CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-319

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
(Carcinogenicity Studies)

NDA No.: 21-319

Applicant: GlaxoSmithKline

Name of Drug: Dutasteride Soft-Geltin Capsules

Documents Reviewed: 1. CDER CAC Executive Meeting Minutes on May 1, 2001

2. Historical Control Data submitted by the sponsor, dated July 2, 2001.

Reviewing Pharmacologist: Laurie McLeod, Ph.D., HFD-580

Statistical Reviewer: Karl K. Lin, Ph.D., HFD-715

Summary of Review

The positive trends in total incidence in hepatocellular adenoma, and hepatocellular adenoma and carcinoma combined in female mice are tested by the permutation trend test (also called Cochran-Armitage trend test using the doses as weights) without and with the incorporation of the historical control data submitted by the sponsor. The analysis results show that the positive trends in total incidence in hepatocellular adenoma, and hepatocellular adenoma and carcinogema combined are statistically significant in both analyses without and with the incorporation of the historical control data (using just either the data from the three studies conducted at [redacted] or the data from 17 studies conducted at [redacted]

In addition, the positive trend in total incidence in interstitial cell tumor in the male rats is also statistically significant.

1. Introduction

There are two carcinogenicity studies, one in mice and one in rats, included in this NDA submission. Two control groups and three treated groups were used in the two studies. 60 animals were used in each group/sex. The doses chosen for the mouse carcinogenicity study were 0, 0, 3, 35 (50 before week 22), and 250 mg/kg/day. There was an extra high male mouse group of 500 mg/kg/day in the mouse study. The doses for the rat carcinogenicity study were 0, 0. 1.5, 7.5, and 53 mg/kg/day for male rats, and 0, 0.8, 6.3, and 15 mg/kg/day for female rats.

CDER Executive Carcinogenicity Assessment Committee (CAC) discussed the results of the two carcinogenicity studies on May 1, 2002 without an internal statistical review. It was concluded by CDER Executive CAC that the designs of the two studies were valid, and that there were positive tumor findings in hepatocellular adnoma, and hepatocellular adenoma and carcinoma combined in female mice, and in interstitial cell tumor in female rats.

The sponsor argued that the positive finding in interstitial cell tumor in male rats was not relevant to humans. The sponsor also argued that the findings in hepatocellular adenoma, and adenoma and carcinoma combined in female mice were false positive findings since the tumor rates in the treated groups were within the ranges of historical control data.

While the Agency is evaluating the validity of the sponsor's argument on the positive finding in interstitial cell tumor in male rats, the sponsor was asked to submit comparable historical control data from the same laboratory that conducted the Dutasteride carcinogenicity studies for the Agency to evaluation its argument on the findings in hepatocellular adenoma, and adenoma and carcinoma combined in female mice. In its July 2, 2001 response to FDA Request/Comment: Nonclinical, the sponsor indicated that there was no oral (gavage) oncology studies in B6C3F1 mice by [redacted] that were contemporary to the Dudasteride studies. However, the sponsor submitted in the response historical control data of hepatocelluar adenoma and carcinoma from three dietary studies using methyl cellulose as vehicle conducted by [redacted] and from 14 gavage studies conducted by [redacted] Among the 14 [redacted] gavage studies, three used methyl cellulose, one used water, and 10 used corn oil as vehicle.

Dr. Laurie McLeod of HFD-580, reviewing pharmacologist of this NDA, has asked Division of Biometrics II to perform a statistical analysis of the above tumor types with the incorporation of the historical control data submitted by the sponsor.

2. Reviewer's Analysis

Tumor data of hepatocellular adenoma and carcinoma in female mice and interstitial cell tumor in male rats are included in Table 1 below.

Table 1

Tumor Incidence Rates of Hepatocellular Adenoma, Adenoma+Carcinoma in Female Mice and Interstitial Cell Tumor in Male Rats

Species/sex	Tumor	Control 1	Control 2	Low	Medium	High
Mouse/female	Hepatocellular adenoma	6	6	8	9	15
Mouse/female	Hepatocellular adenoma+carcinoma	7	8	10	12	18
Rat/male	Interstitial cell tumor	3	1	3	3	12

2.1 Statistical Analysis Without Incorporation of Historical Control Data

The survival-unadjusted Cochran-Armitage trend test using the doses as weights (also called permutation trend test) is used in the analysis of the total tumor incidence data for the following reason. According to the reviewing pharmacologist, the survivals are similar among the treatment groups.

Results of the Cochran-Armitage trend tests on the total incidences of hepatocellular adenoma, and hepatocellular adenoma and carcinoma combined in female mice without incorporation of historical control data are given in Table 2. The results show that there are statistically significant trends in the total incidences of hepatocellular adenoma (asymptotic $p = 0.0045$ and exact $p = 0.0062$), and hepatocellular adenoma and carcinoma combined (asymptotic $p = 0.0031$ and exact $p = 0.0043$) in female mice.

The results of the Cochran-Armitage trend test on the total incidence rates of interstitial cell tumor in male rats without incorporation of historical control data are included in Table 3. The results show that there is a statistically significant trend in the total incidences of interstitial cell tumor in male rats (asymptotic $p < 0.0001$ and exact $p = 0.0001$).

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Table 2

Results of Statistical Analysis of Total Incidences of Hepatocellular Adenoma, and Hepatocellular Adnoma and Carcinoma Combined in Female Mice

Female Mice
Hepatocellular Adenoma
12/120, 8/60, 9/60, 15/60
Scores 0, 3, 35, 250
PERMUTATION TEST

[1 2 by 4 tables and sum of scores from row <row1 >]

Summary of Exact distribution of PERMUTATION statistic:

Min	Max	Mean	Std- dev	Observed	Standardized
0.0000	1.100e+004	2534.	596.0	4089.	2.608

Asymptotic Inference:
One-sided p-value: Pr { Test Statistic .GE. Observed } = 0.0045
Two-sided p-value: 2 * One-sided = 0.0091

Exact Inference:
One-sided p-value: Pr { Test Statistic .GE. Observed } = 0.0062
Pr { Test Statistic .EQ. Observed } = 0.0002
Two-sided p-value: Pr { | Test Statistic - Mean |
.GE. | Observed - Mean | = 0.0063
Two-sided p-value: 2*One-Sided = 0.0124

Elapsed Time is 0:0:0.99

Female Mice
Hepatocellular adenoma and carcinoma combined
15/120, 10/60, 12/60, 18/60
Scores 0, 3, 35, 250
PERMUTATION TEST

[1 2 by 4 tables and sum of scores from row <row1 >]

Summary of Exact distribution of PERMUTATION statistic:

Min	Max	Mean	Std- dev	Observed	Standardized
0.0000	1.375e+004	3168.	651.9	4950.	2.734

Asymptotic Inference:
One-sided p-value: Pr { Test Statistic .GE. Observed } = 0.0031
Two-sided p-value: 2 * One-sided = 0.0063

Exact Inference:
One-sided p-value: Pr { Test Statistic .GE. Observed } = 0.0043
Pr { Test Statistic .EQ. Observed } = 0.0001
Two-sided p-value: Pr { | Test Statistic - Mean |
.GE. | Observed - Mean | = 0.0059
Two-sided p-value: 2*One-Sided = 0.0086

Elapsed Time is 0:0:1.37

Table 3

Results of Statistical Analysis of Total Incidences of
Interstitial Cell Tumor in Male Rats

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                                    Male rats
                                4/120, 3/60, 3/60, 12/60
                                Scores 0, 1.5, 7.5, 53
                                  PERMUTATION TEST

[ 1 2 by 4 tables and sum of scores from row <row1      > ]

Summary of Exact distribution of PERMUTATION statistic:

        Min          Max          Mean       Std- dev      Observed    Standardized
     0.0000         1166.         272.8         92.66         663.0           4.211

Asymptotic Inference:
    One-sided p-value: Pr  {   Test Statistic .GE.  Observed }  =       0.0000
    Two-sided p-value: 2 * One-sided                            =       0.0000

Exact Inference:
    One-sided p-value: Pr  {   Test Statistic .GE.  Observed }  =       0.0001
                       Pr  {   Test Statistic .EQ. Observed }   =       0.0000
    Two-sided p-value: Pr  { | Test Statistic - Mean |
                         .GE.  | Observed - Mean |             =       0.0001
    Two-sided p-value: 2*One-Sided                              =       0.0002

Elapsed Time is 0:0:0.28
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2.2 Statistical Analysis Incorporating Historical Control Data

The historical control data of hepatocellular adnoma, and hepatocellular adenoma and carcinoma combined in female mice from three [redacted] studies submitted by the sponsor are included in Table 4.

The sponsor's arguement that the findings in hepatocellular adenoma, and adenoma and carcinoma combined in female mice were false positive findings because the tumor rates in the treated groups are within the ranges of historical control data can not be justified. This is especially true for helpatocellular adenoma in $B6C3F_1$ mice. As the historical control data in Haseman et al. (1998) indicate, the ranges are huge (4% to 48% for male mice and 2% to 50% for female mice). More appropriate methods for incorporating historical control data in test for positive trend should be used.

The statistical procedure described in Tarone (1982) is used in the analysis of the total incidence rates of hepatocellular adenoma, hepatocellular adenoma and carcinoma combined in female mice with the use of the historical control data submitted by the sponsor.

For a given experiment, the number of animals that develop a tumor in the control group follows the following binomial distribution with parameter p.

$$f(x) = \binom{n}{x} p^x (1-p)^{n-x} \quad \text{for } x = 0, 1, \ldots, n.$$

p is the true spontaneous rate of the tumor. n is the total animals in the control group, and x is the number of animals in the control group developed the tumor.

It is proposed in the paper that the following beta distribution be used to model the distribution of the spontaneous tumor rate p of the control group that varies from experiment to experiment.

$$g(p) = \{\Gamma(\alpha+\beta)/\Gamma(\alpha)\Gamma(\beta)\}\ p^{\alpha-1}(1-p)^{\beta-1}, \qquad \text{for } 0 < p < 1.$$

The mean and variance of the beta distribution are

$$E(p) = \alpha/(\alpha+\beta) \quad \text{and}$$

$$V(p) = (\alpha\beta)/\{(\alpha+\beta)^2(\alpha+\beta+1)\}.$$

The unknown parameters α and β are estimated by the method of moments, i.e., by equating the population mean and variance with the sample mean and variance and solving the two equations to find the estimates of α and β.

The summary statistics of total tumor incidence rates of hepatocellular adenoma, and hepatocellular adenoma and carcinoma combined of the historical control data are included in Table 5 (adenoma data from 3 [redacted] studies), Table 6 (adenoma data from 3 [redacted] and 14 [redacted] studies), Table 7 (adenoma and carcinoma combined data from 3 [redacted] studies), and Table 8 (adenoma and carcinoma combined data from 3 [redacted] studies). The summary statistics are needed for estimating the unknown parameters α and β.

As mentioned above, the parameters α and β of the beta distribution are estimated by the method of moments. For example, the beta distribution for modeling the spontaneous rate of hepatocellular adenoma using the data from the three [redacted] studies is determined by solving the following system of two equations simultaneously using the observed mean and variance from the historical data in Table 5.

$$\alpha/(\alpha+\beta) = 0.06667$$

$$(\alpha\beta)/\{(\alpha+\beta)^2(\alpha+\beta+1)\} = 0.003333.$$

The solution to the system of equations is $\alpha = 1.192$ and $\beta = 16.68$.

Table 4

Historical Control Data of Hepatocellular Adenoma, and Hepatocellular Adenoma and Carcinoma Combined in Female Mice from 3 [redacted]' Studies

Historical Control Data Submitted by Sponsor

B6C3F$_1$ Female Mice

Study No.	Laboratory	Vehicle	Route of Administration	No. of Livers Examined	Hepatocellular Adenoma	Hepatocellular Adenoma %	Hepatocellular Carcinoma	Hepatocellular Carcinoma %	Hepatocellular Adenoma + Carcinoma	Hepatocellular Adenoma + Carcinoma %
1	[redacted]	Methyl cellulose	Dietary	60	6	0.1	1	0.016666667	7	0.116666667
2		Methyl cellulose	Dietary	50	5	0.1	1	0.02	6	0.12
3		Methyl cellulose	Dietary	27	0	0	0	0	0	0
4		Methyl cellulose	Gavage	50	20	0.4	12	0.24	27	0.54
5		methyl cellulose	Gavage	50	11	0.22	13	0.26	20	0.4
6		methyl cellulose	Gavage	50	19	0.38	14	0.28	24	0.48
7		Water	Gavage	51	15	0.294117647	8	0.156862745	22	0.431372549
8		Corn Oil	Gavage	50	11	0.22	2	0.04	13	0.26
9		Corn Oil	Gavage	51	10	0.196078431	3	0.058823529	13	0.254901961
10		Corn Oil	Gavage	50	8	0.16	0	0	8	0.16
11		Corn Oil	Gavage	50	6	0.12	1	0.02	7	0.14
12		Corn Oil	Gavage	50	3	0.06	1	0.02	4	0.08
13		Corn Oil	Gavage	60	17	0.283333333	6	0.1	22	0.366666667
14		Corn Oil	Gavage	50	13	0.26	7	0.14	17	0.34
15		Corn Oil	Gavage	50	8	0.16	4	0.08	11	0.22
16		Corn Oil	Gavage	50	12	0.24	2	0.04	14	0.28
17		Corn Oil	Gavage	50	20	0.4	11	0.22	29	0.58
Total				849	184	0.216725559	86	0.101295642	244	0.287396938

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Table 5

Hepatocellular Adenoma Data Summary

Mean	**0.066667**
Standard Error	0.033333
Median	0.1
Mode	0.1
Standard Deviation	0.057735
Sample Variance	**0.003333**
Kurtosis	#DIV/0!
Skewness	-1.73205
Range	
Minimum	
Maximum	
Sum	0.2
Count	3

Table 6

Hepatocellular Adenoma Summary Data

Mean	**0.211384**
Standard Error	0.028518
Median	0.22
Mode	0.1
Standard Deviation	0.117584
Sample Variance	**0.013826**
Kurtosis	-0.63999
Skewness	0.112251
Range	
Minimum	
Maximum	
Sum	3.593529
Count	17

Table 7

Hepatocellular Adenoma and Carcinoma Summary Data

Mean	**0.078889**
Standard Error	0.039456
Median	0.116667
Mode	#N/A
Standard Deviation	0.06834
Sample Variance	**0.00467**
Kurtosis	#DIV/0!
Skewness	-1.72742
Range	
Minimum	
Maximum	
Sum	0.236667
Count	3

Table 8

Hepatocellular Adenoma and Carcinoma Data Summary

Mean	**0.280565**
Standard Error	0.040915
Median	0.26
Mode	#N/A
Standard Deviation	0.168695
Sample Variance	**0.028458**
Kurtosis	-0.87323
Skewness	0.217637
Range	
Minimum	
Maximum	
Sum	4.769608
Count	17

The beta distributions for modeling the spontaneous rates of hepatocellular adenoma, hepatocellular adenoma and carcinoma combined using data of the three [redacted] studies, and of the three [redacted] studies are given in Table 9.

Table 9

Estimated Values of Beta distribution Parameters α and β

Tumor	Historical data used	Estimated α	Estimated β
Hepatocellular adenoma	3 [redacted] studies	1.192	16.680
	3 [redacted] studies	2.346	8.751
Hepatocellular adenoma + carcinoma	3 [redacted] studies	1.142	13.330
	3 [redacted] studies	1.708	4.378

The positive trend in tumor incidence with the incorporation of historical control data is tested by the following statistic

$$\chi^2 = (\sum x_i d_i - p^{\wedge} \sum n_i d_i)^2 / \{p^{\wedge} q^{\wedge} [\sum n_i d_i^2 - (\sum x_i d_i)^2 / n]\},$$

where $n = n_. + \alpha+\beta$, $p^{\wedge} = (x_. + \alpha) / n$, $q^{\wedge} = 1 - p^{\wedge}$, $n_. = \sum n_i$, and $x_. = \sum x_i$. The summation is from zero to r when there are r + 1 treatment groups in an experiment.

The test statistic χ^2 is distributed asymptotically as a chi square random variable with one degree of freedom.

Putting the tumor data from the current study in Table 1 and the estimated values of α and β (in Table 9) using the historical control data into the above equation, we get χ^2 statistics and asymptotic p-values given in Table 10.

Table 10

Calculated χ^2 Statistics and Asymptotic P-Values of the Tests for Positive Trend with Incorporation of Historical Control Data

Tumor	Historical data used	Calculated χ^2 statistic	Asymptotic p-values
Hepatocellular adenoma	3 [redacted] studies	7.5660	0.005948
	3 [redacted] studies	6.3138	0.009019
Hepatocellular adenoma + carcinoma	3 [redacted] studies	8.2585	0.004056
	3 [redacted] studies	7.1039	0.007692

The results of the asymptotic tests for positive trend incorporating the historical control data submitted by the sponsor show that positive trends in total incidence of hepatocellular adenoma alone, and hepatocellular adenoma and carcinoma combined are statistically significant in female mice using either the data of the three [redacted] studies only or the combined data of the three [redacted] studies.

No exact version of the above Tarone test for trend in tumor incidence is available. There are no exact p-values for comparison with the above asymptotic p-values. It is expected that if there are exact test methods available, the exact p-values may be a little bit larger.

3. References

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