# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-518**

# STATISTICAL REVIEW(S)

# Statistical Review and Evaluation

(Carcinogenicity Studies)

**NDA No.:** 21-518

**Applicant:** Yamanouchi Phaarmaceutical Co., Ltd.

**Name of Drug:** YM905

**Documents Reviewed:** (1) Draft Statistical Review and Evaluation report prepared by Moh-Jee Ng of Division of Biometrics II in 2003 ( included in Appendix A)

(2) 104-Week Carcinogenicity Gavage Study with YM905 in Rats, Supplement Volume to the Final Report, Yamanouchi Phaarmaceutical Co., Ltd., September 26, 2003

(3) YM905 Additional Histopathology Investigation to a Carcinogenicity Study by Oral Gavage Administration to CD-1 Mice for 104 weeks, Final Report, Volume 1, Yamanouchi Phaarmaceutical Co., Ltd., August 11, 2003

**Reviewing Pharmacologist:** Lynnda L. Reid, Ph.D., HFD-580

**Statistical Reviewer:** Karl K. Lin, Ph.D., and Moh-Jee Ng, HFD-715

## Summary of Review

The statistical procedures used by the sponsor's two contract laboratories in the analysis of the amended data of the mouse and the rat studies are consistent with the procedures recommended in the Center's guidance for industry document, and therefore, are deemed as appropriate and acceptable by this reviewer.

This reviewer agrees with the sponsor's overall analysis result that there is no statistically significant positive trend in incidence rate detected in the tumors tested in both males and females in either the mouse or the rat study.

## 1. Introduction

There are two carcinogenicity studies, one in mice and one in rats, included in this NDA submission. The designs of the mouse and the rat studies are summarized in Table 1 in

Moh-Jee Ng's 2003 draft statistical review and evaluation report of two studies included in Appendix A.. The original reports and the electronic data of the mouse and the rat studies were reviewed by Moh-Jee Ng in 2003. Results of her review show that there was no statistically significant positive trend in incidence rate detected in all the tumors tested in both males and females in either the mouse or the rat study.

The above draft review report was based on the sponsor's original reports and electronic tumor data that did not include the histopathological information of the animals in the low and medium groups that survived to the end of the studies (1004 weeks). The results of the original review were evaluated by the CDER Executive CAC. It was determined by the committee that, due to significantly higher death and weight loss in the high-dose groups, all animals in the low and medium dose-groups to be histopathlogically evaluated.

The drug sponsor completed the histopathological evaluation of the animals in the two groups that were not microscopically examined previously and submitted the analysis results to the Agency. Dr. Lynnda Reid, Supervisory Pharmacologist of HFD-580, has requested the Division of Biometrics II to perform another statistical review and evaluation on the sponsor's amended reports that included the histopathological information of the animals that were not previously microscopically examined. This statistical review concentrates on the evaluation of the appropriateness of the statistical methods the sponsor used in its analyses of the amended tumor data.

## 2. Evaluation of the Sponsor's Methods of Data Analysis and Results of the Mouse Study

### 2.1. Sponsor's Analysis and Results

Pages 155-222 of the sponsor's 467-page report titled "YM905, Additional Histopathology Investigations to A Carcinogenicity Study by Oral Gavage Administration to CD-1 Mice for 104 Weeks, Final Report, Volume 1" contains the statistical report of the mouse study. The tumor incidence rates of the mouse study in the original and the amended reports complied by Dr. Lynnda Reid are included in Appendix B. The sponsor's statistical analysis of the amended tumor data was performed by a statistician at —

For non-palpable tumors, each tumor was categorized by the sponsor as non-incidental (fatal) if the tumor was a factor contributing towards the death of the animal, incidental otherwise. For statistical purposes, all animals which died after terminal sacrifice commenced (Week 105) were considered terminal and the tumors observed in these animals were categorized as incidental.

For palpable tumors, each observed tumor was classified by the sponsor as non-incidental (fatal) if it was palpable before death and before the terminal sacrifice commenced, or, if it was a factor contributing towards the death of the animal. The tumor was classified as incidental, if the tumor was first found after death and was not a factor contributing

towards the death of the animal, or, if it was first found in or after the first week of the terminal sacrifice.

Tumor types were selected by the sponsor for full statistical analysis where at least two tumors were observed across the treated groups in which all animals were examined. Statistical analysis was therefore performed by the sponsor upon individual tumor types, for males and females separately.

The life-table method, the prevalence method, and the on-set rate method recommended in the 1980 IARC monograph were used for testing positive trend in incidence in fatal, incidental, and mortality-independent tumors, respectively. For tumor types with 10 or less tumor bearing animals, the exact permutation trend test was performed. The 0.05 significance level was used to determine if a trend test is statistically significant or not.

The results of the sponsor's analysis were presented in Tables 1-26 for male mice and Tables 27-56 for female mice on pages 159-221 of the final report mentioned above. The sponsor's results show that there is not statistically significant positive trend in incidence detected for the tumors tests in both males and females.

**2.2. Reviewer's Comments on the Sponsor's Analysis and Results**

The sponsor's methods of analysis of tumor data are consistent with those recommended in the Center's draft guidance for industry document titled "Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals", May 2001. Therefore, the methods used by the sponsor are appropriate.

The sponsor's conclusion of no statistically significant finding was based on the significance level of 0.05. The Center guidance document recommends the use of levels of significance of 0.025 and 0.005 for tests for trend for rare and common tumors, respectively. The sponsor's use of 0.05 level of significance for tests for trend for all tumors will result in a much larger overall false positive than around 10% if the Center's decision rule is used. Because the larger level of significance was used, the sponsor's finding of no statistically significant trend provides a stronger evidence of no carcinogenic effect of the drug in tested mice than the same finding but using the Center's decision rule.

Moh-Jee Ng's earlier statistical analysis of mortality data of the mouse study show that the survival functions are very statistically significant among the treatment groups in both male and female mice. The analysis of mortality data included all the animals in all the treatment groups. The mortality of the high dose group is much higher than the other groups in both male and female mice. However, the effect of the mortality differences among treatment groups on tumor incidence rates had been taken into consideration by the sponsor's analysis by using survival-adjusted trend tests.

Also Moh-Jee Ng's earlier statistical analysis of body weight data, which also included all animals of all treatment groups, show that the body weight decrements for the 100 mg and 200 mg male groups, and the 200 mg female group are much higher than 10%. The body weight decrements are 25%, 16.7%, and 25% for the above three groups, respectively. The large body weight decrements on those groups may indicate that these two doses are over MTD.

## 3. Evaluation of the Sponsor's Methods of Data Analysis and Results of the Rat Study

### 3.1. Sponsor's Analysis and Results

Pages 14-40 of the sponsor's 509-page report title "Supplement Volume to the Final Report (on the study in rats) contains the statistical report of the rat study. The tumor incidence rates of the rat study in the original and the amended reports complied by Dr. Lynnda Reid are included in Appendix C. The sponsor's statistical analysis of the amended tumor data was performed by a statistician at —

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The sponsor's evaluations of trend and heterogeneity of survival data were performed by life table techniques consisting of Kaplan- Merier product limit estimates and Cox-Tarone binary regression as well as Gehan- Breslow nonparametric score tests. Continuity- corrected one- sided tail probabilities for trend and group comparisons were evaluated at the 5.0% significance level.

Neoplastic lesions were chosen by the sponsor for statistical analyses if the number of lesions in at least one treated group ( Group 2 through 4) differed by at least two over that of the control group. The occult incidental tumors were analyzed by the logistic prevalence test with adjustment for survival. The lethal tumor analysis in the cause of death context ( Peto et al., 1980) involved the Cox- Tarone binary regression as described under survival. For the incidental tumors, if the total incidences in a table was less than 5, exact permutation test was performed. In the cases where the study pathologist assigned a subset of a particular tumor as being the cause of death of those animals ( fatal tumors) and the remaining as being found an incidental context, IARC type cause of death analysis ( Peto et al, 1980) was performed involving all of them. All asymptotic tests used involved a continuity correction for computing the tail probabilities.

The incidental and fatal tumors were evaluated individually as well as combined, where appropriate. One-sided trends in common and rare tumors ( as defined: rare tumor type incidence < 1%, otherwise common tumor type, based on concurrent and/ or historical controls) were evaluated at 0.005 and 0.025 significance levels, respectively. One-sided group comparisons for the high dose group over the control group were evaluated at the 1% significance level for common tumor and 5% significance level for rare tumor ( FDA Draft Guidance for Industry, 2001). All other group comparisons were evaluated at 5.0% significance level.

The sponsor's analysis results were presented on pages 20-40 of the final report of the rat study mentioned above. No significant trend or pairwise group comparisons over the control group were noted in mortality for the males in the sponsor's analysis. For females, a significant positive trend and associated significant increases in mid and high doses were observed in the mortality data.

In the tumor data analysis, the sponsor concluded that there was no statistically significant positive trend or pairwise group differences in incidence rate between treated group versus control group in the tumors tested in males and females.

### 3.2. Reviewer's Comments on the Sponsor's Analysis and Results

The sponsor followed almost exactly the methods of analysis and decision rules recommended in the Center's 2001 guidance for industry document in its statistical analysis of the mortality and tumor data of the rat study with one exception. Therefore, the methods of analysis used by the sponsor in the rat study are appropriate. The only exception is the sponsor's use of the logistic regression method in the test for trend in incidence rate for incidental tumors.

The logistic regression method that has been used by National Toxicology Program (NTP) is an alternative method to the prevalence method recommended in the CDER guidance for industry document and 1980 IARC monograph for testing for positive trend in incidence rate of incidental tumors. The logistic regression method includes survival time in addition to dose as independent variables to adjust for the effect of different mortalities among treatment groups on tumor rate. There have been investigations comparing the two types of tests for trend in incidence in incidental tumors. Reports of the investigations show that in the majority of cases and conditions, the two test methods yield consistent results. Therefore, the results of analysis of data of incidental tumors using the logistic regression procedure should be similar to those using the prevalence method, and should be acceptable.

Like in the evaluation of validity of design in the mouse study, it was found in Moh-Jee Ng's earlier review that the high dose groups of males and females in the rat study have higher than 10% body weight decrements. The large decreases in body weight in the two high dose groups may indicate that the doses 20 mg and 15 mg are over MTD.

## 4. Concluding Remarks

The statistical procedures used by the sponsor's two contract laboratories in the analysis of the amended data of the mouse and the rat studies are consistent with the procedures recommended in the Center's guidance for industry document, and therefore, are deemed as appropriate and acceptable by this reviewer.

This reviewer agrees with the sponsor's overall analysis result that there is no statistically significant positive trend in incidence rate detected in the tumors tested in both males and females in either the mouse or the rat study.

## Appendix A

Draft Statistical Review and Evaluation Report Prepared by Moh-Jee Ng of Division of Biometrics II in 2003

This draft statistical review and evaluation report was prepared based on the sponsor's earlier reports of the mouse and rat studies and the submitted tumor data sets. Both the reports and data sets did not include histopathological data of animals in the low and medium groups that survived to the end of the studies (104 weeks).

The 2003 draft report is included in the following 16 pages.

16 Page(s) Withheld

## Appendix B

### Original and Amended Tumor Incidence Rates of the Mouse Study Complied by Dr. Lynnda Reid

**NDA 21-518: Histopathology - group distribution of neoplastic findings for all mice in 2-year carcinogenicity study.**

Background: At the request of the ExecCAC, all tissues from low- and mid-dose animals were read by the same pathologist who read the original study slides. The Sponsor indicated that over 80% of the tissues were looked at in the original study report. The following is a comparison of the original report with those submitted after reading all slides for all groups. Any values that have changed have been highlighted.

Summary of neoplastic findings for all male animals distributed by organ system. In the original report, only animals with gross lesions were examined from the low- and mid-dose groups. In the requested amended report, all animals were examined (70 micc/group).

| Males | Original Report (80%) | | | | | Amended Report (100%) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 10 | 30 | 100 | 200 | 0 | 10 | 30 | 100 | 200 |
| Adrenals: | | | | | | | | | | |
| Cortical Adenoma | 7 | 6 | 3 | 8 | 2 | 7 | **13** | **4** | 8 | 2 |
| Phaeochromocytoma | - | - | - | 1 | 1 | - | - | - | 1 | 1 |
| Malignant Phaeochromocytoma | 0 | 1 | - | - | - | 0 | 1 | - | - | - |
| Bone: | | | | | | | | | | |
| Osteoma | - | 1 | - | 1 | - | - | 1 | - | 1 | - |
| Brain: | | | | | | | | | | |
| Meningioma (maningeal sarcoma) | - | - | - | - | - | 1 | - | - | - | - |
| Harderian Glands: | | | | | | | | | | |
| Adenoma | 7 | 5 | 7 | 2 | 2 | 7 | **8** | 7 | 2 | 2 |
| Adenocarcinoma | 3 | 3 | 4 | - | - | 3 | 3 | 4 | - | - |
| Hemopoietic: | | | | | | | | | | |
| Malignant Lymphoma | 13 | 12 | 7 | 9 | 5 | 13 | 12 | 7 | 9 | 5 |
| Histoicytic sarcoma | 2 | 6 | 5 | - | 3 | 2 | 6 | 5 | - | 3 |
| Myeloind Leukemia | 1 | - | - | 2 | - | 1 | - | - | 2 | - |
| GI Tract: | | | | | | | | | | |
| Cecum - Adenocarcinoma | 1 | - | - | - | - | 1 | - | - | - | - |
| Colon - Adenoma | - | - | 1 | 1 | - | - | - | 1 | 1 | - |
| Adenocarcinoma | - | - | - | 1 | 1 | - | - | - | 1 | 1 |
| Duodenum - Adenoma | - | - | 1 | - | - | - | - | 1 | - | - |
| Stomach - Squamous cell papilloma | - | 1 | - | - | - | - | 1 | - | - | - |
| Adenoma | - | - | 1 | - | - | - | - | 1 | - | - |
| Tongue - Adenoma | 1 | - | - | - | - | 1 | - | - | - | - |
| Kidneys: | | | | | | | | | | |
| Adenoma | 1 | - | - | 1 | - | 1 | - | - | 1 | - |
| Liver: | | | | | | | | | | |
| Hepatocellular adenoma | 6 | 9 | 10 | 4 | 7 | 6 | **12** | 10 | 4 | 7 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Hepatocellular carcinoma | 4 | 7 | 4 | 1 | 1 | 4 | 7 | 4 | 1 | 1 |
| Hemangioma | 1 | - | - | - | - | 1 | - | - | - | - |
| Hemangiosarcoma | 1 | 4 | 2 | - | - | 1 | 4 | 2 | - | - |
| Cholangioma (M) / Ito cell tumor (F) | - | 1 | - | - | - | - | 1 | - | - | - |
| Lungs: | | | | | | | | | | |
| Bronchioloalveolar Adenoma | 22 | 16 | 17 | 20 | 11 | 22 | 18 | 17 | 20 | 11 |
| Bronchioloalveolar Adneocarcinoma | 6 | 5 | 8 | 2 | 1 | 6 | 5 | 8 | 2 | 1 |
| Pancreas: | | | | | | | | | | |
| Islet cell adenoma | 1 | 1 | - | 2 | - | 1 | 1 | - | 2 | - |
| Pituitary: | | | | | | | | | | |
| Adenoma - Pars Distalis | - | - | - | 1 | - | - | - | 1 | 1 | - |
| Adenoma - Pars Intermedia | - | - | - | - | - | - | - | - | 1 | - |
| Salivary Gland: | | | | | | | | | | |
| Squamous cell carcinoma | - | - | - | 1 | - | - | - | - | 1 | - |
| Testes: | | | | | | | | | | |
| Interstitial (Leydig) cell adenoma | 5 | 1 | 4 | 3 | - | 5 | 1 | 4 | 3 | - |
| Adenoma | - | - | - | - | 1 | - | - | - | - | 1 |
| Thymus: | | | | | | | | | | |
| Thyoma (Lymphoid) | - | 1 | 1 | - | - | - | 1 | 1 | - | - |
| Thyroids: | | | | | | | | | | |
| Follicular cell adenoma | 1 | - | - | 1 | - | 1 | - | 1 | 1 | - |
| C-cell adenoma | - | - | - | - | - | - | 1 | - | - | - |
| Hemangiomas: | | | | | | | | | | |
| Mesenteric lymph node | 1 | - | - | - | - | 1 | - | - | - | - |
| Prostate | - | 1 | - | - | - | - | 1 | - | - | - |
| Spleen | 2 | - | - | 1 | - | 2 | 1 | - | 1 | - |

Summary of neoplastic findings for all female animals distributed by organ system. In the original report, only animals with gross lesions were examined from the low- and mid-dose groups. In the requested amended report, all animals were examined (70 mice/group).

| **Females** | **Original Report (80%)** | | | | | **Amended Report (100%)** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **0** | **10** | **30** | **100** | **200** | **0** | **10** | **30** | **100** | **200** |
| Adrenals: | | | | | | | | | | |
| Phaeochromocytoma | 1 | - | - | - | 1 | 1 | - | - | - | 1 |
| Bone: | | | | | | | | | | |
| Osteoma | - | 1 | 1 | - | - | - | 1 | 1 | - | - |
| Osteosarcoma | - | 1 | - | - | - | - | 1 | - | - | - |
| Chondroma | - | 1 | - | - | 1 | - | 1 | - | - | 1 |
| Brain: | | | | | | | | | | |
| Meningioma | - | 1 | - | - | - | - | 1 | - | - | - |
| Harderian Glands: | | | | | | | | | | |
| Adenoma | 7 | 2 | - | 1 | 2 | 7 | 3 | 3 | 2 | 1 |
| Adenocarcinoma | - | 2 | - | 1 | 2 | - | 2 | - | 1 | 2 |
| Hemopoietic: | | | | | | | | | | |
| Malignant Lymphoma | 13 | 12 | 13 | 6 | 9 | 13 | 12 | 14 | 6 | 9 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Histoicytic sarcoma | 3 | 4 | 6 | 3 | 4 | 3 | 4 | 6 | 3 | 4 |
| GI Tract: | | | | | | | | | | |
| Colon - Adenocarcinoma | - | - | 1 | - | - | - | - | 1 | - | - |
| Jejunum - Adenocarcinoma | - | - | - | - | 1 | - | - | - | - | 1 |
| Stomach - Adenoma | - | 1 | - | - | - | - | 1 | - | - | - |
| Rectum - Squamous cell papilloma | - | 1 | - | - | - | - | 1 | - | - | - |
| Liver: | | | | | | | | | | |
| Hepatocellular adenoma | 2 | 3 | 2 | - | - | 2 | 3 | 2 | - | - |
| Hemangiosarcoma | - | - | 2 | - | - | - | - | 2 | - | - |
| Cholangioma (M) / Ito cell tumor (F) | - | - | 1 | - | - | - | - | 1 | - | - |
| Lungs: | | | | | | | | | | |
| Bronchioloalveolar Adenoma | 15 | 15 | 11 | 7 | 5 | 15 | 15 | 12 | 7 | 5 |
| Bronchioloalveolar Adneocarcinoma | 4 | 4 | - | - | 1 | 4 | 4 | - | - | 1 |
| Mammary: | | | | | | | | | | |
| Adenocarcinoma | 1 | 1 | 2 | 1 | - | 1 | 1 | 2 | 1 | - |
| Ovaries: | | | | | | | | | | |
| Schwannoma | - | 1 | - | - | - | - | 1 | - | - | - |
| Granulosa Cell Tumor | 1 | 2 | 1 | 1 | 0 | 1 | 2 | 1 | 1 | 0 |
| Luteoma | 1 | 3 | 3 | 3 | 1 | 1 | 3 | 3 | 3 | 1 |
| Cystadenoma | - | - | 1 | - | - | - | - | 1 | - | - |
| Leiomyoma | - | - | - | - | 1 | - | - | - | - | 1 |
| Sertoli cell adenoma | 1 | - | - | - | - | 1 | - | - | - | - |
| Tubulostromal adenoma | - | - | 1 | 1 | 0 | - | - | 1 | 1 | 0 |
| Undifferentiated stromal tumor | - | - | 0 | 1 | 0 | - | - | 0 | 1 | 0 |
| Pancreas: | | | | | | | | | | |
| Islet cell adenoma | - | 1 | - | - | - | - | 1 | - | - | - |
| Pituitary: | | | | | | | | | | |
| Adenoma | 3 | 3 | - | - | - | 3 | 3 | - | - | - |
| Spleen: | | | | | | | | | | |
| Hemangioma | - | 1 | - | - | - | - | 1 | - | - | - |
| Hemangiosarcoma | 1 | - | - | - | - | 1 | - | - | - | - |
| Thymus: | | | | | | | | | | |
| Thyoma (Lymphoid) | 6 | 4 | 9 | 4 | 2 | 6 | 4 | 9 | 4 | 2 |
| Thyoma (Epithelial) | - | - | 1 | - | - | - | - | 1 | - | - |
| Uterine / Cervix: | | | | | | | | | | |
| Endometrial Polyp | 1 | 1 | - | 1 | - | 1 | 1 | - | 1 | - |
| Leiomyma | 1 | - | - | 2 | 1 | 1 | - | - | 2 | - |
| Leiomyosarcoma | 1 | 1 | 1 | - | 1 | 1 | 1 | 1 | - | 1 |
| Malignant schwannoma | - | - | - | 1 | - | - | - | - | 1 | - |
| Uterus: | | | | | | | | | | |
| Endometrial Polyp | 4 | 9 | 6 | 3 | 2 | 4 | 9 | 6 | 3 | 2 |
| Leiomyma | 3 | 1 | - | - | - | 3 | 1 | - | - | - |
| Leiomyosarcoma | - | - | - | 1 | - | - | - | - | 1 | - |
| Endometrial adenoma | - | 2 | - | - | - | - | 2 | - | - | - |
| Endometrial stromal cell sarcoma | - | - | 2 | - | 2 | - | - | 2 | - | 2 |
| Histiocytic sarcoma | - | 1 | 1 | - | - | - | 1 | 1 | - | - |
| Vagina: | | | | | | | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Histiocytic sarcoma | 2 | - | - | - | - | 2 | - | - | - | - |
| Fibroma | 1 | - | - | - | - | 1 | - | - | - | - |
| Hemangiomas: | | | | | | | | | | |
| Uterus | 1 | 1 | 2 | - | 1 | 1 | 1 | 2 | - | 1 |
| Hemangiosarcoma: | | | | | | | | | | |
| Uterus | - | 2 | - | - | - | - | 2 | - | - | - |

The final percentage rates for adrenal adenomas are 10, 18.6, 5.7, 11.4 and 2.9% for the 0, 10, 30, 100 and 200 mg/kg groups, respectively. These rates are higher than previously reported by Charles River, even for the control group. However, there is no consistent dose-response pattern and is not statistically significant (Sponsor analyses).

Charles River Historical Data in CD-1 Male Mice (March 2000)

| Location & Tumor | # Studies (# Organs) | # Lesions | Percent | Minimum % | Maximum % |
|---|---|---|---|---|---|
| Adrenals: | 46 (2526) | | | | |
| Cortical Adenoma | | 30 | 1.19 | 1.56 | 7.14 |
| Phaeochromocytoma | | 11 | 0.44 | 1.11 | 5.00 |
| Malignant Phaeochromocytoma | | - | - | - | - |
| Harderian Glands: | 46 (2565) | | | | |
| Adenoma | | 120 | 4.73 | 1.67 | 14.00 |
| Adenocarcinoma | | 11 | 0.43 | 1.43 | 8.33 |
| Liver: | 46 (2571) | | | | |
| Hepatocellular adenoma | | 269 | 10.46 | 2.86 | 28.00 |
| Hepatocellular carcinoma | | 136 | 5.29 | 1.54 | 16.00 |
| Hemangioma | | 9 | 0.35 | 1.54 | 4.00 |
| Hemangiosarcoma | | 29 | 1.13 | 1.11 | 5.00 |
| Lungs: | 46 (2575) | | | | |
| Bronchioloalveolar Adenoma | | 368 | 14.29 | 2.00 | 42.00 |
| Bronchioloalveolar adneocarcinoma | | 177 | 6.87 | 1.43 | 26.00 |

— Historical Data in CD-1 Female Mice (March 2000)

| Location & Tumor | # Studies (# Organs) | # Lesions | Percent | Minimum % | Maximum % |
|---|---|---|---|---|---|
| Hemopoietic: | 48 (2822) | | | | |
| Malignant Lymphoma | | 274 | 9.71 | 1.67 | 50.00 |
| Histoicytic sarcoma | | 111 | 3.93 | 1.67 | 18.33 |
| Lungs: | 48 (2773) | | | | |
| Bronchioloalveolar Adenoma | | 236 | 8.51 | 1.67 | 26.67 |
| Bronchioloalveolar adneocarcinoma | | 113 | 4.08 | 0.77 | 18.37 |
| Uterus: | 48 (2812) | | | | |
| Endometrial Polyp | | 146 | 5.19 | 1.67 | 17.14 |
| Leiomyma | | 40 | 1.42 | 1.43 | 7.50 |
| Leiomyosarcoma | | 36 | 1.28 | 0.86 | 6.00 |
| Endometrial adenoma | | 3 | 0.11 | 1.54 | 2.00 |

| | | | | | |
|---|---|---|---|---|---|
| Endometrial stromal cell sarcoma | | 33 | 1.17 | 1.43 | 8.00 |
| Hemangioma | | 15 | 0.53 | 1.25 | 4.62 |
| Hemangiosarcoma | | 14 | 0.50 | 0.77 | 4.08 |



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## Appendix C

### Original and Amended Tumor Incidence Rates of the Rat Study Complied by Dr. Lynnda Reid

**NDA 21-518: Histopathology - group distribution of neoplastic findings for all rats in 2-year carcinogenicity study** (R905-TX-024)

Background: At the request of the ExecCAC, all tissues from low- and mid-dose animals were read by the same pathologist who read the original study slides. The Sponsor indicated that over 60% of the tissues were looked at in the original study report. The following is a comparison of the original report with those submitted after reading all slides for all groups. Any values that have changed have been highlighted.

In the original report, there were no increases in tumor incidence or onset in drug-treated animals when compared to concurrent controls. The most common neoplastic findings were pituitary adenomas in both sexes, benign interstitial cell tumor of the testes in all males and large granular lymphocytic leukemia primarily in males but also in females across groups. There was also a high incidence of islet cell carcinoma in the pancreas of controls males, but not in any of the treatment groups.

| **Males Rats** (n=60/group) | Original Report (60%) | | | | Amended Report (100%) | | | |
|---|---|---|---|---|---|---|---|---|
| | **0** | **30** | **10** | **20** | **0** | **30** | **10** | **20** |
| **Adrenal Cortex:** | | | | | | | | |
| Adenoma | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Osteosarcoma | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |
| **Mesothelioma** | 0 | 0 | 0 | 0 | 0 | 0 | **1** | 0 |
| Adrenal Medulla: | | | | | | | | |
| Pheochromocytoma | 5 | 0 | 0 | 0 | 5 | 0 | 0 | 0 |
| Complex Pheochromocytoma | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Malignant Pheochromocytoma | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |
| **Bone (sternum):** | | | | | | | | |
| **Osteosarcoma** | 1 | 0 | 0 | 0 | **0** | 0 | 0 | **1** |
| Brain/spinal cord: | | | | | | | | |
| Multicentric glial neoplasm | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| **Epididymis:** | | | | | | | | |
| **Mesothelioma** | 3 | 0 | 0 | 1 | 3 | 0 | **2** | 1 |
| Harderian Glands: | | | | | | | | |
| Squamous cell carcinoma | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Heart: | | | | | | | | |
| Mesothelioma | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| **Hemopoietic:** | | | | | | | | |
| Malignant Lymphoma | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| **Myeloid Leukemia** | 21 | 21 | 21 | 16 | 21 | **25** | **23** | 16 |
| GI Tract: | | | | | | | | |
| Cecum - Mesothelioma | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Colon - Mesothelioma | | | | | 0 | 0 | 1 | 0 |
| **Duodenum - Mesothelioma** | 0 | 0 | 0 | 0 | 0 | 0 | **1** | 0 |
| - Leiomyosarcoma | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Stomach - Adenomatous polyp | | | | | 0 | 0 | 1 | 0 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Kidneys:** | | | | | | | | |
| **Mesothelioma** | 1 | 0 | 0 | 0 | 1 | 0 | **1** | 0 |
| **Papilloma - transitional cell** | 0 | 0 | 0 | 0 | 0 | **1** | 0 | 0 |
| **Liver:** | | | | | | | | |
| **Hepatocellular adenoma** | 4 | 1 | 2 | 5 | 4 | **4** | **3** | 5 |
| Mesothelioma | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| Lungs: | | | | | | | | |
| Mesothelioma | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| Osteosarcoma (metastatic) | 1 | 0 | 0 | 1 | - | - | - | - |
| Mammary Gland: | | | | | | | | |
| Fibroadenoma | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |
| **Pancreas:** | | | | | | | | |
| **Mesothelioma** | 0 | 0 | 0 | 0 | 0 | 0 | **1** | 0 |
| **Adenoma - Islet cell** | 3 | 1 | 0 | 1 | 3 | 1 | **1** | 1 |
| Carcinoma - Islet cell | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| **Pituitary:** | | | | | | | | |
| **Adenoma** | 24 | 22 | 15 | 14 | 24 | **28** | **20** | 14 |
| **Craniopharyngioma** | 0 | 0 | 0 | 0 | 0 | **1** | 0 | 0 |
| **Prostate:** | | | | | | | | |
| **Mesothelioma** | 1 | 0 | 0 | 0 | 1 | 0 | **1** | 0 |
| Salivary Gland: | | | | | | | | |
| Sarcoma | 0 | 0 | 2 | 1 | 0 | 0 | 2 | 1 |
| Seminal Vesicle: | | | | | | | | |
| Mesothelioma | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Skeletal Muscle: | | | | | | | | |
| Carcinoma - basal cell | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| **Skin:** | | | | | | | | |
| **Squamous cell papilloma** | 0 | 2 | 0 | 1 | 0 | **3** | **1** | 1 |
| Basal cell adenoma | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| **Keratoacanthoma** | 3 | 0 | 1 | 3 | 3 | 0 | **2** | 3 |
| Trichoepithelioma | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Preputial gland adenoma | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Basal cell carcinoma | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Squamous cell carcinoma | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Firbrosarcoma | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Subcutaneous Tissue: | | | | | | | | |
| Fibroma | 4 | 1 | 0 | 0 | 4 | 1 | 0 | 0 |
| Leiomyoma. | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Fibrosarcoma | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Myxosarcoma | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |
| Osteosarcoma | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Sarcoma | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Sarcoma (associated w/implant) | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| **Testes:** | | | | | | | | |
| **Interstitial (Leydig) cell adenoma** | 49 | 39 | 40 | 43 | 49 | **41** | **45** | 43 |
| **Mesothelioma** | 4 | 0 | 0 | 1 | 4 | 0 | **1** | 1 |
| **Thyroids:** | | | | | | | | |
| Follicular cell adenoma | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| **Follicular cell carcinoma** | 1 | 0 | 1 | 0 | 1 | **1** | 1 | 0 |
| **C-cell adenoma** | 1 | 1 | 1 | 1 | 1 | 1 | **3** | 1 |
| **C-cell carcinoma** | 2 | 1 | 0 | 3 | 2 | **3** | **3** | 3 |
| **Urinary bladder:** | | | | | | | | |
| **Mesothelioma** | 2 | 0 | 0 | 0 | 2 | 0 | **1** | 0 |
| Carcinoma - transitional cell | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| **Zymbal's gland:** | | | | | | | | |
| **Adenoma** | 0 | 0 | 0 | 0 | 0 | 0 | **1** | 0 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Carcinoma | 0 | 2 | 0 | 0 | 0 | 2 | 0 | 0 |
| Hemangiosarcomas: | | | | | | | | |
| Mesenteric lymph node | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |

| **Females Rats** (n=60/group) | Original Report (60%) | | | | Amended Report (100%) | | | |
|---|---|---|---|---|---|---|---|---|
| | **0** | **30** | **10** | **20** | **0** | **30** | **10** | **20** |
| **Adrenal Cortex:** | | | | | | | | |
| **Adenoma** | 1 | 0 | 0 | 1 | 1 | 0 | **1** | 1 |
| **Adrenal Medulla:** | | | | | | | | |
| **Pheochromocytoma** | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| Malignant Pheochromocytoma | 2 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| Brain/spinal cord: | | | | | | | | |
| Mixed glioma | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| **Cervix:** | | | | | | | | |
| **Endometrial stromal polyp** | 0 | 0 | 1 | 1 | 0 | **2** | **3** | 1 |
| Carcinoma | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| **Leiomyosarcoma** | 1 | 0 | 0 | 0 | 1 | 0 | **1** | 0 |
| **Endometrial stromal sarcoma** | 0 | 0 | 1 | 0 | 0 | 0 | **0** | 0 |
| **Heart:** | | | | | | | | |
| **Endocardial Schwannoma** | 0 | 0 | 0 | 0 | 0 | **1** | **1** | 0 |
| **Hemopoietic:** | | | | | | | | |
| **Myeloid Leukemia** | 9 | 13 | 8 | 8 | 9 | **12** | **11** | 8 |
| **Kidneys:** | | | | | | | | |
| Papilloma - transitional cell | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Carcinoma - transitional cell | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |
| **Nephroblastoma** | 0 | 0 | 0 | 0 | 0 | 0 | **1** | 0 |
| **Liver:** | | | | | | | | |
| **Hepatocellular adenoma** | 0 | 0 | 0 | 0 | 0 | **1** | 0 | 0 |
| Mammary Gland: | | | | | | | | |
| Fibroadenoma | 2 | 4 | 3 | 1 | 2 | 4 | 3 | 1 |
| Ovary: | | | | | | | | |
| Carcinoma -invasive transitional cell | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| **Pancreas:** | | | | | | | | |
| **Adenoma - Islet cell** | 1 | 1 | 0 | 0 | 1 | **1** | 0 | 0 |
| **Pituitary:** | | | | | | | | |
| **Adenoma** | 22 | 16 | 18 | 17 | 22 | **19** | **23** | 17 |
| Carcinoma | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Skin: | | | | | | | | |
| Squamous cell papilloma | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 |
| basal cell adenoma | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Subcutaneous Tissue: | | | | | | | | |
| Fibroma | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| **Thyroids:** | | | | | | | | |
| **Follicular cell adenoma** | 0 | 0 | 0 | 0 | 0 | 0 | **1** | 0 |
| Follicular cell carcinoma | 2 | 0 | 0 | 1 | 2 | 0 | 0 | 1 |
| **C-cell adenoma** | 2 | 0 | 0 | 2 | 2 | 0 | **2** | 2 |
| **C-cell carcinoma** | 3 | 0 | 0 | 0 | 3 | **2** | **1** | 0 |
| **Urinary bladder:** | | | | | | | | |
| **Papilloma - transitional cell** | 0 | 0 | 0 | 0 | 0 | **1** | 0 | 0 |
| **Uterus:** | | | | | | | | |
| **Endometrial stromal polyp** | 8 | 5 | 7 | 4 | 8 | 7 | 6 | 4 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Endometrial stromal sarcoma** | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 1 |
| Zymbal's gland: | | | | | | | | |
| Adenoma | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |

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APPEARS THIS WAY
ON ORIGINAL

— Historical Data in male CDF® (F-344)/ – BR rats

| Location & Tumor | # Studies (# Organs) | # Lesions | Percent | Minimum % | Maximum % |
|---|---|---|---|---|---|
| Adrenals: | | | | | |
| Cortical Adenoma | 4 (228) | 1 | 0.4% | 0.0% | 1.7% |
| Phaeochromocytoma | 4 (228) | 18 | 7.9% | 4.0% | 11.7% |
| Malignant Phaeochromocytoma | 4 (228) | 2 | 0.9% | 0.0% | 2.0% |
| Bone (Femur): | | | | | |
| Osteosarcoma | 4 (228) | 1 | 0.4% | 0.0% | 1.7% |
| Brain/Spinal Cord | | | | | |
| Mixed glioma | 4 (228) | 0 | 0.0% | | |
| Harderian Glands: | | | | | |
| Squamous cell carcinoma | | | | | |
| Hemopoietic: | | | | | |
| Myeloid Leukemia | 4 (228) | 69 | 30.3% | 10.0% | 50.0% |
| Kidneys: | | | | | |
| Papilloma - transitional cell | 1 (60) | 0 | 0.0% | | |
| Liver: | | | | | |
| Hepatocellular adenoma | 4 (228) | 9 | 3.9% | 0.0% | 6.7% |
| Lungs: | | | | | |
| Mesothelioma | | | | | |
| Osteosarcoma (metastatic) | | | | | |
| Mammary Gland: | | | | | |
| Fibroadenoma | | | | | |
| Pancreas: | | | | | |
| Mesothelioma | | | | | |
| Adenoma - Islet cell | | | | | |
| Carcinoma - Islet cell | | | | | |
| Pituitary: | | | | | |
| Adenoma<br>Craniopharyngioma | | | | | |
| Prostate: | | | | | |
| Mesothelioma | | | | | |
| Salivary Gland: | | | | | |
| Sarcoma | | | | | |
| Seminal Vesicle: | | | | | |
| Mesothelioma | | | | | |
| Skeletal Muscle: | | | | | |
| Carcinoma - basal cell | | | | | |
| Skin: | | | | | |
| Squamous cell papilloma | | | | | |
| Basal cell adenoma | | | | | |
| Keratoacanthoma | | | | | |
| Trichoepithelioma | | | | | |
| Preputial gland adenoma | | | | | |
| Basal cell carcinoma | | | | | |
| Squamous cell carcinoma | | | | | |
| Firbrosarcoma | | | | | |
| Subcutaneous Tissue: | | | | | |
| Fibroma | | | | | |
| Leiomyoma | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Fibrosarcoma | | | | | |
| Myxosarcoma | | | | | |
| Osteosarcoma | | | | | |
| Sarcoma | | | | | |
| Sarcoma (associated w/implant) | | | | | |
| Testes: | | | | | |
| Interstitial (Leydig) cell adenoma | | | | | |
| Mesothelioma | | | | | |
| Thyroids: | | | | | |
| Follicular cell adenoma | | | | | |
| Follicular cell carcinoma | | | | | |
| C-cell adenoma | | | | | |
| C-cell carcinoma | | | | | |
| Urinary bladder: | | | | | |
| Mesothelioma | | | | | |
| Carcinoma - transitional cell | | | | | |
| Zymbal's gland: | | | | | |
| Adenoma | | | | | |
| Carcinoma | | | | | |
| Hemangiosarcomas: | | | | | |
| Mesenteric lymph node | 4 (228) | 1 | 0.4% | 0.0% | 1.7% |

NTP Historical Data in female CDF® (F-344) - 3R rats (2000)

| Location & Tumor | # Studies (# Organs) | # Lesions | Percent | Minimum % | Maximum % |
|---|---|---|---|---|---|
| Hemopoietic: | | | | | |
| Malignant Lymphoma | | | | | |
| Histoicytic sarcoma | | | | | |
| Lungs: | | | | | |
| Bronchioloalveolar Adenoma | | | | | |
| Bronchioloalveolar adneocarcinoma | | | | | |
| Uterus: | | | | | |
| Endometrial Polyp | | | | | |
| Leiomyma | | | | | |
| Leiomyosarcoma | | | | | |
| Endometrial adenoma | | | | | |
| Endometrial stromal cell sarcoma | | | | | |
| Hemangioma | | | | | |
| Hemangiosarcoma | | | | | |

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
---
Karl Lin
10/12/04 10:04:41 AM
BIOMETRICS

S. Edward Nevius
10/13/04 05:22:38 PM
BIOMETRICS
Concur with review.

NDA 21-518 Vesicare
Solifenacin succinate 5 and 10 mg

CAC/ECAC Report

See enclosed ECAC Meeting Minutes, dated May 27, 03.



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ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

# Statistical Review and Evaluation

## CLINICAL STUDIES

| | |
|---|---|
| NDA: | 21-518 / SN 000 |
| Name of drug: | Vesicare (solifenacin succinate) 5 or 10 mg tablets |
| Applicant: | Yamanouchi Pharma America, Inc. |
| Indication: | — |
| | — |
| Documents reviewed: | Statistical section documents in electronic document room: |
| | \\CDSESUB1\N21518\N_000\2002-12-19\clinstat |
| | Statistical datasets in electronic document room: |
| | \\CDSESUB1\N21518\N_000\2002-12-19\crt |
| Project manager: | Jean King |
| Clinical reviewer: | Guodong Fang, M.D. |
| Dates: | Received 12/19/02; user fee (10 months) 10/19/03 |
| Statistical reviewer: | Kate Meaker, M.S. |
| Statistics team leader: | Mike Welch, PhD |
| Biometrics division director: | S. Edward Nevius, PhD |

Keywords: NDA review, clinical studies

# 1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

## 1.1 CONCLUSIONS AND RECOMMENDATIONS

There are four randomized, double-blind, placebo-controlled, parallel-arm, multicenter clinical studies of primary interest for assessing the efficacy of Vesicare 5 or 10 mg tablets. All four studies include the 10 mg Vesicare dose, and two studies include the 5 mg dose. For the primary endpoint, the mean change in number of micturitions per 24 hours, both Vesicare doses are statistically significantly better than placebo in all comparisons. The same is true for one of the two secondary variables of interest to the Medical Officer: the mean change in volume voided per micturitions. On the other secondary variable of interest to the Medical Officer, the mean change in number of incontinence episodes, the Vesicare doses are statistically significantly better than placebo in three of the four studies. These results support the efficacy of Vesicare 5 or 10 mg tablets [redacted]

## 1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

This application contains four key studies for assessing the efficacy of Vesicare for [redacted] All are randomized, double-blind, placebo-controlled, parallel-group, fixed-dose, multicenter studies. The two primary studies, 905-CL-013 and 905-CL-014, were conducted in the U.S. and include the 10 mg Vesicare dose compared to placebo. Two additional efficacy studies, 905-CL-015 and 905-CL-018, were conducted in Europe and include both the 5 mg and 10 mg Vesicare doses compared to placebo. The sponsor enrolled at least 260, and upward to 340 subjects, per group in the four studies. In the European studies, a hierarchical testing method was used to first compare the 10 mg Vesicare dose to placebo, and then compare the 5 mg Vesicare dose to placebo.

## 1.3 PRINCIPAL FINDINGS

The single primary efficacy endpoint is the mean change from baseline in the number of micturitions per 24 hours. In all four studies, the 10 mg Vesicare dose was statistically significantly different from placebo for this endpoint. The mean reduction was 1.1 to 1.5 episodes per day greater in the Vesicare 10 mg group than in the placebo group. In the two European studies, the 5 mg Vesicare dose was also statistically significantly different from placebo for this endpoint, with a mean reduction of 0.8 to 1.0 episodes greater in the Vesicare 5 mg group than in the placebo group.

The Medical Officer requested I review two secondary variables as additional support for efficacy. These endpoints are the mean change from baseline in number of incontinence episodes per 24 hours and the mean change from baseline in volume voided per micturitions.

For the mean volume voided endpoint, both the 10 mg and 5 mg Vesicare dose were statistically significantly different from placebo in all the comparisons. The treatment effect ranged from 25.3 to 44.5 mL/micturition higher for the Vesicare 10 mg group over the placebo group, and 20.1 to 25.4 mL/micturition higher for the Vesicare 5 mg group over the placebo group.

For the incontinence episodes endpoint, the 10 mg Vesicare dose was statistically significantly different from placebo in the two U.S. studies and in one of the European studies (905-CL-015). The treatment effect was 0.7 to 0.9 episodes per day greater reduction in the Vesicare group than in placebo. The 5 mg Vesicare dose was also statistically significantly different from placebo in study 905-CL-015 (treatment effect of 0.7 episodes greater reduction over placebo). In the remaining study, 905-CL-018, the 10 mg Vesicare dose was not statistically significantly different from placebo for the incontinence episodes endpoint, and the comparison of the 5 mg dose to placebo was not done because of the hierarchical testing method. The observed effect size for the 10 mg group was only 0.3 episodes over placebo for this study.

The Clinical Studies section in the sponsor's proposed labeling — These results should not be included in labeling since the

## 2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

### 2.1 INTRODUCTION AND BACKGROUND

This application requests approval for two doses, 5 mg and 10 mg, of Vesicare for the — .

Two 4-week Phase 2 trials were conducted to select the doses to be continued in Phase 3 development. Four 12-week Phase 3 studies provide the supportive evidence for efficacy in this application.

### 2.2 DATA ANALYZED AND SOURCES

This NDA is an electronic application. All reports and data were provided electronically to the electronic document room. Datasets were in the SAS export data format. Full linking and documentation was provided for all datasets.

Four clinical studies are the focus of this review. All are randomized, double-blind, placebo-controlled, parallel-arm, fixed-dose studies. Complete details are provided in Table 1. Study 905-CL-015 included an active-control arm, Tolterodine 2mg, but that group was not used for any comparisons in this review.

Table 1: Controlled Clinical Studies

| Study Number (Dates Conducted) | Number of Centers (Locations) | Total Sample Size | Type of Control | Design | Duration of Treatment |
|---|---|---|---|---|---|
| 905-CL-013<br><br>(2/01 – 10/01) | 33<br><br>United States | Vesicare 10 mg n=340<br>Placebo n=332 | Placebo | Randomized, Double-blind, Parallel-arm, Fixed-dose | 12 weeks |
| 905-CL-014<br><br>(1/01 – 1/02) | 33<br><br>United States | Vesicare 10 mg n=318<br>Placebo n=316 | Placebo | Randomized, Double-blind, Parallel-arm, Fixed-dose | 12 weeks |
| 905-CL-015<br><br>(2/01 – 1/02) | 98<br>Europe, Australia, New Zealand, South Africa | Vesicare 10 mg n=279<br>Vesicare 5 mg n=269<br>Placebo n=266<br>Tolterodine 2 mg n=267 | Placebo | Randomized, Double-blind, Parallel-arm, Fixed-dose<br><br>(Double-dummy was used to blind active-control) | 12 weeks |
| 905-CL-018<br><br>(5/01 – 3/02) | 83<br>Europe, Australia, New Zealand, South Africa | Vesicare 10 mg n=301<br>Vesicare 5 mg n=308<br>Placebo n=302 | Placebo | Randomized, Double-blind, Parallel-arm, Fixed-dose | 12 weeks |

## 2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

### 2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

The sponsor reported comparisons of Vesicare 5 or 10 mg to placebo in each of the four placebo-controlled efficacy studies. All four of these studies included a comparison of Vesicare 10 mg to placebo, and each demonstrated that Vesicare 10 mg is statistically

significantly superior to placebo in reducing the number of micturitions per 24 hrs. The two European studies included a comparison of the Vesicare 5 mg to placebo, and both demonstrated that Vesicare 5 mg is statistically significantly superior to placebo in reducing the number of micturitions per 24 hrs. Based on these results, the sponsor concludes that the studies support the efficacy of both doses of Vesicare.

### 2.3.2 STATISTICAL METHODOLOGIES

The primary endpoint is the mean change from baseline in the number of micturitions per 24 hrs. Secondary endpoints of interest to the Medical Officer are the mean change in number of incontinence episodes and the mean change in volume voided. These endpoints were all treated as continuous variables.

The analysis plans for the efficacy endpoints were the same in all four placebo-controlled efficacy study protocols. The planned analysis was an ANOVA model with factors for treatment, site, and the interaction term. The protocol planned to check for the required normality assumptions, and if not met, to use the van Elteren test, a non-parametric method controlling for site. An ANCOVA model with baseline as the covariate was also planned as a secondary analysis.

The planned analysis included all subjects who received drug, have baseline data, and at least one on-treatment observation. This is referred to by the sponsor as the Full Analysis Set (FAS), and is an appropriate definition of the patient population for an analysis of a change from baseline endpoint.

### 2.3.3 DETAILED REVIEW OF INDIVIDUAL STUDIES

#### 2.3.3.1 Study 905-CL-013

Study 905-CL-013 is a Phase 3, randomized, double-blind, parallel-group, multicenter, placebo-controlled study conducted in the U.S. There are 2 treatment groups: Vesicare 10 mg and placebo. The primary objective of this study was to confirm the efficacy of Vesicare 10 mg versus placebo in reducing the number of micturitions per 24 hours in subjects with overactive bladder.

Patients were age 18 or older, with overactive bladder, determined by urinary frequency, urgency, and/or urge incontinence, as recorded in a daily diary during screening. A total of 672 were enrolled and randomly assigned to receive either placebo (n=332) or Vesicare 10 mg (n=340). The treatment groups were similar with respect to demographic and baseline characteristics.

The dropout rate was similar for the two groups (18% in placebo; 21% in Vesicare group), with no notable differences in the time until discontinuation. In both groups the most common reason given for discontinuation was adverse events, with a higher rate in the

Vesicare group (11%) than in the placebo group (5%). This imbalance was anticipated due to two specific adverse events, dry mouth and constipation, which were more common in the Vesicare group. The sponsor did secondary analyses comparing results for completers to results for dropouts which confirmed the efficacy results were consistent across both subgroups.

The primary efficacy endpoint is the mean change from baseline in the number of micturitions per 24 hrs. Secondary endpoints of interest to the Medical Officer are the mean change in number of incontinence episodes and the mean change in volume voided. These were planned as secondary endpoints, not as co-primary endpoints. An adjustment to the statistical significance level is not required because these secondary endpoints were not preplanned as primary, are not required for efficacy, and are not appropriate for claims.

The analysis plan for all three of these endpoints was to use an ANOVA model with terms for treatment, site, and the interaction. The protocol specified that, if the normality assumptions for the ANOVA model were not met, then van Elteren's nonparametric method would be used to test for treatment differences while controlling for site.

In my analyses, I agree with the model and method planned in the protocol, and confirmed the results reported by the sponsor. In the analyses, the normality assumptions were not met, so the reported p-values are from van Elteren's test (Table 2). Secondary analyses using and ANCOVA model with baseline as the covariate confirmed the primary analysis results. The conclusion is that Vesicare 10 mg is statistically significantly superior to placebo for all three efficacy endpoints of interest. This study supports the efficacy of Vesicare 10 mg.

Table 2: Study 905-CL-013 Efficacy Results

| | Placebo | Vesicare 10 mg |
|---|---|---|
| Randomized | 332 | 340 |
| **Primary Endpoint:** | | |
| **Number of Micturitions / 24 Hours** | | |
| N | 309 | 306 |
| Baseline Mean | 11.5 | 11.7 |
| Mean Change from Baseline (std. err) | -1.5 (0.15) | -3.0 (0.15) |
| p-value (Vesicare vs. placebo) | | <0.001 |
| **Secondary Endpoint:** | | |
| **Number of Incontinence Episodes / 24 Hours** | | |
| N | 237 | 225 |
| Baseline Mean (std. err) | 3.0 | 3.1 |
| Mean Change from Baseline (std. err) | -1.1 (0.16) | -2.0 (0.19) |
| p-value (Vesicare vs. placebo) | | <0.001 |
| **Secondary Endpoint:** | | |
| **Volume Voided (mL/Micturition)** | | |
| N | 308 | 306 |
| Baseline Mean (std. err) | 190.3 | 183.5 |
| Mean Change from Baseline (std. err) | 2.7 (3.15) | 47.2 (3.79) |
| p-value (Vesicare vs. placebo) | | <0.001 |

Source: Clinical Study Report Tables 10-2, 10-5, 10-7

2.3.3.2 Study 905-CL-014

The design of Study 905-CL-014 is identical to Study 905-CL-013 (Section 2.3.3.1). It is a Phase 3, randomized, double-blind, parallel-group, multicenter, placebo-controlled study. It was conducted in the U.S. There are 2 treatment groups: Vesicare 10 mg and placebo. The primary objective of this study was to confirm the efficacy of Vesicare 10 mg versus placebo in reducing the number of micturitions per 24 hours in subjects with overactive bladder.

Patients were age 18 or older, with overactive bladder, determined by urinary frequency with urgency and/or urge incontinence, as recorded in a daily diary during screening. A total of 634 were enrolled and randomly assigned to receive either placebo (n=316) or Vesicare 10 mg (n=318). The treatment groups were similar with respect to demographic and baseline characteristics.

The dropout rate was similar for the two groups (14% in placebo; 15% in Vesicare group), with no notable differences in the time until discontinuation. In both groups the most common reason given for discontinuation was adverse events, with a somewhat higher rate in the Vesicare group (9%) than in the placebo group (5%). This imbalance was anticipated due to two specific adverse events, dry mouth and constipation, which were more common in the Vesicare group. The sponsor did secondary analyses comparing results for completers

to results for dropouts which confirmed the efficacy results were consistent across both subgroups.

The primary efficacy endpoint is the mean change from baseline in the number of micturitions per 24 hrs. Secondary endpoints of interest to the Medical Officer are the mean change in number of incontinence episodes and the mean change in volume voided. These were planned as secondary endpoints, not as co-primary endpoints. An adjustment to the statistical significance level is not required because these secondary endpoints were not preplanned as primary, are not required for efficacy, and are not appropriate for claims.

The analysis plan for all three of these endpoints was to use an ANOVA model with terms for treatment, site, and the interaction. The protocol specified that, if the normality assumptions for the ANOVA model were not met, then van Elteren's nonparametric method would be used to test for treatment differences while controlling for site. If normality assumptions were met, and the interaction term was not significant (at $\alpha$=0.10) that term would be dropped from the ANOVA model.

In my analyses, I agree with the model and method planned in the protocol, and confirmed the results reported by the sponsor. In the analyses, the normality assumptions were met, and the interaction term was not significant. Therefore the reported p-values are from the ANOVA model with terms for treatment and site (Table 3). The conclusion is that Vesicare 10 mg is statistically significantly superior to placebo for all three efficacy endpoints of interest. This study supports the efficacy of Vesicare 10 mg.

Table 3: Study 905-CL-014 Efficacy Results

| | Placebo | Vesicare 10 mg |
|---|---|---|
| Randomized | 316 | 318 |
| **Primary Endpoint: Number of Micturitions / 24 Hours** | | |
| N | 295 | 298 |
| Baseline Mean | 11.8 | 11.5 |
| Mean Change from Baseline (std. err) | -1.3 (0.16) | -2.4 (0.15) |
| p-value (Vesicare vs. placebo) | | <0.001 |
| **Secondary Endpoint: Number of Incontinence Episodes / 24 Hours** | | |
| N | 238 | 230 |
| Baseline Mean (std. err) | 2.9 | 2.9 |
| Mean Change from Baseline (std. err) | -1.2 (0.15) | -2.0 (0.15) |
| p-value (Vesicare vs. placebo) | | <0.001 |
| **Secondary Endpoint: Volume Voided ( mL/Micturition)** | | |
| N | 293 | 298 |
| Baseline Mean (std. err) | 175.7 | 174.2 |
| Mean Change from Baseline (std. err) | 13.0 (3.45) | 46.4 (3.73) |
| p-value (Vesicare vs. placebo) | | <0.001 |

Source: Clinical Study Report Tables 10-2, 10-5, 10-7

2.3.3.3 Study 905-CL-015

Study 905-CL-015 is a randomized, double-blind, parallel-group placebo- and active-controlled multicenter study conducted in Europe, Australia, New Zealand, and South Africa. This study included four treatment groups: two dose levels of Vesicare (5 mg or 10 mg), placebo, and tolterodine as an active-control. The primary objective was to assess the efficacy of the Vesicare 5 mg and 10 mg doses compared to placebo in patients with overactive bladder. Comparisons to tolterodine were planned as secondary, and are not of interest in assessing efficacy for this application.

Patients were age 18 or older, with symptoms of overactive bladder (including urinary frequency, urgency, or urge incontinence). A total of 1081 subjects were enrolled and randomly assigned to receive either placebo (n=267), Vesicare 5 mg (n=279), Vesicare 10 mg (n=269) or tolterodine (n=266). The treatment groups were similar with respect to demographic and baseline characteristics.

The dropout rate was similar for the four groups, from 7% in the Vesicare 10 mg group, 10% in each of the Vesicare 5 mg and tolterodine groups, up to 12% in the placebo group. There were no notable differences in the time until discontinuation or the reasons for discontinuation. The rate of discontinuations due to adverse events was lower in this study than in the two US studies, ranging from 2-4% across the groups.

The primary efficacy endpoint is the mean change from baseline in the number of micturitions per 24 hrs. Secondary endpoints of interest to the Medical Officer are the mean change in number of incontinence episodes and the mean change in volume voided. These were planned as secondary endpoints, not as co-primary endpoints. An adjustment to the statistical significance level is not required because these secondary endpoints were not preplanned as primary, are not required for efficacy, and are not appropriate for claims.

The primary efficacy analyses in this study include a hierarchical plan for comparisons of each of the Vesicare doses to placebo. As prospectively described in the statistical analysis plan, first the Vesicare 10 mg dose group would be compared to placebo. If that test was significant at $\alpha$=0.05, then the Vesicare 5 mg group would be compared to placebo, also at $\alpha$=0.05. If the comparison of the 10 mg group to placebo was not significant, the comparison of the 5 mg group would not be performed. This hierarchical approach is an appropriate method to control the overall significance level for multiple comparisons.

The analysis plan for all three of these endpoints was to use an ANOVA model with terms for treatment as a fixed factor and site as a random effect due to the large number (98) of sites. The protocol specified that, if the normality assumptions for the ANOVA model were not met, then the Wilcoxon rank-sum nonparametric method would be used to test for treatment differences.

In my analyses, I agree with the model, method, and hierarchical testing approach planned in the protocol, and confirmed the results reported by the sponsor. In the analyses, the normality assumptions were met. Therefore the reported p-values are from the ANOVA model with terms for treatment and site (Table 4). The conclusion is that both the Vesicare 5 mg and 10 mg doses are statistically significantly superior to placebo for all three efficacy endpoints of interest. This study supports the efficacy of the Vesicare 5 mg or 10 mg dose.

Table 4: Study 905-CL-015 Efficacy Results

| | Placebo | Vesicare | |
|---|---|---|---|
| | | 5 mg | 10 mg |
| Randomized | 267 | 279 | 269 |
| **Primary Endpoint: Number of Micturitions / 24 Hours** | | | |
| N | 253 | 266 | 264 |
| Baseline Mean | 12.2 | 12.1 | 12.3 |
| Mean Change from Baseline (std. err) | -1.2 (0.20) | -2.2 (0.18) | -2.6 (0.16) |
| p-value (Vesicare vs. placebo) | | <0.001 | <0.001 |
| **Secondary Endpoint: Number of Incontinence Episodes / 24 Hours** | | | |
| N | 153 | 141 | 158 |
| Baseline Mean (std. err) | 2.7 | 2.6 | 2.6 |
| Mean Change from Baseline (std. err) | -0.8 (0.18) | -1.4 (0.15) | -1.5 (0.18) |
| p-value (Vesicare vs. placebo) | | 0.008 | 0.004 |
| **Secondary Endpoint: Volume Voided ( mL/Micturition)** | | | |
| N | 253 | 266 | 264 |
| Baseline Mean (std. err) | 143.8 | 149.6 | 147.2 |
| Mean Change from Baseline (std. err) | 7.4 (2.28) | 32.9 (2.92) | 39.2 (3.11) |
| p-value (Vesicare vs. placebo) | | <0.001 | <0.001 |

Source: Clinical Study Report Tables 11, 12, 15, 16, 17, 18

2.3.3.4 Study 905-CL-018

Study 905-CL-018 is very similar to Study 905-CL-015, with the key difference being that this study does not include an active-control arm. It is a randomized, double-blind, parallel-group placebo-controlled multicenter study conducted in Europe, Australia, New Zealand, and South Africa. This study included three treatment groups: two dose levels of Vesicare (5 mg or 10 mg) and placebo. The primary objective was to assess the efficacy of the Vesicare 5 mg and 10 mg doses compared to placebo in patients with overactive bladder.

Patients were age 18 or older, with symptoms of overactive bladder (including urinary frequency, urgency, or urge incontinence). A total of 911 subjects were enrolled and randomly assigned to receive either placebo (n=302), Vesicare 5 mg (n=301), or Vesicare 10 mg (n=308). The treatment groups were similar with respect to demographic and baseline characteristics.

The dropout rate was similar for the three groups, with 7% in the Vesicare 5 mg group, 8% in the Vesicare 10 mg group, up to 10% in the placebo group. There were no notable differences in the time until discontinuation or the reasons for discontinuation. The rate of discontinuations due to adverse events was lower in this study than in the two US studies, ranging from 2-4% across the groups. This was the same range seen in the other European study.

The primary efficacy endpoint is the mean change from baseline in the number of micturitions per 24 hrs. Secondary endpoints of interest to the Medical Officer are the mean change in number of incontinence episodes and the mean change in volume voided. These were planned as secondary endpoints, not as co-primary endpoints. An adjustment to the statistical significance level is not required because these secondary endpoints were not preplanned as primary, are not required for efficacy, and are not appropriate for claims.

The primary efficacy analyses in this study include a hierarchical plan for comparisons of each of the Vesicare doses to placebo. As prospectively described in the statistical analysis plan, first the Vesicare 10 mg dose group would be compared to placebo. If that test was significant at $\alpha$=0.05, then the Vesicare 5 mg group would be compared to placebo, also at $\alpha$=0.05. If the comparison of the 10 mg group to placebo was not significant, the comparison of the 5 mg group would not be performed. This hierarchical approach is an appropriate method to control the overall significance level for multiple comparisons.

The analysis plan for all three of these endpoints was to use an ANOVA model with terms for treatment as a fixed factor and site as a random effect due to the large number (83) of sites. The protocol specified that, if the normality assumptions for the ANOVA model were not met, then the Wilcoxon rank-sum nonparametric method would be used to test for treatment differences.

In my analyses, I agree with the model, method, and hierarchical testing approach planned in the protocol, and confirmed the results reported by the sponsor. In the analyses, the normality assumptions were met. Therefore the reported p-values are from the ANOVA model with terms for treatment and site (Table 5).

The conclusion is that both the Vesicare 5 mg and 10 mg doses are statistically significantly superior to placebo for the primary endpoint, and one of the secondary endpoints (mean volume voided). However, the comparison of Vesicare 10 mg to placebo was not statistically significant for the other secondary endpoint, mean change in number of incontinence episodes. The comparison of the Vesicare 5 mg dose to placebo was not performed for this endpoint as specified in the hierarchical testing approach.

Only the single primary endpoint was predefined as being required to support efficacy. Therefore, this study supports the efficacy of the Vesicare 5 mg and 10 mg doses.

Table 5: Study 905-CL-018 Efficacy Results

| | Placebo | Vesicare | |
|---|---|---|---|
| | | 5 mg | 10 mg |
| Randomized | 302 | 301 | 308 |
| **Primary Endpoint: Number of Micturitions / 24 Hours** | | | |
| N5Baseline Mean | 281 | 286 | 290 |
| Mean Change from Baseline (std. err) | 12.3 | 12.1 | 12.1 |
| p-value (Vesicare vs. placebo) | -1.7 (0.19) | -2.5 (0.17) | -2.9 (0.18) |
| | | 0.002 | <0.001 |
| **Secondary Endpoint: Number of Incontinence Episodes / 24 Hours** | | | |
| N | 153 | 173 | 165 |
| Baseline Mean (std. err) | 3.2 | 2.7 | 2.8 |
| Mean Change from Baseline (std. err) | -1.3 (0.19) | -1.6 (0.16) | -1.6 (0.18) |
| p-value (Vesicare vs. placebo) | | no test | 0.22 |
| **Secondary Endpoint: Volume Voided ( mL/Micturition)** | | | |
| N | 281 | 286 | 290 |
| Baseline Mean (std. err) | 147.2 | 148.5 | 145.9 |
| Mean Change from Baseline (std. err) | 11.3 (2.52) | 31.8 (2.93) | 36.6 (3.04) |
| p-value (Vesicare vs. placebo) | | <0.001 | <0.001 |

Source: Clinical Study Report Tables 11, 12, 15, 16, 17, 18

### 2.3.4 STATISTICAL REVIEWER'S FINDINGS

The results of each of the four placebo-controlled studies reviewed strongly support the efficacy of Vesicare 10 mg. The two European studies also support the efficacy of the Vesicare 5 mg dose. These effect sizes are consistent across the studies. Together the overall body of evidence is sufficient to support the efficacy of the Vesicare 5 mg and 10 mg doses.

## 2.4 STATISTICAL AND TECHNICAL ISSUES

There were two statistical issues which were addressed in the analyses. The first was the anticipated potential for a higher dropout rate due to two specific adverse events (dry mouth and constipation) in the Vesicare groups than in placebo. The impact of these dropouts was assessed using subgroup analyses comparing completers to dropouts. The results showed similar treatment effect sizes across both subgroups as were seen in the primary analysis. This confirmed that any difference in dropouts was not impacting the efficacy conclusions.

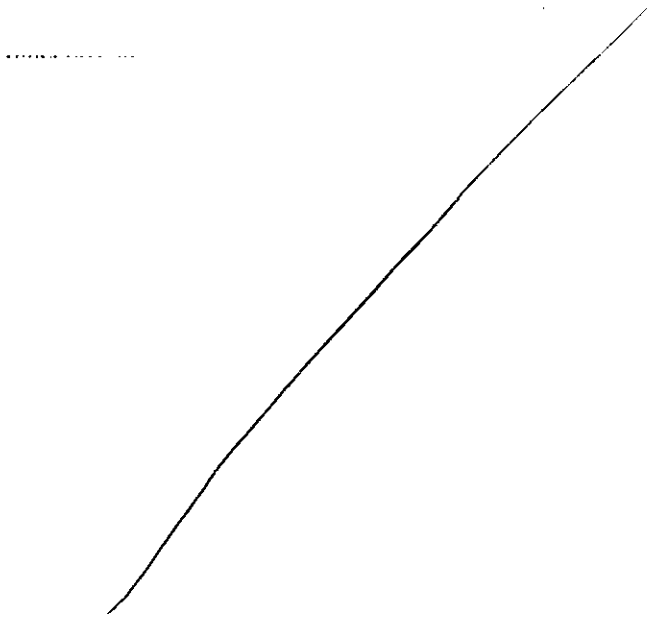
The other statistical issue was the need to protect the overall statistical significance level when doing multiple comparisons for the Vesicare 5 mg and 10 mg doses to placebo. This occurred in the two European studies (905-CL-015 and -018). A hierarchical approach was pre-specified in the statistical analysis plan. First the comparison of the Vesicare 10 mg group to placebo would be performed at $\alpha$=0.05. If that test was statistically significant, then the comparison of the Vesicare 5 mg group to placebo would be performed, also at $\alpha$=0.05. This is an appropriate method to address the issue of multiple comparisons.

## 2.5 CONCLUSIONS AND RECOMMENDATIONS

This application contains four well-designed, placebo-controlled studies to assess efficacy. The results are consistent and are statistically significant in favor of Vesicare versus placebo for the primary efficacy endpoint and one of the secondary endpoints of interest. For the other secondary endpoint of interest, three of the four studies show statistical significance for Vesicare over placebo. The results of these four studies support the efficacy claim for both doses of Vesicare for the treatment of [redacted] overactive bladder.

## 2.6 COMMMENTS ON LABEL

The Clinical Studies section of the proposed package insert (Vol. 1) These should not be allowed in the label, the protocols. I have underlined the specific statements in the label text (below) which I prefer be removed.



In the sponsor's Table in the proposed label, the rows for should be removed. These were , which the Medical Officer did not request for statistical review. In addition, the p-value should

The sponsor's proposed Table 1 also This is inappropriate, Results for each study should be presented separately, either in table or text form.

1 Draft Labeling Page(s) Withheld

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/s/
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Katherine Meaker
10/16/03 12:46:53 PM
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Mike Welch
10/16/03 02:05:18 PM
BIOMETRICS
Concur with review.

**Screening of New NDA for Statistical Filing**
**Division of Biometrics II**

**NDA #:** 21-518

**Applicant:** Yamanouchi

**Trade/Generic Name:** Vesicare (solifenacin succinate)

**Indication:** [redacted]

**Date of Submission:** Dec 19, 2002

**User Fee Goal Date:** Oct 19, 2003

**Project Manager:** Jean King (HFD-580)

**Medical Reviewer:** Guodong Fang

**Statistical Reviewer:** Kate Meaker

**Comments:** This NDA is fileable from a statistical perspective. This application includes 4 pivotal Phase 3 studies, 905-CL-015, -018, -013, and –014, which provide the primary basis of effectiveness of solifenacin succinate 5 mg and 10 mg for the treatment of overactive bladder. Supportive evidence of effectiveness is provided by the Phase 2 studies, 905-CL-05 and –06. Statistical review will focus on the two U.S. studies (-13 and -014). The entire submission is in electronic format and consists of special analysis data sets and other data layouts and documentation intended to facilitate the statistical and clinical reviews.

| 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 |

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Mike Welch
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