Category E
10/2019-9/2020 Fiscal Year

Species: Canine

Studies:	**Number of Animals**:	**Max Duration**:
(b) (4) 008-PH40	4	10 days/dosing
(b) (4) 014-PH40	21	10 days/dosing

Inflammatory pain

Procedure Summary:
Beagle dogs underwent unilateral injections of kaolin suspension in order to create a model of inflammatory pain. Lameness and paw edema were assessed ~1-2 days prior to kaolin injection, and 4, 28, 52, 76, 100, 124, 148, 172, and 244 hours after kaolin injection. Lameness lasted ~7 days following kaolin injection. All animals received a single dose. After minimum 35 day monitoring period, the twenty of the animals were given an additional 14 day washout period, then redosed.

Explanation for use of Dogs:
(b) (4) 008-PH40: Dogs are a defined model for the assessment of inflammatory pain and can also serve as a target species for future test article evaluation (that is, dogs may be used as the subjects in this research with the ultimate goal being the development of therapies to treat inflammatory pain in dogs). Further, dogs offer a different dimension to the study of pain and pain therapeutics. While a majority of pain research can be and is done in rodents, rodents notoriously do not show robust affective signs of pain (such as pain-suppressed behaviors), which are key facets of pain in humans. As such, for many later stage investigational pain therapies, assessments in dog models of pain prove to be the most highly translatable preclinical models.

(b) (4) 014-PH40: Dogs are a defined model for the assessment of pain and inflammation. Additionally, dogs were the target species for this test article application for the two studies listed above. Dogs are chosen as the subjects in these research studies since the ultimate goal was the development of therapies to treat pain and inflammation in dogs. As such, for many later stage investigational pain therapies, assessments in dog models of pain prove to be the most highly translatable preclinical models.

Explanation for why analgesics cannot be used:
(b) (4) 008-PH40: The purpose of this study was to determine what pain behaviors are present and over what time course following kaolin injections, as such analgesics could not be administered without compromising the study endpoints. The inflammatory pain state lasts from ~1 to ~2 weeks post-injection. In order to understand the extent and time course of the development of any pain/distress and lameness that develops over the course of this study, animals were assessed frequently by trained staff to determine any changes in lameness and inflammation. Animals were also evaluated frequently by a test facility veterinarian. This provided a frequent and thorough assessment of the animals' welfare during the course of the study.

(b) (4) 014-PH40: The purpose of this study was to assess the effectiveness of novel analgesics (test article) and meloxicam (control article) in reducing inflammation-induced pain behaviors following kaolin injections, and as such we could not administer pain relieving agents without compromising the study endpoints. The inflammatory pain state lasts from ~1 to ~2 weeks post-injection. Over the course of the study, animals were assessed frequently by trained staff to determine any changes in lameness and inflammation. Animals were also evaluated frequently by a test facility veterinarian. This also provided a frequent and thorough assessment of the animals' welfare during the course of the study.

Care for injury or lameness not associated with the study-specific procedures may include hot compresses, cold compresses, and routine wound care procedures, application of topical antiseptics, routine bandage care, and administration of antibiotics if the injured tissue is infected.

The kaolin induced inflammation resolved over time and the animals enrolled on these studies returned to a baseline state after a period of time.

Category E
10/2019-9/2020 Fiscal Year

Species: Rabbits
Studies: (b) (4) 1084-IR11
(b) (4) 036-IR19

Number of Animals: 14
(b) (4) 1084- IR11: 3
(b) (4) 036-IR19: 11

Max Duration: 3 days

Skin Irritation Test

Procedure Summary:

(b) (4) 1084-IR11:
Two test and two negative control articles (gauze moistened with water or vehicle without test article) were applied directly to the clipped skin on the dorsum. The application sites were wrapped with a bandage (semi-occlusive) for a minimum of 4 hours. At the end of the contact duration, the dressings were removed. Observations were performed on each application site 1 ± 0.1, 24 ± 2, 48 ± 2, and 72 ± 2 hours after unwrap. The tissue reactions were graded for erythema and edema for each application site at each time interval. The 1 ± 0.1 hour observation period was performed to ensure there are no immediate adverse clinical signs for the animals. Animals were euthanized following the 72 ± 2 hour score.

(b) (4) 036-IR19:
A series of abrasions were made (approximately 2.5 cm x 2.5 cm) in a # shape in the keratinous layer (avoiding injury to the dermis) in designated quadrants. The test and control article was applied directly to clipped skin via a 2.5 cm x 25 cm non-occlusive dressing (e.g. sterile gauze) saturated with 0.5mL of the test article or control. The gauze was fixed in place with tape, and the application sites were wrapped with an occlusive dressing for 24 ± 0.5 hours. At the end of the contact duration, the dressings were removed and the sites where the test article and control patches were located were marked with permanent ink. Where appropriate, residual test article was removed by washing with lukewarm water or other suitable non-irritating solvent, followed by careful drying. Observations were performed on each application site 1 ± 0.1, 24 ± 2, 48 ± 2, and 72 ± 2 hours after unwrap. The 1 ± 0.1 hour observation period was performed to ensure there are no adverse clinical signs for the animals. A final body weight and photographs of the test and control administration sites were taken prior to euthanasia.

Explanation for use of Rabbits:

Irritation has been studied extensively in rabbits, and is a required model for irritation testing among the regulatory bodies. Rabbits are widely used for testing irritation potential of test materials. Rabbits and humans have similarities in their immune system, particularly their skin reactivity that make them a good screening model for compounds that are intended to come in contact with humans. Rabbits are one of the preferred animal species for irritation testing due to their ability to readily display irritation responses.

Explanation for why analgesics cannot be used:
This study was designed to test the irritation potential of medical devices. The use of anesthetics, analgesics, or tranquilizers to alleviate pain was prohibited due to the potential molecular interaction between the drugs and the compounds associated with the medical device. This interaction could have caused a response (inhibitory or synergistic) that could have affected the outcome of the study. In order to effectively evaluate the characteristics of the device, the use of medications was contraindicated.

Federal Regulatory agency requiring procedure:
ISO 10993-10:2010
JMHLW PFSB/ELD/OMDE Notification No. 0301-20 (2012): Part 5 Test for Irritation