sites appeared clinically normal. Injection site reactions, after subsequent doses at intervals of 30 or 60 days, were similar to those noted after the first dose. The reactions at sites receiving multiple injections also gradually diminished and the sites were essentially normal in appearance by 2 to 4 months after the last dosing.

For all sacrifices up to Day 134 (2 to 6 weeks after the most recent treatment), residual test material was grossly visible at the local injection sites within the muscle and in some cases in small raised areas on the adjacent superficial muscle surface. The residual material within some injection sites was firm and well-defined while in others it was more diffuse and viscous. As the study progressed, less residual material was present. Adhesions were present in the subcutaneous region between the skin and superficial muscle surface at the injection sites in some animals (261/o). Tissue adhesion was rarely evident at the 6-month post-dose sacrifices (Days 210, 240 and 301).

Microscopically, residual test material was readily identified in injection site sections as retractile material. The residual material was progressively degraded, in that, by the 6-month post-dose sacrifices, significantly less foreign material was present compared to sites from earlier sacrifices.

The predominant histopathological findings consisted of an inflammatory reaction with fibrosis. For most sites evaluated approximately 2 weeks after dosing, chronic active inflammation (moderate to severe) was observed and was characterized predominantly by macrophages and multinucleated giant cells as well as neutrophils, eosinophils and lymphoplasmacytic cells. A component of granulomatous inflammation (minimal to severe) was also present in occasional sites at 2 weeks post-dose but this change was more obvious in sites examined at longer intervals after dosing. At the Day 44 sacrifice for Group 1 animals, chronic active inflammation was observed at sites from the left leg (2 weeks post-dose), whereas granulomatous inflammation was seen in the right leg sites (6 weeks post-dose). In Group 4 animals sacrificed at Day 134, 2 of 4 animals presented with primarily granulomatous inflammation, whereas the remaining exhibited chronic active inflammation. Minimal to moderate degeneration/regeneration of skeletal muscle was also observed at some injection sites primarily at earlier sacrifices. Minimal to moderate edema was noted in some, but not all injection sites at the 2-week post-dose sacrifices (Days 18, 44, 74 and 134) and was slightly more prominent with multiple dosings. Occasional minimal injection site hemorrhage observed in a few animals was attributed to the dosing procedure.

The recovery sacrifices conducted 6 months after the last dosing and up to 10 months after the first dosing (Group 1), demonstrated that polymer degradation was progressive and that it was accompanied by evidence of reversal of local inflammation and fibrosis. At the recovery time points, chronic active inflammation was no longer present and a lower incidence and/or severity of granutomatous inflammation was observed. Similarly, minimal to moderately severe fibrosis, most apparent at earlier sacrifices had diminished significantly by the time of the recovery sacrifices.

Study title: Investigative Local Tolerance Study of Medisorb® Naltrexone in Dogs Following Intramuscular Administration ([redacted] 6403-123 Sponsor Reference No: AT-21-06)

In a previous study with beagle dogs (Alkermes Reference AT-21-05), an injection site reaction (a localized swelling) was clinically evident following intramuscular administration of Medisorb Naltrexone. In other species (rabbits, monkeys and humans), Medisorb Naltrexone did not produce similar reactions following intramuscular administration. The purpose of this investigative study was to further assess the injection site response following intramuscular administration of Medisorb Naltrexone in dogs. The study was designed to assess the following: 1) the effect of dose on the severity of injection site reactions to Medisorb Naltrexone, and 2) the effect of using a different lot of Medisorb Naltrexone to that used in study AT-21-05 on the severity of injection site reactions.

Four male and four female purebred beagle dogs approximately 7 to 10 months of age and 6.2 to 11.5 kg at study initiation, were utilized in the study. Medisorb Naltrexone was suspended in 1.2 mL of Medisorb Diluent just prior to administration (within approximately 5 to 10 minutes). The nominal microsphere concentration was approximately 280 mg/mL. For Group 3 (4 mL dose volume), three vials were pooled to deliver each microsphere dose. For Groups 1 and 2 (1 mL dose volume), one vial was used for each dose.

All animals survived to the scheduled necropsy. There were no adverse body weight changes during the study. Clinical effects were limited to injection site reactions, as described below. Following intramuscular injection of Medisorb Naltrexone, a clinically evident injection site reaction (a localized swelling) developed. This reaction was similar to that observed in the AT-21-05 dog study. The injection site reactions were dose related in that the onset of the reaction was earlier, the size of the swelling was larger and the reaction was more persistent in animals that received 4 mL compared to those that received a 1 mL dose. Swelling was noted in both Group 3 animals, beginning on Days 2 or 4 and was still observed on Day 15. Serosanguineous discharge was also present for one Group 3 animal (#H3 8505) on Day 10. Swelling was present in most animals in Groups 1 and 2 ranging between Days 7 and 15. Reddened skin was noted at a saline control injection site for one Group 3 animal on Day 7. No other findings were apparent for saline control injection sites.

At necropsy, residual test material was observed at most injection sites, either within the muscle and/or as a raised area in the adjacent subcutaneous region. Some injection sites exhibited a pale fluid filled pocket surrounding the test material within the muscle. In addition, tissue adhesion was present in the subcutaneous region between the skin and just above the muscle at the injection sites of some animals. Macroscopically, a greater amount of residual test material was observed for sites which received 4 mL compared to those that received 1 mL. No macroscopic findings were noted for saline control sites.

Study title: Investigative Local Tolerance Study of Medisorb® Naltrexone in

Rabbits Following Intramuscular Administration 6403-122 Sponsor Reference No: AT-21-07)

In a previous study with beagle dogs (Alkermes Reference AT-21-05), an injection site reaction (a localized swelling) was clinically evident following intramuscular administration of Medisorb Naltrexone. In other species (rabbits, monkeys and humans), Medisorb Naltrexone did not produce similar reactions following intramuscular administration. The purpose of this investigative study was to assess the local tolerance for Medisorb® Naltrexone when administered intramuscularly as a single dose or as two consecutive doses to rabbits. Three male and three female Hra:(NZW)SPF Rabbits, approximately 18 to 20 weeks of age and 2.5 to 3.0 kg at study initiation, were utilized in the study.. Medisorb Naltrexone was suspended in 1.2 mL of Medisorb Diluent just prior to administration (within approximately 5 minutes). The nominal microsphere concentration was approximately ng/mL and the target dose volume for each intramuscular injection was approximately 3.0 mL (a maximum intramuscular volume in rabbits). Two vials were pooled to deliver a single dose. The nominal dose per injection for Medisorb Naltrexone was approximately ng (approximately 294 mg of naltrexone). All animals were clinically normal throughout the study and survived to the scheduled necropsy. There were no adverse effects on body weights during the study. Intramuscular injection of Medisorb Naltrexone or Medisorb Diluent did not result in any adverse reactions at the local injection sites. A slight raised area was noted one hour after dosing for one animal each from Group 2 on Day 1 and Group 3 on Day 8. The raised areas in both animals did not persist and injection sites were clinically normal one day after dosing. No other test or vehicle control related injection site findings were noted clinically. The macroscopic findings were limited to the intramuscular injection sites. At necropsy, a light focus interpreted as residual test materials was observed at all intramuscular Medisorb Naltrexone dose sites. Findings for all injection sites consisted of a single, firm and tan area within the muscle. One or two distinct firm tan areas were observed within the muscle. A small light focus area of residual material on the surface of the muscle was also observed. There were no macroscopic findings for any of the vehicle control treated sites. There were no other macroscopic findings reported.

Genetic toxicology:

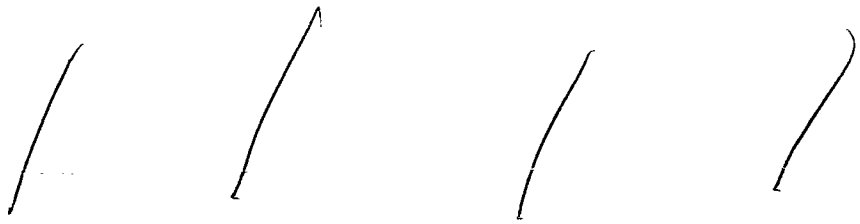
The Sponsor is referencing the genetic toxicology data that was evaluated for the Revia NDA and described in the approved label. The Sponsor also submitted their evaluation of the genetic testing results and copies of the published literature that served as the basis of the Revia genetic toxicology submission. Of the genetic toxicity studies conducted with naltrexone, only the Drosophila sex linked recessive lethal assay was positive. Specifically, a concentration of 10 mg/ml naltrexone was found to consistently increase recessive lethal frequency of the experimental groups 2-3x over their controls. Naltrexone was administered at 7.0 x 10.0 mg to the flies either by feeding (6 tests) in 10% sucrose or by injection (2 tests) in saline. Up to four broods, were examined covering several stages of spermatogenesis; sperm (Brood I)), spermatids (Brood II), spermatocytes (Brood III), and spermatogonid (Brood IV). The results showed a

consistent positive response at 10 mg/ml in the post meiotic cells. Both injection and feeding studies produced similar responses at this concentration.

Naltrexone was also tested in in vivo chromosome alteration studies with both somatic cell and germinal cell risk assessments completed. Doses of 90, 300, and 900 mg/kg were administered by gavage to rats. Animals were killed at 6, 24, and 48 hrs, and after an acute exposure and at 6 hrs after a 5 day subchronic exposure. No evidence for either clastogenicity or mitotic inhibition was obtained.

Naltrexone was evaluated for its ability to induce reciprocal translocations in mouse sperm cells using the Heritable Translocation Assay (HTA). Male mice were treated by oral gavage with 103, 343, and 1030 mg/kg/day for seven weeks. One hundred F_1 male progeny from crosses of the exposed males to unexposed females were mated sequentially to three sets of females and the embryos scored for evidence of semisterility. All semisterile and sterile males were examined cytologically. No confirmed translocation carriers were found in the control or treatment groups with the exception of TEM, the positive control. No non-disjunction in the experimental animals was found. Inconsistency was seen in the in vitro cytogentic evaluations, in the metaphase analysis. One study reported positive results in lymphoblast cells but a second study reported negative results in CHO cells. Similar inconsistency was observed in the Sister Chromatid Exchange assay, positive results in long-term human lymphoblast cells but negative results were reported in CHO cells. Anaphase analysis in vitro was the only consistent observation of a positive nature.

Secondary DNA repair tests with *E. coli* and WI-38 cells indicated weak non specific DNA damage. Urine analysis, which is not generally considered to be directly applicable to genetic risk evaluation, was found to be positive.



Carcinogenicity: No carcinogenicity study is done with the current formulation. Available carcinogenicity data fot the Naltrexone and PLG polymer is discussed later in this section.

Reproductive toxicology: The Revia NDA contains Segment I fertility and general reproductive toxicity study of naltrexone administered via gavage to Cr:Rats. The doses tested were 0, 20, 60, and 200 mg/kg/day. One female rat died (1/30) after 12 days of drug administration (high dose). The dam was described as thin in appearance. Necropsy findings indicated hemorrhage/brown color in the lungs, pitted surface in the

heart, and enlargements in thymus, mediastinal lymph nodes, and caecum. In addition a membrane-encased mass of soft, co animalsagulated white opaque material was found to fill the thoracic cavity and encase the lungs and heart and/or ungroomed coat, and vocalization was seen both in male and female. In males, dose related increase in excreted seminal plugs and hyperactivity/hypersensitivity, and in females chromorhinorrhea, were observed. Postmortem findings obtained at scheduled necropsy for both male and female rats indicated no drug related lesions. For F_0 generation female rats, the incidence of pseudopregnancy was significantly increased at high dose animals (7-20%) compared with the vehicle. The incidence for rats with any resorptions were 3 (27.3%), 3 (21.4%), 8 (66.7%), and 8 (80%) for vehicle, low, mid, high dose of naltrexone, respectively. This corresponds to average resorptions per litter of 0.3, 0.2, 1.2, and 2.6. All resorptions were early. No change in the average of corpora lutea, implantations litter sizes (live and dead), live fetuses, and the incidence of fetal gross external malformations was seen after naltrexone administration. Likewise, there were no alterations in fetal sex ratio or average fetal weights evident.

Natural delivery data showed one low dose dam and one mid dose dam (mated with vehicle control) each had no surviving litter beyond day 2 post parturition. This finding may have been either a drug-mediated effect on maternal behavior (poor maternal care, e.g. failing to remove placentas and umbilical cords from live born pups) or one secondary to pup mortality. Administration of naltrexone to dams mated with vehicle control males significantly increased the absolute incidence of stillborn pups. Although not significant, the average number of stillborn pups per litter and the incidence of delivering stillborn pups were increased in treated dams mated either with treated or vehicle control males. The incidence of dams delivering stillborn pups in vehicle control (both males and females untreated), and 0, low, mid and high dose naltrexonc groups was 2 (l4.3%), 1 (8.3%), 1 (7.7%), and 3 (27.3%), respectively with an average of 0.1, 02, 0.1 and 0.3 stillborn pups per litter. In these same respective groups, the incidence of stillbirth was 2 (1.4%), 2 (1.4%), 1 (0.6%), and 3 (2.0%). One (11.1%) of the vehicle control dams (mated with treated? males) and three (42.9%) of the treated dams (mated with vehicle control males) delivered stillborn pups; with averages 0.l and 0.9 stillbirths per litter, respectively; the incidence of stillborn pups in these same respective groups was 1 (0.8%) and 6 (6.2%). Necropsy of F_1 generation rats showed no abnormalities in pups that either died during the first 21 days postpartum or on scheduled sacrifice at day 21 postpartum. Possible drug related behavioral signs were seen in F_1 generation pups, such as weak appearance, coldness to touch, and absence of nursing.

At weaning, average body weights of the pups born to high dose dams were significantly lower than the vehicle control rats; however, during the post weaning to cohabitation period average body weights were similar for all groups. A significant increase in average body weights of F_1 generation male rats was observed at scheduled sacrifice. No changes in average body weights of F_1 generation female rats were found throughout the gestation period. No drug related postmortem findings were disclosed for F_1 generation males or females either at scheduled sacrifice or at caesarean sectioning. The reproductive capacity of F_1 generation rats (including mating, fertility, caesarean

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