22R0009

OPTIONAL COLUMN E EXPLANATION FORM

IV RISING DOSE TOXICOLOGY STUDY

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 2. Number of animals classified as category "E" - 1.

3. Species (common name)____Non-human Primates___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These animals were dosed with a pharmaceutical compound.

One animal was euthanized as scheduled for the study on day 19. However, this animal demonstrated decreased locomotor activity, hunched posture and labored respiration on study day eight and slight clincial signs on days nine and ten. Compound administration was stopped for 7 days, and then resumed on day 15. There were no additional signs of pain or distress.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922).

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1. Registration Number: 22-R-0009

2. Number of animals used in this study – 4. Number of animals classified as category "E" - 2.

3. Species (common name)____Non-human Primates___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These animals were dose with a pharmaceutical compound.

One animal demonstrated muscle tremors on study day 10, and vocalization and muscle tremors on study day 11. No other significant clinical observations were made and the animal was euthanized as scheduled on study day 15. A second animal demonstrated clinical signs including muscle tremors, salivation and decreased locomotor activity on day nine. There were no significant clinical observations thereafter, and so the animal was euthanized as scheduled on day 15.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

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