safety Results:

Safety was evaluated in 93 subjects in the AndroGel[®] treatment group and 87 subjects in the Placebo treatment group. The mean exposure was 140.1 days in the AndroGel[®] treatment group and 163.5 days in the Placebo treatment group. Over half of the subjects were treated for

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- There were no deaths during the study.
- A total of 20 subjects withdrew from the study due to a TEAE (AndroGel[®], 12 subjects, 12.9%; Placebo, 8 subjects, 9.2%). Withdrawals for discontinuations due to increases in PSA were more common in the AndroGel[®] treatment group (8 subjects, 8.6%) than in the Placebo treatment group (3 subjects, 3.4%). Withdrawals due to diabetes mellitus were more common in the Placebo treatment group (3 subjects, 3.4%) than in the AndroGel[®] treatment group (1 subject, 1.1%).
- The percentage of subjects with related TEAEs was similar in the AndroGel[®] (22 subjects, 23.7%) and Placebo (20 subjects, 23.0%) treatment groups. Prostate specific antigen increases related to treatment were more common in the AndroGel[®] treatment group (8 subjects, 8.6%) than in the Placebo treatment group (5 subjects, 5.7%).
- Mean values for Hgb and Hct significantly increased in the AndroGel[®] treatment group and decreased in the Placebo treatment group; however, none of the values were markedly abnormal.
- The percentage of subjects with TEAEs of special interest (androgenic effects) in subjects (N=27) who achieved target total testosterone levels (600-1000 ng/dL) was lower than in subjects with testosterone levels in the low normal range (400-600 ng/dL).

Date of the report: 20 JUN 2008