Category E Explanation
Registration Number: 33-R-0008

In a preclinical study to determine the activity of a novel anti-infective agent, ten Syrian golden hamsters that received a challenge dose with SARS CoV-2 succumbed to infection. In this assay, prevention of virus-induced mortality and moribundity are the key experimental endpoints used to evaluate agent efficacy.

Prior to study initiation, a literature search was performed to identify alternate test systems that could generate data that are sufficient to: (a) support a rigorous scientific assessment of agent efficacy and (b) demonstrate evidence of agent efficacy that is sufficient to be accepted by the United States Food and Drug Administration (FDA). This literature search did not identify any alternate models suitable to replace the current *in vivo* assay.

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Registration Number: 33-R-0008

In two separate preclinical toxicology studies of a novel RNAi therapeutic to treat cancer, a total of 13 marmosets demonstrated clinical evidence of toxicity resulting in mortality. Toxic effects included vomiting, diarrhea, and inactivity. Marmosets were observed at least twice daily throughout the studies to identify toxic effects and to identify animals that should be considered for euthanasia *in extremis* due to the development of a moribund state (as defined by institutional Standard Operating Procedures). All marmosets in both studies underwent a complete necropsy with tissue collection; a full set of tissues from each animal was evaluated histopathologically. Data from these studies were critical parameters supporting the selection of appropriate doses of these therapeutic agents for use in clinical trials, and to identify sensitive target organs that should be monitored in those trials.

Analgesic agents cannot be administered in such studies for the following reasons:

- Many common analgesics (*e.g.,* non-steroidal anti-inflammatory drugs) can modulate the activity of enzymes involved in drug metabolism, with resulting effects on agent absorption, distribution, metabolism, and/or excretion (ADME). For this reason, co-administration of analgesic agents in a preclinical toxicology study may have a significant impact on agent toxicity with resulting influences on study results.
- Administration of analgesics may mask clinical signs of toxicity, and thereby reduce the sensitivity of the test system to identify toxicologic effects of mild to moderate severity.

The animal species, number of experimental groups, and group sizes used in these studies were selected to meet published FDA and ICH standards for the design of preclinical safety assessments of novel therapeutic agents. The use of appropriate non-rodent test systems for preclinical toxicology studies is mandated by U.S. and international regulatory agencies, and no *in vitro* alternatives are accepted by these agencies. The use of a non-human primate species such as marmosets is required for preclinical safety assessments of mRNAi therapeutic agents due to the potential for artefactual immune responses that may be induced in dogs and other non-rodent species. Furthermore, literature searches performed prior to the initiation of these studies were not successful in identifying alternate model systems that are both (a) scientifically rigorous and (b) acceptable to the FDA and other regulatory agencies.

In a preclinical toxicology study of a novel therapeutic agent to treat phenylketonuria, a total of seven marmosets demonstrated evidence of drug toxicity that included diarrhea, vomiting, and/or inactivity. NHPs were observed at least twice daily throughout the studies to identify toxic effects and to identify animals that should be considered for euthanasia *in extremis* due to the development of a moribund state (as defined by institutional Standard Operating Procedures). All moribund animals and all animals that were found dead in each study underwent a complete necropsy with tissue collection; a full set of tissues from each animal was evaluated histopathologically. Data from these studies were critical parameters supporting the selection of appropriate doses of these agents for use in clinical trials. These data are also used to identify sensitive target organs that should be monitored in clinical trials.

Analgesic agents cannot be administered in preclinical toxicology studies for the following reasons:

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