CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022219Orig1s000

STATISTICAL REVIEW(S)
STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA#: 22219

Drug Name: Aveed (Testosterone undecanoate)

Indication(s): Testosterone replacement therapy in men with hypogonadism

Applicant: Endo Pharmaceuticals

Date(s): Submission Date: 08/29/2013
          PDUFA Due Date: 02/28/2014

Review Priority: Standard

Biometrics Division: Division of Biometrics 3

Statistical Reviewer: Mahboob Sobhan, Ph.D., Statistical Team Leader

Medical Division: Division of Reproductive and Urological Drug Products

Clinical Team: Guodong Fang, MD., Clinical Reviewer
               Mark Hirsch, MD., Clinical Team Leader

Project Manager: Jeannie Roule

Keywords: NDA review, clinical study
This supplement pertains to Aveed (testosterone undecanoate) labeling in the PLR format. No new efficacy data was used in the PLR conversion. Therefore, no statistical input was necessary.
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/s/

MAHBOOB SOBHAN
02/04/2014
Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number: 22-219
Drug Name: Aveed (Testosterone undecanoate)
Indication(s): Adult male hypogonadism
Applicant: Endo Pharmaceuticals Solutions, Inc.
Date (s): Submission: 29/11/2013
Review Priority: Standard
Biometrics Division: Division of Biometrics III (HFD-725)
Statistical Reviewer: Mahboob Sobhan, Ph.D. (HFD-725)
Medical Division: Division of Bone, Reproductive and Urological Drug Products (HFD-580)
Clinical Team: Mark Hirsch, M.D. (HFD-580)
Guodong Fang, M.D. (HFD-580)
Project Manager: Jeannie Roule (HFD-580)

Keywords: NDA review, Clinical studies.
This is a memo pertaining to sponsor’s re-submission of NDA in response to the December 2, 2009 Action letter. In our earlier statistical review, we concluded that testosterone undecanoate (TU) was efficacious in treating hypogonadism in adult males. There were no new efficacy data submitted for our review to further substantiate or change the efficacy data. This resubmission contains sponsor's response to safety concerns related to severe post-injection reactions. The clinical reviewer’s report addresses the adequacy of this response to support the approvability of this product.
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/s/

MAHBOOB SOBHAN
05/28/2013
Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number: 22-219
Drug Name: Aveed (Testosterone undecanoate)
Indication(s): Testosterone replacement therapy in males
Applicant: Endo Pharmaceuticals Solutions, Inc.
Date (s): Submission: 3/2/2009
Review Priority: Standard
Biometrics Division: Division of Biometrics III (HFD-725)
Statistical Reviewer: Mahboob Sobhan, Ph.D. (HFD-725)
Medical Division: Division of Reproductive and Urological Drug Products (HFD-580)
Clinical Team: Mark Hirsch, M.D. (HFD-580)
                 Harry Handlesman, M.D. (HFD-580)
Project Manager: Jeannie Roule (HFD-580)

Keywords: NDA review, Clinical studies.
This is a memo pertaining to sponsor’s re-submission of NDA \( (b)(4) \) to address the clinical and chemistry, manufacturing, and control (CMC) deficiencies noted in the original NDA \( (b)(4) \) (dated 8/27/2007) which was communicated to the sponsor in the approvable letter dated 6/27/2008. In our earlier statistical review, we concluded that testosterone undecanoate (TU) was efficacious in treating hypogonadism in adult males. There were no new efficacy data submitted for our review to further substantiate or change the efficacy data in the label. We have reviewed the new label and from a statistical perspective, our conclusion remained unchanged.
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/s/
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Mahboob Sobhan
7/21/2009 05:07:21 PM
BIOMETRICS
## Clinical Studies

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<thead>
<tr>
<th><strong>NDA/Serial Number:</strong></th>
<th>22-219</th>
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</thead>
<tbody>
<tr>
<td><strong>Drug Name:</strong></td>
<td>Nebido™ (Testosterone undecanoate)</td>
</tr>
<tr>
<td><strong>Indication(s):</strong></td>
<td>Treatment of hypogandism in adult male.</td>
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<tr>
<td><strong>Applicant:</strong></td>
<td>Indevous Pharmaceuticals, Inc.</td>
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<tr>
<td><strong>Date(s):</strong></td>
<td>Submitted: 8/24/2007</td>
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<td><strong>Biometrics Division:</strong></td>
<td>Division of Biometrics III (HFD-725)</td>
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<td><strong>Statistical Reviewer:</strong></td>
<td>Mahboob Sobhan, Ph.D. (HFD-725)</td>
</tr>
<tr>
<td><strong>Medical Division:</strong></td>
<td>Division of Reproductive and Urological Drug Products (HFD-580)</td>
</tr>
</tbody>
</table>
| **Clinical Team:**     | Mark Hirsch, M.D. (HFD-580)  
Harry Handlesman, M.D. (HFD-580) |
| **Project Manager:**   | Eufrecina Deguia (HFD-580) |

**Keywords:** NDA review, Clinical studies.
INTRODUCTION

1.1 Background

The applicant, Indevous Pharmaceuticals, is seeking approval of Nebido (testosterone undecanoate) in castor oil and benzyl benzoate solution, for intramuscular (IM) depot injection intended as long-acting therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

To support the safety and efficacy of Nebido, this submission contains data from one study (IP157-001) conducted in the US. In this study, the efficacy was evaluated via surrogate outcomes, namely, pharmacokinetics of total testosterone (T) from testosterone undecanoate (TU).

1.2 Study Description

**Design:** Study IP157-001 was a multicenter, 2-arm, randomized, uncontrolled, open-label study conducted in the U.S. The objective of the study was to evaluate the pharmacokinetics (of T) from two doses of TU 750 mg and TU 1000 mg, IM injection given every 12 weeks, via measurement of T concentrations in up to 110 hypogonadal men per dose group, for a total of up to 220 patients. This study was conducted in three parts:

- **Part A:** In this part, a total of 237 patients (120 in TU 750 mg and 117 in TU 1000 mg) randomized to receive treatment every 12 weeks. Pharmacokinetic (PK) assessment was made at steady state following the 4th injection.

- **Part B:** In part B, the original plan was to enroll 130 patients to receive TU1000 mg at baseline, 8 weeks later, and every 12 weeks thereafter. But the design was modified to enroll patients with Nebido 1000 mg at baseline, Nebido 750 mg given at 8 weeks later, and then Nebido 750 mg given every 10 weeks thereafter. PK was assessed at steady state, following the 3rd injection.

- **Part C:** This part included only 1 arm, TU 750 mg LOADING given at baseline, at 4 weeks, and every 10 weeks thereafter.

Part B patients were enrolled after all patients in part A had been randomized, and part C patients were enrolled after all patients in part B had been enrolled. The primary objective in part A was to evaluate pharmacokinetics of TU 750 mg and TU 1000 mg IM injection, given over the 12-week interval following the 4th injection, via multiple measurements of serum total testosterone (T) in order to demonstrate that TU doses provide adequate testosterone replacement therapy (TRT) as measured by $C_{avg}$, while not providing excessive TRT as measured by $C_{max}$.

The objective in part C was to assess whether steady state had been achieved by the 3rd injection (by measuring an additional trough at the 5th injection). The steady state assessment included data from 3rd, 4th, and 5th injection visit at weeks 14, 24, and 34, respectively.
Efficacy Outcomes: The efficacy outcomes are the assessment of T concentration $C_{\text{avg}}$ and $C_{\text{max}}$ compared to FDA threshold defined below:

1. $C_{\text{avg}}$ within the normal range of 300 – 1000 ng/dL in at least 75% of the patients, with the lower bound of a 2-sided 95% confidence interval not below 65% and;

2. $C_{\text{max}}$ values: $>1500$ ng/dL in $\geq 85\%$ of patients,
   $\geq 1800$ ng/dL - $< 2500$ ng/dL in $\leq 5\%$ of patients, and
   $\geq 2500$ ng/dL in no patient.

The method of steady state assessment included (1) visual inspection of group-mean troughs at weeks 14, 24, and 34; and (2) use of a sequential statistical testing procedure (using Helmert contrast method) in order to assess the first time point in which steady state was observed. In Helmert method, the average serum total T of an earlier time point is compared with the average of a later time point to test the null hypothesis that the early time point is equal or greater than later time point. When the null hypothesis is not rejected ($p>0.05$), the test will indicate steady state has been attained. The testing was performed sequentially, as follows:

Test 1: Trough 2 versus the average of trough 3 and 4 (if $p>0.05$, declare SS, otherwise proceed to test 2)
Test 2: Trough 3 versus 4 (if >0.05, declare SS, otherwise no SS at 4th injection)

1.2 Review Issues

Division’s request the sponsor submitted data from part C of the study where Nebido 750 loading regimen was assessed by an additional trough measurement at the 5th injection visit that allowed a rigorous evaluation of whether steady state had been achieved by the 3rd injection or not. Therefore, this review pertains to statistical analysis of PK data in part C only. Details on the Safety issues can be found in Clinical Reviewer’s report.

1.3 Results

A total of 117 patients were evaluable for PK assessment. As shown in Table 1, the point estimate, i.e., the percent of patients meeting FDA threshold (using $C_{\text{avg}}$) is 94% with a lower bound of the 95% confidence interval of approximately 90%, which is higher than the FDA threshold of a minimum of 65%. Using $C_{\text{max}}$ assessment, treatment with Nebido 750 mg LOADING also did not result in excessively high T concentrations as shown in Table 2. Fewer than 8% of the patients exceeded the 1500 ng/dL threshold, while none exceeded $\geq 1800$ ng/dL threshold. Therefore, treatment with Nebido 750 mg provided adequate Testosterone replacement in hypogonadal men.
Table 1: Number and Percent of Patients (95% Confidence Interval) for Nebido 750 mg LOADING Meeting FDA $C_{\text{avg}}$ Threshold – PK Population (N=117), Study IP157-001, Part C.

<table>
<thead>
<tr>
<th>$C_{\text{avg}}$ range</th>
<th>N (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(300, 1000) ng/dL</td>
<td>110 (94.0)</td>
<td>(89.6, 98.4)</td>
</tr>
<tr>
<td>Outside (300, 1000) ng/dL</td>
<td>7 (6.0)</td>
<td>--</td>
</tr>
</tbody>
</table>

Source: Clinical study report dated 8/6/2007

Table 2: Number and Percent of Patients for Nebido 750 LOADING Exceeding FDA $C_{\text{max}}$ Threshold, PK Population (N=117), Study IP157-001 Part C.

<table>
<thead>
<tr>
<th>$C_{\text{max}}$ range</th>
<th>N (%) Exceeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1500 ng/dL</td>
<td>9 (7.7)</td>
</tr>
<tr>
<td>&gt;=1800 - &lt;2500 ng/dL</td>
<td>0 (0)</td>
</tr>
<tr>
<td>&gt;=2500 ng/dL</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

The steady state PK population included a total of 105 patients. Table 3 shows the average T concentration from 2nd through 5th injection for these patients. The mean concentrations and the standard deviations between injections were relatively close except at injection 2. A repeated measures analysis of variance (ANOVA) model was used to perform the statistical analysis. P-values for the comparison of trough means between injections shows that steady state had been achieved by 3rd injection (p= 0.72) as per test 1.

Table 3: Mean trough concentrations and p-values for the comparison of injections

<table>
<thead>
<tr>
<th>Time</th>
<th>Serum Total Testosterone (ng/dL) (N=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Injection 2</td>
<td>312.2 (104.8)</td>
</tr>
<tr>
<td>“  3</td>
<td>340.0 (122.2)</td>
</tr>
<tr>
<td>“  4</td>
<td>325.0 ( 99.6)</td>
</tr>
<tr>
<td>“  5</td>
<td>341.0 (108.0)</td>
</tr>
</tbody>
</table>

Source: Table 3, Helmert contrast output, section 6.1.2, dated January 29, 2008

2.0 CONCLUSIONS

The results support the efficacy of Nebido TU 750 mg LOADING in the treatment of hypogonadism in adult male as indicated by the attainment of steady state by the 3rd injection. The intensive sampling for PK outcomes ($C_{\text{avg}}$ and $C_{\text{max}}$) also met FDA threshold for approvability and, therefore, can be extrapolated to represent PK outcomes under extended dosing beyond 3 injections.
I. Summary

Data from two studies: A European study (study 306605 which is still ongoing but only data collected up to October 2006 was part of this submission) and a U.S. study (study IP157-001) were the basis of this submission. The objectives of the studies were to describe the clinical efficacy of testosterone undecanoate (TU) 1000 mg given intramuscularly every 12 weeks for testosterone replacement therapy in hypogonadal men. Study 306605 was a single arm, open-label with TU 1000 mg, while study IP157-001 was a two arm, randomized study where patients were treated with either TU 750 mg or TU 1000 mg.

The primary endpoints were changes in prostate specific antigen (PSA) in the European study and changes in PK profile of serum total testosterone, as measured by Cavg and Cmax.

Summary of Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Site(s)</th>
<th>No. of Patients Randomized/Treatments</th>
<th>Duration of Treatment</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>306605</td>
<td>16 centers in Germany</td>
<td>Total enrolled: 90 TU 1000 mg</td>
<td>3 years</td>
<td>• Changes in PSA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• T at trough, clinical lab. outcomes</td>
</tr>
<tr>
<td>IP157-001</td>
<td>54 US centers</td>
<td>Total Enrolled: 237 TU 750 mg: 120 TU 1000 mg: 117</td>
<td>3 years</td>
<td>• Changes in PK profiles</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Other lab. outcomes</td>
</tr>
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The following items were checked to determine the fileability conclusion.

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<tr>
<th>Items:</th>
<th>Check (Yes, No, N/A)</th>
<th>Comments:</th>
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<tbody>
<tr>
<td>Index sufficient to locate reports, tables, etc.</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Original protocols and subsequent amendments included in the submission.</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Designs utilized appropriate for the indications requested.</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Endpoints and methods of analyses spelled out in the protocols.</td>
<td>Yes</td>
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<tr>
<td>Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made</td>
<td>No</td>
<td>Not planned</td>
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<tr>
<td>Sufficient data listings and intermediate analysis tables to permit a statistical review</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Data and reports from primary studies submitted as per guidance.</td>
<td>yes</td>
<td>EDR</td>
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<tr>
<td>Results from Sub-groups analyses by gender, race, and ethnicity were provided.</td>
<td>yes</td>
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</table>

II. Conclusion

After the preliminary review of the submission, we have not identified any deficiencies that would be a reason for refuse-to-file. All data sets are accessible and statistical analysis can be performed. The sponsor provided the required information in this NDA to perform statistical evaluation and, therefore, this NDA should be filed.
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/s/
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Mahboob Sobhan
10/17/2007 10:47:47 AM
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