CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021463Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-463 Resubmission
Drug Name:	Fortesta (testosterone) 2% Gel
Indication(s):	Testosterone replacement therapy in male hypogonadism
Applicant:	Endo Pharmaceuticals Inc.
Date(s):	Submission Date: 6/30/2010
	PDUFA Due Date: 12/30/2010
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Kate Dwyer, Ph.D.
Concurring Reviewer:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Reproductive and Urologic Drug Products, HFD-580
Clinical Team:	Guodong Fang, M.D., Clinical Reviewer (HFD-580)
	Mark Hirsch, M.D., Clinical Team Leader (HFD-580)
Project Manager:	Jeannie Roule

Keywords: NDA review, clinical studies

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1. INTRODUCTION

1.1 Background

NDA 21-463 for Fortesta (testosterone) 2% Gel was originally submitted on May 31, 2002 by Cellegy Pharmaceuticals Inc. On July 3, 2003, a Non Approvable letter was issued by the agency to address the deficiencies noted in the application. The deficiencies include lack of evidence to support the safety of daily use and lack of information to support the dose of the product. In November 2006, the NDA was transferred to ProStraken Pharmaceuticals Inc. and they resubmitted the NDA on April 17, 2009 based on the results from a new phase 3 Study FOR01C. The study FOR01C was redesigned with new dose regime to address the deficiencies. Note that on September 8, 2009 prior to PDUFA date of October 17, 2009, the ownership of this NDA was transferred to Endo Pharmaceuticals Inc. On October 16, 2009, another CR letter was issued by the Agency to inform the clinical deficiency noted in the Application for study FOR01C.

The reason for the CR letter was due to issues raised by the Division of Scientific Investigations (DSI), FDA from the audit of the (b) (4) in (b) (4), which assayed the specimens for the pivotal study, FOR01C. Form 486 was issued to (b) (4) by DSI to address the deficiencies. In response, the Applicant chose to re-assay all available testosterone samples (backup samples stored at -70°C) from the FOR01C clinical study in fully validated bioanalytical runs in order to obtain valid data.

This resubmission includes the results of the re-assayed data to support the original assessment of the safety and efficacy data of Fortesta. The focus of this review is on the validity and analysis of the re-assayed data.

1.2 Study Description

Study FOR01C was a multicenter, open label, single-arm, dose-titration trial in hypogonadal males conducted in the US. The serum testosterone samples were taken at screening, baseline (Day 1), and on Day 14±3, Day 35±3, Day 60±3, and Day 90±3. Dose adjustment was based on the 2-hour post dose serum testosterone concentration on Day 14±3, Day 35±3, and Day 60±3. In addition, complete 24-hour pharmacokinetic profiles were drawn on Days 35±3 and 90±3 and included up to 10 samples (nominal times=0, 0:30, 1:00, 2:00, 4:00, 6:00, 8:00, 10:00, 12:00, 24:00). Sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol (E2) concentrations were obtained at two hours after study drug application on Days 35 ± 3 and Day 90 ± 3.

The primary and the secondary endpoints were C_{avg} and C_{max} on Day 90±3 based on the 24-hour pharmacokinetic profile. The efficacy was assessed based on the threshold set by the Division as defined below:

(1) C_{avg} within the normal range of 300 – 1140 ng/dL in at least 75% of the patients, with the lower bound of a 2-sided 95% confidence interval not below 65%;

(2) C_{max} in $\leq$ 1500 ng/dL in $\geq$85% of patients, within $\geq$ 1800 to $\leq$ 2500 ng/dL in $\leq$ 5% of patients, and in > 2500 ng/dL in no patients.

The primary efficacy analysis was based on the modified-intent-to-treat (MITT) population defined as subjects who had at least one application of the study drug and had more than one of the total serum testosterone values obtained during the 24-hour sampling period on Day 90.

1.3 Validity of Total Testosterone Re-assay Data

In Form 486 issued by DSI, 290 of the original serum testosterone samples were identified as invalid, because these samples did not meet the bioanalytical acceptance criteria. As shown in Table 1, these 290 invalid samples represented 8% (290/3696) of the total number of serum testosterone samples analyzed. Of these, 90% (261/290) were re-assayed. In order to support the original assessment of the safety and efficacy of Fortesta, the Applicant chose to re-assay all available backup samples including these invalid results.

Table 1: Summary of the Number of Samples by Day Which Had Invalid Results (All Subjects)

Day	Number of Invalid Results[a]	Number of Invalid Results Which Did Not Have a Valid Re-assay	Number of Invalid Results for Which Valid Results Could Be Obtained by Re-assaying a Backup Sample (%)
Any day in study	290	29	261 (90%)
Day 90[b]	153	7	146 (95%)
Day 35[b]	97	7	90 (93%)
Screening, Baseline, Day 14, or Day 60[c]	40	15	25 (63%)

[a] Invalid results are those that came from assays which did not meet the bioanalytical acceptance criteria

[b] Samples collected on Days 35 and 90 comprise complete 24-hour profiles. Each profile includes up to 10 samples.

[c] Samples collected at baseline, Day 14, or Day 60 were only from 2 hours post-FORTESTA application.

(Source: Summary of Clinical Efficacy, Study FOR01C Report; Table 1, page 7)

As shown in Table 2, on Day 90 there were 1374 original samples, of which 1247 samples (over 90% of the original samples) were re-assayed. For 127 samples which had no back-up sample available, 121 had valid original samples. Thus only 6 samples out of 1374 total samples (less than 1%) did not have valid sample from neither original nor re-assay samples. For sensitivity analysis, samples with no re-assayed data were imputed using the valid original samples.

Table 2: Number (%) of Samples on Day 90: MITT Population

Original Assay Results	Number of Original Sample N	Re-assayed Available		Re-assayed Unavailable	
		N	%	N	%
Valid	1222	1101	90.1%	121	9.9%
Invalid	152	146	96.1%	6	3.9%
Total	1374	1247	90.8%	127	9.2%

(Source: Summary of Clinical Efficacy, Study FOR01C Report; Table 3, page 8)

The Concordance Correlation Analyses were used to study the similarity between the original values and re-assayed values. The Concordance Correlation Coefficient (CCC) and its 2-sided 95% confidence interval (CI) between the original assay value and re-assayed value for total testosterone are shown in Table 3.

Table 3: Summary of Concordance Correlation Coefficients between the Original and Re-assayed Total Serum Testosterone Values

	Subjects	Concordance Correlation Coefficient	95% CI
All Values from all Days	3318	0.947	(0.943, 0.950)
All Values for Day 90	1253	0.941	(0.935, 0.947)
All Valid Values from all Days	3052	0.948	(0.945, 0.952)
All Valid Values for Day 90	1107	0.941	(0.934, 0.947)

(Source: Applicant and Reviewer's Analysis)

In summary, based on the high percentage of re-assayed data and strong concordance between the two samples, the re-assayed samples are acceptable.

1.4 Efficacy Results

The efficacy results for original and re-assayed values are presented in Table 4 and Table 5. The Agency considers efficacy results from re-assayed values to be the primary efficacy results and these results are used in final labeling.

Among 129 patients with valid re-assayed values, 77.5% of the patients had their testosterone levels within the normal range with the lower bound of the 95% CI of 70.3% on Day 90, which met the threshold. For the re-assayed C_{max} assessment on Day 90, the results also met the predefined threshold for demonstrating efficacy. As shown in Table 4, more than 94.6% patients had C_{max} less than 1500 ng/dL, fewer than 2% of patients exceeding 1800 ng/DL and none exceeding 2500 ng/DL.

Table 4: Percent of Subjects with Total Serum Testosterone C_{avg} and C_{max} at Day 90 for All Modified Intent-to-Treat (MITT) Subjects

Assay	N (number of Samples)	% Subjects (95% CI)	% Subjects		
		C_{avg} Within [300, 1140 ng/dL]	C_{max} ≤ 1500 ng/dL	C_{max} Within [1800, 2500 ng/dL]	C_{max} > 2500 ng/dL
Original	138 (1374)	76.1 (69.0, 83.2)	91.3	4.3	0
Re-assay	129 (1247)	77.5 (70.3, 84.7)	94.6	1.6	0
Re-assay imputing with valid original values[a]	138 (1368)	76.8 (69.8, 83.9)	92.8	2.9	0

[a] When a backup sample was not available for re-assay
(Source: Summary of Clinical Efficacy: Study FOR01C; Table 4, page 4)

For patients with BMI less than 35 kg/m^2, the results are presented in Table 5 for the original, re-assayed and imputed re-assayed values. These results also met the predefined threshold for demonstrating efficacy. Noted that one additional patient (ID 032-050) with BMI greater than 35 kg/m^2 was excluded from the subgroup analysis than what reported by the Applicant.

Table 5: Percent of Subjects with Total Serum Testosterone C_{avg} and C_{max} at Day 90 with BMI < 35 kg/m^2: MITT Population

Assay	N (number of Samples)	% Subjects (95% CI)	% Subjects		
		C_{avg} Within [300, 1140 ng/dL]	C_{max} ≤ 1500 ng/dL	C_{max} Within [1800, 2500 ng/dL]	C_{max} > 2500 ng/dL
Original	132 (1316)	75.0 (67.6-82.4)	91.7	3.8	0
Re-assay	124 (1202)	76.6 (69.2-84.1)	94.4	1.6	0
Re-assay imputing with valid original values[a]	132 (1310)	75.8(68.5-83.1)	93.2	2.3	0

[a] When a backup sample was not available for re-assay
(Source: Reviewer's Analysis)

2. SUMMARY AND CONCLUSIONS

Results from phase 3 study FOR01C with original and re-assayed values support the efficacy of Fortesta for testosterone replacement in male hypogonadism. The study confirmed that with the right starting dose of Fortesta, sampling time points and the titration schedules, testosterone levels were achieved within the physiologic range for the majority of the patients. Fortesta also minimized supraphysiologic concentrations of testosterone levels.

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/s/

KATE L DWYER
11/18/2010

MAHBOOB SOBHAN
11/19/2010

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA: 21-463 / Resubmission Class 2 **Applicant:** Endo Pharmaceuticals Inc. **Stamp Date:** 6/30/2010

Drug Name: Fortesta (testosterone 2% Gel) **45 day Meeting Date:** 8/4/2010

Indication: Testosterone replacement therapy in male hypogonadism

Medical Officer: Guodong Fang, M.D. **Project Manager:** Jeannie Roule

A: Summary

NDA 21-463 for Fortigel (testosterone) 2% Gel was originally submitted on May 31, 2002 by Cellegy Pharmaceuticals Inc. On July 3, 2003, a Non Approvable letter was issued by the agency to address deficiencies of the application. In November 2006, NDA 21-463 was transferred to ProStraken Pharmaceuticals Inc. NDA 21-463 was resubmitted based on the results from a new phase 3 Study FOR01C by Prostraken on April 17, 2009. Note that on September 8, 2009 before the PDUFA date of October 17, 2009, the ownership of this NDA was transferred to Endo Pharmaceuticals Inc. On October 16, 2009, a CR letter was issued by the Agency to inform the clinical deficiencies. This submission includes an amendment (resubmission) to NDA21-463 which provided reanalysis of the re-assayed data for Study FOR01C in order to support the original assessment of safety and efficacy of Fortesta.

This filing review will determine whether the format and content of the safety and efficacy database for this NDA is sufficiently complete for substantive statistical review as per study protocol.

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).			X	
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

B: Conclusion

After preliminary review of the submission of the following checklist items, this submission is fileable from statistical point of view.

Potential review issues to be forwarded to the Applicant for the 74-day letter:

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Kate Dwyer, Ph. D.	8/16/2010
Reviewing Statistician	Date
Mahboob Sobhan, Ph. D.	8/16/2010
Supervisor/Team Leader	Date

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/s/

KATE L DWYER
09/27/2010

MAHBOOB SOBHAN
09/27/2010

Addendum to Statistical Review

NDA/Serial Number:	NDA 21-463 Resubmission
Applicant:	Endo Pharmaceuticals, Inc.
Product:	Fortesta (testosterone) 2% Gel
Indication:	Testosterone replacement therapy in males with hypogonadism
Dates:	Submission Date: 4/17/2009 PDUFA Due Date: 10/17/2009
Statistical Team:	Kate Dwyer, Ph.D., Statistical Reviewer, Division of Biometrics 3 Sonia Castillo, Ph.D., Acting Team Leader, Division of Biometrics 3
Clinical Team:	Guodong Fang, M.D., Medical Reviewer, Division of Reproductive and Urologic Products Suresh Kaul, M.D., Team Leader, DRUP
Project Manager:	Jeannie Roule
Key Words:	Clinical studies, NDA review

This addendum updates the statistical review of this NDA for Fortesta (testosterone) 2% Gel to include information about the validity of the primary and important efficacy data used to claim efficacy. A DSI investigation of the laboratory used to assay total testosterone levels from blood samples drawn during the study resulted in the issuance of an FDA Form 483 citing deficiencies. The deficiencies were that the laboratory:

- Did not meet quality control guidelines
- Failed to meet calibration criteria
- Did not follow standard operating procedures

The total testosterone levels were used to calculate the primary efficacy endpoint (C_{avg} 0-24 hr on Day 90 ± 3) and secondary efficacy endpoint (C_{max} on Day 90 ± 3). Because of these deficiencies, the total testosterone data are not reliable and, therefore, efficacy has not been demonstrated for this product based on these data.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21463	ORIG-1	PROSTRAKAN LTD	FORTIGEL (TESTOSTERONE GEL) 2%

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/s/

KATE L DWYER
10/08/2009

SONIA CASTILLO
10/08/2009
signing for Mahboob Sobhan

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-463 Resubmission
Drug Name:	Fortigel (testosterone) 2% Gel
Indication(s):	Testosterone replacement therapy in male hypogonadism
Applicant:	Endo Pharmaceuticals Inc.
Date(s):	Submission Date: 4/17/2009
	PDUFA Due Date: 10/17/2009
Review Priority:	Priority
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Kate Dwyer, Ph.D.
Concurring Reviewer:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Reproductive and Urologic Drug Products, HFD-580
Clinical Team:	Guodong Fang, M.D., Clinical Reviewer (HFD-580)
	Suresh Kaul, M.D., Clinical Team Leader (HFD-580)
Project Manager:	Jeannie Roule

Keywords: NDA review, clinical studies

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1. INTRODUCTION

1.1 Background

NDA 21-463 for Fortigel (testosterone) 2% Gel was originally submitted on May 31, 2002 by Cellegy Pharmaceuticals Inc. On July 3, 2003, a Non Approvable letter was issued by the agency to address deficiencies of the application. In November 2006, NDA 21-463 was transferred to ProStraken Pharmaceuticals Inc.

To address the concerns communicated in the Non Approvable letter, a new phase III study FOR01C was submitted for special protocol assessment on February 21, 2007 by ProStrakan. A Type A Meeting was held on May 24, 2007 to discuss the study design. NDA 21-463 was resubmitted based on the results from this new phase 3 study FOR01C. This review will focus on this pivotal Phase 3 study FOR01C: "an open label phase 3 study of Fortigel (testosterone) 2% gel in hypogonadal males". Note that on September 8, 2009 before the PDUFA date of October 17, 2009, the ownership of this NDA was transferred to Endo Pharmaceuticals Inc.

1.2 Study Description

Study FOR01C was a multicenter, open label, non-comparative trial in hypogonadal males conducted in US. The objective of the study was to evaluate the pharmacokinetics of Fortigel as testosterone replacement therapy in male hypogonadism.

A total of 149 eligible patients were enrolled in the study and patients who had prior testosterone replacement therapy completed a washout period. All patients enrolled in the study applied Fortigel once each morning to the thighs at a starting dose of 40 mg per day. The dose of study drug was adjusted to between a minimum of 10 mg per day and a maximum of 70 mg per day on the basis of total serum testosterone concentrations obtained at two hours after study drug application on Days 14, 35, and 60 (± 3 days). Serum testosterone concentrations were obtained at two hours after study drug application on Days 14, 35, 60, and 90 (± 3 days). In addition, 24-hour pharmacokinetic (PK) profiles for these parameters were obtained on Days 35 ± 3 and Day 90 ± 3. Sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol (E2) concentrations were obtained at two hours after study drug application on Days 35 ± 3 and Day 90 ± 3.

The efficacy outcomes were the assessment of serum total testosterone concentration C_{avg} and C_{max} on Days 90 (± 3 days) compared to the threshold defined below:

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

(2) C_{max} values: $\leq$ 1500 ng/dL in $\geq$85% of patients.
$\geq$ 1800 to $\leq$ 2500 ng/dL in $\leq$ 5% of patients.
> 2500 ng/dL in 0 patients.

1.3 Results

Of the total 149 treated patients, 138 patients were evaluable for PK assessment. As showed in Table 1, 76.1 % of the patients had their testosterone levels within the normal range and the lower bound of the 95% CI was 69.0% on Day 90, which achieved the threshold. Using C_{max} assessment on Day 90, the results also met the predefined criteria. As showed in Table 2, more than 91.3% patients had Cmax less than 1500 ng/dL, fewer than 5% of patients exceed 1800 ng/DL and none exceed 2500 ng/DL.

Table 1: Summary Statistics of C_{avg} on Day 90 ± 3

	N (%)	95% CI
C_{avg} (300, 1000) ng/dL	105 (76.1)	(69.0, 83.2)
C_{avg} Outside (300, 1000) ng/dL	33 (23.9)	--

Table 2: Summary Statistics of C_{max} on Day 90 ± 3

C_{max}	N (%)
% Patients with Values ≤ 1500 ng/dL	126 (91.3)
% Patients with Values 1800 – 2500 ng/dL	6 (4.3)
% Patients with Values > 2500 ng/dL	0 (0)

2. SUMMARY AND CONCLUSIONS

Results from phase 3 study FOR01C support the efficacy of Fortigel for testosterone replacement in male hypogonadism. The study confirmed that with the right starting dose of Fortigel, sampling time points and the titration schedules, testosterone levels were achieved within the physiologic range for the majority of the patients. Fortigel also minimized supraphysiologic concentrations of testosterone levels.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21463	ORIG-1	PROSTRAKAN LTD	FORTIGEL (TESTOSTERONE GEL) 2%
NDA-21463	ORIG-1	PROSTRAKAN LTD	FORTIGEL (TESTOSTERONE GEL) 2%

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/s/

KATE L DWYER
09/16/2009

MAHBOOB SOBHAN
09/16/2009

Memo for the Record

Date: Jan 8, 2003

NDA: 21-463

Applicant: Cellegy

Trade/Generic Name: Tostrex (2% testosterone gel)

Indication: Testosterone replacement therapy in adult males with hypogonadism

Date of Submission: May 31, 2001

Filing Date: Jul 31, 2002

User Fee Goal Date: Mar 31, 2003

Project Manager: Deguia

Medical Reviewer: Benson

Comments: A single principal study (T-00-02-01) supports efficacy. This is an open label, uncontrolled study. Efficacy is based on percentage of patients who achieve and maintain pre-defined average and maximum testosterone concentration levels. Study results are descriptive only. A written statistical review will not be needed.

cc
NDA 21-463 (DFS)
HFD-580 Deguia, Benson
HFD-715 Welch, Nevius

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/s/

Mike Welch
1/8/03 11:02:49 AM
BIOMETRICS

Screening of New NDA for Statistical Filing
Division of Biometrics II

NDA #: 21-463

Applicant: Cellegy

Trade/Generic Name: Tostrex (2% testosterone gel)

Indication: Testosterone replacement therapy in adult males with hypogonadism

Date of Submission: May 31, 2001

Filing Date: Jul 31, 2002

User Fee Goal Date: Mar 31, 2003

Project Manager: Deguia

Medical Reviewer: Benson

Comments: This NDA is fileable from a statistical perspective. A single principal study (T-00-02-01) supports efficacy. This is an open label, uncontrolled study. Efficacy is based on percentage of patients who achieve and maintain pre-defined average and maximum testosterone concentration levels. Study results are descriptive only. A separate statistical review will not be needed. A short review memo should suffice for verification of sponsor's results.

Checklist for Fileability	Remarks (NA if not applicable)
Index sufficient to locate study reports, analyses, protocols, ISE, ISS, etc.	OK
Original protocols & subsequent amendments submitted	OK
Study designs utilized appropriate for the indications requested	OK
Endpoints and methods of analysis spelled out in the protocols	OK
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	NA
Appropriate references included for novel statistical methodology (if present)	NA
Data and reports from primary studies submitted to EDR according to Guidances	Access to EDR data OK
Safety and efficacy for gender, racial, geriatric, and/or other necessary subgroups investigated	OK

Reviewer: M. Welch

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/s/

Mike Welch
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BIOMETRICS