CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

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

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 22-410
Drug Name:	Suboxone (Buprenorphine and Naloxone)
Indication(s):	Two Year Carcinogenicity in Rats
Applicant:	Sponsor: Reckitt & Colman Products Limited, Danson Lane, Hull, HU87DS, UK Test facility: (b) (4)
Documents Reviewed:	Submission: Electronic, Dated: Dec. 9, 2003 (Sponsor's date of issue) Data: No data were submitted
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Biometrics Division:	Division of Biometrics -6
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Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Anesthesia, Analgesia, and Rheumatology Products
Reviewing Pharmacologist:	Elizabeth Bolan, Ph.D.
Project Manager:	Mathew Sullivan
Keywords:	Carcinogenicity, Dose response

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1. Background

In this submission the sponsor included a report of an animal carcinogenicity study in rats. This study was intended to assess the carcinogenic potential of suboxone (Buprenorphine and Naloxon) in rats when administered orally through dietary mixture at appropriate drug levels for about 104 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Bolan.

2. Design

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and two identical control groups. Two hundred and sixty OFA Alpk:AP$_f$SD rats of each sex were randomly allocated to treated and control groups in equal size of 52 animals. The dose levels for treated groups were 100, 450, and 1800 ppm. In this review these dose groups would be referred to as the low, medium, and high dose group, respectively. The two controls will be referred to as Control 1 and Control 2. The controls received the vehicle (CT1 diet).

Prior to the start of the study, all rats were examined to ensure that they were normal. The cageside observations that included recording any changes in clinical condition or behavior were made twice daily. Detailed clinical observations, included the finding of abnormalities were recorded at least weekly, at the same time that the bodyweights were recorded, where applicable.

All tissues of animals found dead or killed inter currently, all animals in both control groups and the high dose group, all gross lesions, tumors, suspected tumors and associated tissues were submitted for histology. In addition, the following tissues from the mid and low dose groups were submitted for histology: males - testes, pituitary gland, liver, spleen, adrenal glands, eye, lachrymal gland, seminal vesicles and voluntary muscle, and females – adrenal glands, uterus, pituitary gland, mammary gland, liver, spleen and eye.

2.1. Sponsor's analyses

2.1.1. Survival analysis

Survival function of each treatment group was estimated using the Kaplan-Meier product limit method for each sex. Mortalities that were the result of animals killed in moribund conditions or at scheduled termination were considered to be censored observations. Intergroup comparisons of mortality, comparing each treatment group with the pooled control group, and an overall test for dose response relationship were performed using the logrank test.

Sponsor's findings: Sponsor's analysis showed that there were no statistically significant differences in survival in the individual group comparisons. Overall, there was a statistically significant dose response relationship ($p<0.05$) in mortality for the males. Female survival in the 450 and 1800 ppm groups was statistically significantly lower ($p<0.05$ and $p<0.01$, respectively) in comparison with the control group. Survival for the females in the 100 ppm group was also slightly lower than the controls, but this difference did not achieve statistical significance. Overall, there was a statistically significant dose response relationship ($p<0.01$) in mortality for the females.

2.1.2. Tumor data analysis

Tests for dose response relationships were performed using the Cochran-Armitage test (Gart et al 1986). The pairwise comparisons of incidence rates of tumor types in each treated group with the pooled control group

were performed using the Fisher's Exact test. In addition, age adjusted tests were performed using a prevalence analysis (assuming tumors were incidental), a death rate analysis (assuming all tumors were observed in a fatal context) and a combined analysis allowing for the observed context as described in Peto et al (1980). All statistical tests were two-sided.

Adjustment for the multiplicity: The sponsor did not mention of any method for multiple testing adjustment.

Sponsor's findings: The sponsor's analysis showed that the incidence of unilateral leydig cell adenomas reached statistical significance only in the 1800 ppm group, (p=0.008) in male rats. The increased incidence of unilateral leydig cell adenomas in animals in the 1800 ppm group was also above that for historical controls. The sponsor's analysis also showed that the incidence of bilateral leydig cell adenomas reached statistical significance (p=0.001) in all groups administered suboxone in male rats. The increased incidence of bilateral leydig cell adenomas was also above that for historical controls in all groups administered suboxone.

2.2. Reviewer's analyses

To verify some of the sponsor's findings and to perform additional analysis suggested by the reviewing pharmacologist, this reviewer performed some independently analyses. Data for this reviewer's analyses were taken from the sponsor's summary tables given in their final report (submitted electronically). It may be mentioned that the raw data were not available and were never submitted to the agency.

2.2.1. Survival analysis

Since the raw data were not available, this reviewer could not perform any survival analysis of the animals.

2.2.2. Tumor data analysis

Since the raw data were not available a formal and complete analysis of the tumor incidence was not possible. On the suggestion of the reviewing pharmacologist, this reviewer only performed a brief analysis of the following selected tumor types.

Selected tumor types: (1) Unilateral benign Leydig cell adenoma of the testes, (2) Bilateral benign Leydig cell adenoma of the testes, (3) Adenoma of the uterus, (4) Adenocarcinoma of the uterus, and (5) Large granular lymphocyte leukemia of the lymphoreticular system (male and female). The pharmacologist also wanted to perform analysis on combined incidences of the uterine adenomas and adenocarcinomas.

Noting that the two control groups were identical, in this reviewer's analysis the two control groups were combined together to form a single control (pooled control). This kind of pooling increases the power of the test and reduces the dimension of the multiplicity of testing.

For the tumor data analyses, this reviewer performed dose response relationship tests (wherever it was possible) and pairwise comparisons of pooled control with each of the treated groups using the Cochran-Armitage test (1955).

Multiple testing adjustment: For the adjustment of multiple testing of dose response relationship, the FDA guidance for the carcinogenicity study design and data analysis suggests the use of test levels α=0.005 for common tumors and α=0.025 for rare tumors for a submission with two species, and a significance level

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