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Fortsættes ...

DESCRIPTION

FIELD OF THE INVENTION

[0001] The present invention relates to an inappetence-controlling compound for use to control inappetence in animals. In particular, the current invention is directed to a novel use of an inappetence-controlling compound to potentially induce increased food intake and lean muscle growth in animals suffering from inappetence.

BACKGROUND OF THE INVENTION

[0002] Like humans, companion animals and livestock can suffer from inappetence and other disorders that can result in loss of lean muscle, an inability to participate in physical activity, and other undesirable outcomes for the companion animal and the owner. For instance, companion animals undergoing chemotherapy or afflicted with cancer, heart disease, or chronic kidney disease can suffer from inappetence, weight loss, general frailty, and/or cachexia. Moreover, the conditions or afflictions inducing the inappetence, weight loss, general frailty and/or cachexia can be at least partially exacerbated by the fact that the diets of these animals consist of fewer calories, vitamins, minerals, protein, and other necessary nutritional components, due to the decrease in food intake. As a result, these animals can exhibit a decrease in lean muscle, general weakness including a weakened immune system, possibly making the animals susceptible to infections.

[0003] Furthermore, although a general increase in food consumption could be helpful to animals, it is important that these animals do not experience a significant increase in deposition of adipose tissue. Accordingly, it would be desirable to have a composition and a method of using the composition to control inappetence while not inducing a significant increase in adipose tissue. Methods for increasing growth hormone levels, lean muscle mass and physical performance in human adults is discussed in White, J. Clin. Endocrin Metabolism; 2009, 94(4) 1198-1206. Macrocyclic compounds and selective androgen receptor modulators (SARMs) for the treatment of various conditions are described in US 2009/170757 and US 2010/249228, respectively. To date, there are no approved veterinary active pharmaceutical ingredients for the treatment of inappetence, unwanted weight loss, general frailty, wasting, and other related afflictions, complications, and maladies. As such, it is desired to have a compound or treatment for use in treating inappetence in animals, including companion animals.

[0004] It is also desirable to have a compound that increases lean muscle mass in companion animals, but this is especially desirable in livestock. Increasing lean muscle mass is important for the overall health of companion animals and livestock. A compound for controlling inappetence while building lean muscle mass has not been previous provided in the art. Thus, there is a need for a compound capable of decreasing inappetence while building lean muscle mass.

SUMMARY OF THE INVENTION

[0005] The present invention relates to the use of compositions of an inappetence-controlling compound in increasing lean muscle mass. In particular, the present invention provides a pharmaceutical composition for use in treating inappetence in a dog or cat, wherein the composition is for oral administration. The composition comprises a therapeutically effective amount of capromorelin comprising a concentration of between about 3.0 milligrams and about 4.5 milligrams of capromorelin per kilogram of body weight of the dog or cat and one or more pharmaceutically acceptable excipients or carries. The composition is formulated for administration at least once per day, wherein upon administration to the dog or cat, the dog or cat increases food intake by at least 50% when compared to no administration, and the lean muscle mass increases by at least 5% of the dog or cat when compared to no administration. Embodiments are provided by the claims. The inappetence-controlling compound comprises the ghrelin agonist, capromorelin and is administered to one or more companion animals (canines or felines). The composition comprising the ghrelin agonist is preferably provided in a therapeutically effective amount to treat inappetence-induced weight loss and to promote the addition of lean muscle mass. In some embodiments, the capromorelin-containing composition is administered to the companion animals through a variety of different pathways, including the oral cavity and optionally intravenously, and can be administered at least once or twice per day during the treatment regimen. The compound can be a pill or a liquid and can be flavored to mask any unpleasant or bitter taste. Moreover, in some embodiments, the capromorelin-containing composition is administered to the companion animal in conjunction with a chemotherapeutic regimen to at least partially prevent, inhibit, control, and/or alleviate inappetence associated with chemotherapy treatment. In another embodiment, the capromorelin-containing composition is administered as a part of food product, a treat, and/or a chew. For example, in a preferred embodiment the food product, treat, or chew is manufactured such that the capromorelin-containing composition is integrated into the product prior to reaching the consumer. Alternatively, the capromorelin-containing composition can be formulated as a liquid and sprayed on an animal food product, such as feed for livestock. In an alternate embodiment, the capromorelin-containing composition is added to a preformed food product, treat, or chew prior to feeding the companion animals.

[0006] A method for increasing lean muscle mass in a non-human animal is described. This method comprises the step of administering a capromorelin composition to a non-human animal. The method preferably also alleviates weight loss. The capromorelin composition is orally administered. The dose of the capromorelin composition is preferably a therapeutically effective dose of a capromorelin composition. The capromorelin composition may optionally include one or more flavoring agents or flavor-masking agents, however this is not required. The therapeutically effective dose of the capromorelin composition induces the non-human animal to consume greater amounts of food relative to those animals experiencing inappetence but not receiving the capromorelin composition or when compared to no food consumption by the animal. Further, the therapeutically effective dose of the capromorelin composition increases lean muscle mass relative to those animals not receiving the capromorelin composition. Lean muscle mass is increased by at least 5%. The concentration of capromorelin in the composition may be provided as 3.0 mg or 4.0 mg or values in-between, where the amount of capromorelin is per kilogram body weight of the animal. The capromorelin composition may comprise a sufficient amount of capromorelin to achieve a Cmax of around 150 nanograms of capromorelin or a metabolite thereof per milliliter of plasma at a Tmax of around two hours. Moreover, the capromorelin composition may be administered to the non-human animal in conjunction with a chemotherapeutic regimen to at least partially prevent, inhibit, control, and/or alleviate inappetence associated with the chemotherapy. Lean muscle mass is also increased.

[0007] Also described herein is a method of treating a non-human animal experiencing inappetence-induced weight loss. The method preferably comprises the steps of determining that the non-human animal is experiencing inappetence-induced weight loss and administering at least one dose of a capromorelin-containing composition to the non-human animal. The method may further include the step of observing an indicator (e.g., food consumption, body weight, leans muscle mass, levels of insulin-like growth factor, growth hormone, etc.) or obtaining a sample from the non-human animal and measuring an amount of the plasma marker (e.g., levels of insulin-like growth factor, growth hormone, etc.) in the sample. The dose of the capromorelin-containing composition can be adjusted in light of the amount of the plasma marker in the sample. The composition may be administered to the non-human animal until the animal gains a sufficient amount of weight. The plasma marker may be at least one of insulin-like growth factor-1, cortisol, capromorelin, and combinations thereof. For example, the dose of the capromorelin-containing composition may be increased to a level that induces an increase in the amount insulin-like growth factor-1 in the sample. The dose of the capromorelin-containing composition may be decreased to correspondingly decrease the amount of cortisol in the sample. The method may further comprise the step of obtaining a serum sample from the non-human animal, where the serum sample optionally can be analyzed for the level of certain plasma markers or changes in the level of certain plasma markers over time.

[0008] The present invention provides a pharmaceutical composition for treatment of inappetence in the non-human animals dogs or cats as defined in claim 1. The pharmaceutical composition comprises a therapeutically effective amount of capromorelin and at least one carrier or pharmaceutically acceptable excipient. Optionally, the pharmaceutical composition also includes at least one of a flavoring agent or a flavor-masking agent (e.g., a sweetening agent, a savory agent, a bittering agent, a souring agent, etc.). Moreover, in certain embodiments, the pharmaceutical composition includes either an emulsifying agent or a viscosifying agent, or combinations thereof. For example, the pharmaceutical composition preferably comprises about 0.01% to about 10% weight per volume of the emulsifying agent and/or the viscosifying agent, where values such as 0.03%, 0.2%, 0.4%, 0.6%, 0.8%, 1.0%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, and 10% weight per volume of the emulsifying agent and/or the viscosifying agent are envisioned. The concentration of capromorelin in the composition may be provided as 3.0 mg or 4.0 mg or values in-between, where the amount of capromorelin is per kilogram body weight of the animal. In an additional embodiment of the present invention, the pharmaceutical composition includes a carrier and the volume of the dose can be contained within a syringe for oral administration. In a preferred embodiment the capromorelin-containing composition comprises a sufficient amount of capromorelin to achieve a Cmax of around 150 nanograms of capromorelin or a metabolite thereof per milliliter of plasma at a Tmax of around two hours. The pharmaceutical composition of the present invention is formulated for oral administration. The pharmaceutical composition of the present invention may additionally be formulated for intravenous, intramuscular, and/or subcutaneous administration. In embodiments comprising a carrier, the carrier may comprise a salt or buffer solution that can be mixed with the capromorelin. An embodiment comprising a salt or buffer solution may be administered via intravenous or subcutaneous administration. The dose of the pharmaceutical composition of the present invention is provided in a dose of between about 3 and about 4.5 milligrams of capromorelin per kilogram of body weight. The dose of the pharmaceutical composition of the present invention is administered to the non-human animal at least once a day or at least twice per day for a predetermined time period, while further subsequent does are envisioned. In one embodiment, the predetermined time period for administration is about seven days.

[0009] Also described is a further method for treating weight loss in a companion animal. Preferably, a method of building lean muscle mass in an animal or livestock is also described. The method preferably includes the steps of determining that the companion animal is experiencing weight loss and administering at least one dose of a capromorelin-containing composition to the animal. The method may include the step of administering the composition to the animal using a syringe. The method optionally includes a further step of assessing one or more plasma markers of the animal that are associated with weight loss. Preferably, the dose of the capromorelin-containing composition is adjusted in view of the assessment of the one or more plasma markers. The plasma markers preferably include, but are not limited to, insulin like growth factor-1, cortisol, capromorelin, and combinations thereof. For example, the dose of the capromorelin-containing composition can be increased or decreased depending on the level of the plasma marker present in the animal. The pharmaceutical composition of the present invention is administered to the companion animal at least once or twice per day. Further, the concentration of capromorelin in the composition may be provided as 3.0 mg or 4.0 mg or values in-between, where the amount of capromorelin is per kilogram body weight of the animal. The capromorelin-containing composition may comprise a sufficient amount of capromorelin to achieve a Cmax of around 150 nanograms of capromorelin or a metabolite thereof per milliliter of plasma at a Tmax of around two hours. The composition is administered to the companion animal by oral administration. Optionally, an indicator is assessed in order to determine if the animal requires subsequent doses or an increased amount of the capromorelin- containing composition. The indicators include, but are not limited to, change in weight, weight gain, weight loss, change in food intake, and increase or decrease in lean muscle mass.

[0010] Also disclosed herein is a further method for treating non-human animals with a pharmaceutical composition that can induce a healthy weight gain in the non-human animals, where non-human animals include, but are not limited to, companion animals. For example, efficient and/or improved weight gain is preferably induced after the pharmaceutical composition of the present invention is administered to non-human animal. The pharmaceutical composition is administered to the non-human animals via oral administration and optionally one or more other routes of administration, preferably selected from the group consisting of, but not limited to, intravenous, or as an implant disposed within the cutaneous or muscle tissue of the livestock. Alternatively, the pharmaceutical composition can be mixed with feed provided to the non-human animals for sustenance. Further alternatively, the composition can be administered as a pill, a tablet, an implant, a patch, a film, an injection, a suppository, transdermally, spray for food products, liquid filled syringe, etc., or combinations thereof. The composition may be administered to the livestock as a portion of a food product (e.g., livestock feed) such that the normal feeding process results in administration of the composition to the livestock. The concentration of capromorelin in the composition may be provided as 3.0 mg or 4.0 mg, or values in-between, where the amount of capromorelin is per kilogram body weight of the animal.

[0011] The pharmaceutical composition of the present invention is provided for oral administration suitable for the treatment of inappetence in dogs or cats. The oral pharmaceutical composition includes a therapeutically effective amount of capromorelin. The concentration of capromorelin may comprise amounts of about 3.0 mg and about 4.0 mg of capromorelin per kilogram of body weight of the dogs or cats.

[0012] A method for treating inappetence in a non-human animal is also described. The method preferably includes the steps of administering a pharmaceutical composition to the non-human animal at least once per day until sufficient weight gain occurs. In some aspects, sufficient weight gain includes a 5%, 10%, or 20% increase in body weight relative to the body weight of the non-human animal prior to receiving the pharmaceutical composition. Preferably, the pharmaceutical composition includes approximately 3 milligrams of capromorelin per kilogram of body weight of the non-human animal.

[0013] In addition, a method of maintaining a body weight in a companion animal is also disclosed. The method preferably includes the steps of administering an amount of a capromorelin-containing composition to the companion animal and monitoring the weight of the companion animal to determine that the body weight of the animal is being maintained. The composition may be orally administered or administered as a part of a chew, a treat, or a food product.

[0014] A method for achieving desired pharmokinetic values by administration of a pharmaceutical composition and a carrier is also disclosed. The composition administered as part of the method preferably includes a sufficient amount of capromorelin to achieve a C_{max} of around 150 nanograms of capromorelin or a metabolite thereof per milliliter of plasma at a T_{max} of around 2 hours. Alternatively, the composition includes a sufficient amount of capromorelin to achieve a C_{max} of around 905 nanograms of capromorelin or a metabolite thereof per milliliter of plasma at a T_{max} of around 25 minutes. Preferably, the Tmax is from about twenty-five minutes to 2 hours, where the Tmax may be 25 minutes, 30 minutes, 1 hour, or 2 hours. The Cmax preferably ranges from about 100 ng/mL to about 1000 ng/mL.

[0015] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs at the time of filing. If specifically defined, then the definition provided herein takes precedent over any dictionary or extrinsic definition. Further, unless otherwise required by context, singular terms shall include pluralities, and plural terms shall include the singular. Herein, the use of "or" means "and/or" unless stated otherwise.

<u>BRIEF DESCRIPTION OF THE DRAWINGS</u>

[0016]

FIG. 1 is a line graph depicting a comparison between a first capromorelin treatment regimen (3 milligrams of capromorelin per kilogram of body weight administered twice per day), a second capromorelin treatment regimen, and a negative control (6 milligrams of capromorelin per kilogram of body weight administered once per day).

FIG. 2 is a line graph depicting the food intake data of **FIG. 1** from only male beagles.

FIG. 3 is a line graph depicting the food intake data of **FIG. 1** from only female beagles.

FIG. 4 is a line graph depicting a comparison between the first capromorelin treatment regimen, the second capromorelin treatment regimen, and the negative control.

FIG. 5 is a line graph depicting a comparison between the first capromorelin treatment regimen, the second capromorelin treatment regimen, and the negative control.

FIG. 6 is a line graph depicting the weight gain from baseline data depicted in **FIG. 5** from only male beagles.

FIG. 7 is a line graph depicting the weight gain from baseline data depicted in **FIG. 5** from only female beagles.

FIG. 8 is a line graph depicting measurements of capromorelin concentration in the serum in male and female dogs treated with the first treatment regimen, the second treatment regimen, and the negative control.

FIG. 9 is a line graph depicting the serum concentration of capromorelin depicted in **FIG. 8** from only male beagles.

FIG. 10 is a line graph depicting the serum concentration of capromorelin depicted in **FIG. 8** from only female beagles.

FIG. 11 is a line graph depicting measurements of insulin-like growth factor-1 concentration in the serum in male and female dogs treated with the first treatment regimen, the second treatment regimen, and the negative control on a first day of treatment.

FIG. 12 is a line graph depicting measurements of insulin-like growth factor-1 concentration in the serum in male and female dogs treated with the first treatment regimen, the second treatment regimen, and the negative control on a second day of treatment.

FIG. 13 is a line graph depicting measurements of insulin-like growth factor-1 concentration in the serum in male and female dogs treated with the first treatment regimen, the second treatment regimen, and the negative control on a fourth day of treatment.

FIG. 14 is a line graph depicting measurements of insulin-like growth factor-1 concentration in the serum in male and female dogs treated with the first treatment regimen, the second treatment regimen, and the negative control on a seventh day of treatment.

FIG. 15 is a bar graph depicting measurements of insulin-like growth factor-1 concentration in the serum in male and female dogs treated with the first treatment regimen, the second treatment regimen, and the negative control three days after completion of the treatment regimens.

FIG. 16 is a line graph depicting measurements of growth hormone concentration in the serum in male and female dogs treated with the first treatment regimen, the second treatment regimen, and the negative control on a first day of treatment.

FIG. 17 is a line graph depicting measurements of growth hormone concentration in the serum in male and female dogs treated with the first treatment regimen, the second treatment regimen, and the negative control on a second day of treatment.

FIG. 18 is a line graph depicting measurements of growth hormone concentration in the serum in male and female dogs treated with the first treatment regimen, the second treatment regimen, and the negative control on a fourth day of treatment.

FIG. 19 is a line graph depicting measurements of growth hormone concentration in the serum in male and female dogs treated with the first treatment regimen, the second treatment regimen, and the negative control on a seventh day of treatment.

FIG. 20 is a bar graph depicting measurements of growth hormone concentration in the serum in male and female dogs treated with the first treatment regimen, the second treatment regimen, and the negative control three days after completion of the treatment regimens.

FIG. 21 is a line graph depicting measurements of cortisol concentration in the serum in male and female dogs treated with the first treatment regimen, the second treatment regimen, and the negative control on a first day of treatment.

FIG. 22 is a line graph depicting measurements of cortisol concentration in the serum in male and female dogs treated with the first treatment regimen, the second treatment regimen, and the negative control on a second day of treatment.

FIG. 23 is a line graph depicting measurements of cortisol concentration in the serum in male and female dogs treated with the first treatment regimen, the second treatment regimen, and the negative control on a seventh day of treatment.

FIG. 24 is a bar graph depicting measurements of cortisol concentration in the serum in male and female dogs treated with the first treatment regimen, the second treatment regimen, and the negative control three days after completion of the treatment regimens.

FIG. 25 is a line graph depicting the results of experiments testing the first capromorelin treatment regimen in combination with a positive control (i.e., intravenous administration) and two flavoring formulations as measured by capromorelin concentration in the serum of male and female beagles over eight hours.

FIG. 26 is a line graph depicting the results of experiments testing the first capromorelin treatment regimen in combination with an additional three flavoring formulations as measured by capromorelin concentration in the serum of male and female beagles over eight hours.

FIG. 27 is a bar graph depicting serum concentrations of insulin-like growth factor-1 in the male and female beagles from the experiments with results depicted in **FIGS. 25** and **26.**

FIG. 28 is a line graph depicting the results of experiments testing the first capromorelin treatment regimen in combination with four flavoring formulations as measured by capromorelin concentration in the serum of male and female beagles over eight hours.

FIG. 29 is a bar graph depicting serum concentrations of insulin-like growth factor-1 in the male and female beagles from the experiments with results depicted in **FIG. 28.**

FIG. 30 is a bar graph depicting the overall food consumed by beagles in response to receiving different concentrations and treatment regimens of a capromorelin composition.

FIG. 31 is a line graph depicting the daily average food consumption by beagles in response to receiving different concentrations and treatment regimens of a capromorelin composition.

FIG. 32 is a line graph depicting the average body weight of beagles that have received different concentrations and treatment regimens of a capromorelin composition.

FIG. 33 is a line graph depicting measurements of capromorelin concentration in the serum of beagles on day 1 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 34 is a line graph depicting measurements of capromorelin concentration in the serum of beagles on day 7 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 35 is a line graph depicting measurements of insulin-like growth factor-1 concentration in the serum of beagles on day 1 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 36 is a line graph depicting measurements of insulin-like growth factor-1 concentration in the serum of beagles on day 4 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 37 is a line graph depicting measurements of insulin-like growth factor-1 concentration in the serum of beagles on day 7 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 38 is a bar graph depicting measurements of insulin-like growth factor-1 concentration in the serum of beagles after seven days of treatment with different concentrations and treatment regimens of a capromorelin composition and three days without treatment (*i.e.*, Day 10).

FIG. 39 is a line graph depicting measurements of growth hormone concentration in the serum of beagles on day 1 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 40 is a line graph depicting measurements of growth hormone concentration in the serum of beagles on day 4 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 41 is a line graph depicting measurements of growth hormone concentration in the serum of beagles on day 7 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 42 is a bar graph depicting measurements of growth hormone concentration in the serum in beagles after seven days of treatment with different concentrations and treatment regimens of a capromorelin composition and three days without treatment (*i.e.*, day 10).

FIG. 43 is a line graph depicting measurements of cortisol concentration in the serum of beagles on day 1 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 44 is a line graph depicting measurements of cortisol concentration in the serum of beagles on day 4 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 45 is a line graph depicting measurements of cortisol concentration in the serum of beagles on day 7 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 46 is a bar graph depicting measurements of cortisol concentration in the serum in beagles after seven days of treatment with different concentrations and treatment regimens of a capromorelin composition and three days without treatment (*i.e.*, Day 10).

FIG. 47 is a line graph depicting serum concentrations of capromorelin over twelve hours in cats that have received an intravenous injection of 0.75 milligrams of capromorelin per kilogram of body weight.

FIG. 48 is a line graph depicting serum concentrations of capromorelin over twelve hours in cats that have received an oral administration of 3 milligrams of capromorelin per kilogram of body weight.

FIG. 49 is a bar graph depicting serum concentrations of insulin-like growth factor-1 in cats that have received the intravenous and oral administrations of capromorelin.

FIG. 50 is a line graph depicting the daily average food consumption by cats in response to receiving different concentrations and treatment regimens of a capromorelin composition.

FIG. 51 is a bar graph depicting the average body weight of cats that have received different concentrations and treatment regimens of a capromorelin composition.

FIG. 52 is a line graph depicting measurements of capromorelin concentration in the serum of cats on day 1 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 53 is a line graph depicting measurements of capromorelin concentration in the serum of cats on day 4 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 54 is a bar graph depicting serum concentrations of capromorelin in cats three days after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 55 is a line graph depicting measurements of insulin-like growth factor-1 concentration in the serum of cats on day 1 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 56 is a line graph depicting measurements of insulin-like growth factor-1 concentration in the serum of cats on day 4 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 57 is a bar graph depicting serum concentrations of insulin-like growth factor-1 in cats after seven days of treatment with different concentrations and treatment regimens of a capromorelin composition and three days without treatment (*i.e.*, day 10).

FIG. 58 is a line graph depicting measurements of cortisol concentration in the serum of cats on day 1 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 59 is a line graph depicting measurements of cortisol concentration in the serum of cats on day 4 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 60 is a bar graph depicting serum concentrations of cortisol in cats three days after seven days of treatment with different concentrations and treatment regimens of a capromorelin composition and three days without treatment (*i.e.*, day 10).

FIG. 61 is a line graph depicting measurements of food consumed by animals over the course of an experiment in which the animals were treated with different concentrations and treatment regiments of a capromorelin composition.

FIG. 62 is a line graph depicting serum concentrations of capromorelin in animals on Day 1 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 63 is a line graph depicting serum concentrations of capromorelin in animals on Day 7 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 64A is a line graph depicting serum concentrations of IGF-1 in animals on Day 1 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 64B is a line graph depicting serum concentrations of IGF-1 in animals on Day 4 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 65 is a line graph depicting serum concentrations of IGF-1 in animals on Day 7 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 66 is a bar graph depicting serum concentrations of IGF-1 in animals after seven days of treatment with a capromorelin composition and two days without treatment (*i.e.*, day 9).

FIG. 67 is a line graph depicting serum concentrations of growth hormone in animals on Day 1 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 68 is a line graph depicting serum concentrations of growth hormone in animals on Day 4 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 69 is a line graph depicting serum concentrations of growth hormone in animals on Day 7 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 70 is a bar graph depicting serum concentrations of growth hormone in animals after seven days of treatment with treatment regimens of a capromorelin composition and two days without treatment (*i.e.*, day 9).

FIG. 71 is a line graph depicting serum concentrations of cortisol in animals on Day 1 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 72 is a line graph depicting serum concentrations of cortisol in animals on Day 4 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 73 is a line graph depicting serum concentrations of cortisol in animals on Day 7 after being treated with different concentrations and treatment regimens of a capromorelin composition.

FIG. 74 is a bar graph depicting serum concentrations of cortisol in animals after seven days of treatment with treatment regimens of a capromorelin composition and two days without treatment (*i.e.*, day 9).

FIG. 75 is a bar graph depicting mean weight gain in animals during a five-day study comparing two formulations of a capromorelin-containing composition.

FIG. 76 is a line graph depicting food consumption by animals during a five-day study comparing two formulations of a capromorelin-containing composition.

FIG. 77 a line graph depicting mean serum concentrations of capromorelin in animals on Day 5 after being treated with two formulations of a capromorelin-containing composition.

FIG. 78 is a bar graph depicting mean serum IGF-1 concentrations in animals on Day 5 after being treated with two formulations of a capromorelin-containing composition.

FIG. 79 is a chart depicting acceptability observations over a six-day period in cats that received an oral administration of a capromorelin-containing composition.

FIG. 80 is a chart depicting acceptability observations over a six-day period in cats that received an oral administration of a capromorelin-containing composition.

FIG. 81 is a chart depicting acceptability observations over a six-day period in cats that received an oral administration of a capromorelin-containing composition.

FIG. 82 is a chart depicting acceptability observations over a six-day period in cats that received an oral administration of a capromorelin-containing composition.

FIG. 83 is a bar graph depicting body weight measurement of animals over the course of an experiment in which the animals were treated with different formulations of a capromorelin composition.

FIG. 84 is a chart depicting measurements of food intake prior to and during over a six-day period in cats that received an oral administration of a capromorelin-containing composition.

FIG. 85 is a chart depicting measurements of food intake (in grams) prior to and during over a six-day period in cats that received an oral administration of a capromorelin-containing composition.

FIG. 86 is a line graph depicting measurements of food consumed by animals over the course of an experiment in which the animals were treated with different formulations of a capromorelin composition.

FIG. 87 is a line graph depicting serum concentrations of capromorelin in animals on Day 6 after being treated with different formulations a capromorelin composition.

FIG. 88 is a bar graph depicting serum concentrations of IGF-1 in animals on Day 6 after being treated with different formulations of a capromorelin composition.

FIG. 89 is a line graph depicting body weight measurement of animals over the on Days 1 and 8 of an experiment in which the animals were treated with different doses of a formulation of a capromorelin composition.

FIG. 90 is a bar graph depicting body weight measurement of animals over the on Days 1 and 8 of an experiment in which the animals were treated with different doses of a formulation of a capromorelin composition.

FIG. 91 is a line graph depicting measurements of food consumed by animals over the course of an experiment in which the animals were treated with different doses of a formulation of a capromorelin composition.

FIG. 92 is a line graph depicting the correlation between changes in food consumption versus changes in body weight for the experiments of FIGS. 89-91.

FIG. 93 a line graph depicting the daily average food consumption by cats in response to receiving different concentrations of a capromorelin composition.

FIG. 94 is a bar graph depicting the average body weight of cats that have received different concentrations of a capromorelin composition.

FIG. 95 is a line graph depicting measurements of capromorelin concentration in the serum of cats on day 1 after being treated with different concentrations of a capromorelin composition.

FIG. 96 is a line graph depicting measurements of capromorelin concentration in the serum of cats on day 10 after being treated with different concentrations of a capromorelin composition.

FIG. 97 is a line graph depicting measurements of IGF-1 concentration in the serum of cats on day 1 after being treated with different concentrations of a capromorelin composition.

FIG. 98 is a line graph depicting measurements of IGF-1 concentration in the serum of cats on day 10 after being treated with different concentrations of a capromorelin composition.

FIG. 99 is a bar graph depicting measurements of IGF-1 concentration in the serum of cats after ten days of treatment with different concentrations of a capromorelin composition and two days without treatment (*i.e.*, day 12).

FIG. 100 is a bar graph depicting measurements of IGF-1 concentration in the serum of cats after ten days of treatment with different concentrations of a capromorelin composition and five days without treatment (*i.e.*, day 15).

FIG. 101 is a line graph depicting measurements of cortisol concentration in the serum of cats on day 1 after being treated with different concentrations of a capromorelin composition.

FIG. 102 is a line graph depicting measurements of cortisol concentration in the serum of cats on day 10 after being treated with different concentrations of a capromorelin composition.

FIG. 103 is a bar graph depicting measurements of cortisol concentration in the serum of cats after ten days of treatment with different concentrations of a capromorelin composition and two days without treatment (*i.e.*, day 12).

FIG. 104 is a bar graph depicting measurements of cortisol concentration in the serum of cats after ten days of treatment with different concentrations of a capromorelin composition and five days without treatment (*i.e.*, day 15).

FIG. 105 is a line graph depicting measurements of capromorelin concentration in the serum of cats on day 0 (i.e., the first day of experimentation) after receiving an intravenous administration of capromorelin at a concentration of 0.75 mg/kg.

FIG. 106 is a line graph depicting measurements of capromorelin concentration in the serum of cats on day 0 (i.e., the first day of experimentation) after receiving an oral administration of capromorelin at a concentration of 3.0 mg/kg.

FIG. 107 is a bar graph depicting measurements of IGF-1 concentration in the serum of cats on day 0 (i.e., the first day of experimentation) after receiving different treatments of a capromorelin composition.

FIG. 108 is a table depicting pharmacokinetic data in cats that received an intravenous administration of a capromorelin composition.

FIG. 109 is a table depicting pharmacokinetic data in cats that received an oral administration of a capromorelin composition.

FIG. 110 is a bar graph depicting body weight measurements of cats that have been exposed to different treatments using a capromorelin composition over the course of a fourteen day experiment.

FIG. 111 is a line graph depicting food intake measurements over the course of a fourteen day experiment.

FIG. 112 is a line graph depicting measurements of capromorelin concentration in the serum of cats on day 0 (i.e., the first day of experimentation) after receiving either an intravenous administration of capromorelin at a dose of 0.75 mg/kg or a subcutaneous administration of capromorelin at a dose of 2 mg/kg.

FIG. 113 is a line graph depicting measurements of capromorelin concentration in the serum of cats on day 13 (i.e., the fourteenth day of experimentation) after receiving subcutaneous administrations of capromorelin at a dose of 2 mg/kg for 14 days.

FIG. 114 is a bar graph depicting measurements of IGF-1 concentration in the serum of cats on day 0 (i.e., the first day of experimentation) after receiving an intravenous administration of a capromorelin composition.

FIG. 115 is a bar graph depicting measurements of IGF-1 concentration in the serum of cats on days 0 (i.e., the first day of experimentation) and 13 (i.e., the fourteenth day of experimental) after receiving a subcutaneously administered capromorelin treatment regimen.

FIG. 116 is a line graph depicting measurements of capromorelin concentration in the serum of cats on day 0 (i.e., the first day of experimentation) after receiving either an intravenous administration of capromorelin at a dose of 0.75 mg/kg or a subcutaneous administration of capromorelin at a dose of 2 mg/kg.

FIG. 117 is a table depicting pharmacokinetic data in cats that received an intravenous administration of a capromorelin composition.

FIG. 118 is a table depicting pharmacokinetic data in cats that received a subcutaneous administration of a capromorelin composition.

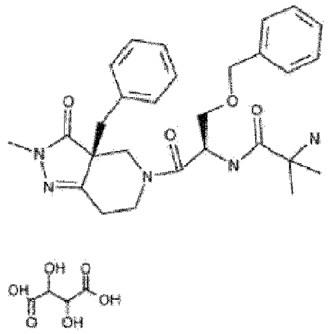
DETAILED DESCRIPTION OF THE INVENTION

[0017] The compositions provided herein can be used for treatment, prevention, alleviation, and/or control of inappetence-induced weight loss in animals as defined in claim 1. The animals may be companion animals. Preferably, upon administration of the pharmaceutical composition of the present invention to a non-human animal the composition induces the production of one or more molecules that can cause the non-human animal to experience a hunger sensation. A method of increasing the production of one or more molecules that cause the animal to experience a hunger sensation is described. The method includes the step of administering a composition comprising capromorelin to an animal exhibiting inappetence.

[0018] A method for increasing lean muscle mass is also described. The method includes the step of administering a composition comprising capromorelin. Preferably, administration of the capromorelin-containing composition to a non-human animal induces one or more molecules that increase lean muscle mass. The food consumed as a result of the increased hunger sensation, resulting from administration of the capromorelin-containing composition, may be used in building lean muscle in lieu of a significant amount of adipose deposition. The composition of the present invention increases lean muscle mass by at least 5%, at least 10% or at least 15%. The pharmaceutical composition of the present invention comprises the ghrelin agonist capromorelin. Preferably, the pharmaceutical composition of the present invention includes at least one flavoring agent or a flavor-masking agent. The present invention is based on, at least in part, the finding that treatment of companion animals and livestock afflicted with inappetence-induced weight loss that receive one or more doses of the pharmaceutical composition described herein exhibit increased body weights, increased food consumption, and increased serum levels of one or more relevant proteins and/or other molecules, such as, but not limited to, insulin-like growth factor-1 (hereinafter "IGF-1"), growth hormone (hereinafter "GH"), and/or cortisol.

[0019] Further, a method of increasing serum levels of one or more relevant proteins and/or other molecules, used as plasma markers, such as, but not limited to insulin-like growth factor-1 (hereinafter "IGF-1"), growth hormone (hereinafter "GH"), and/or cortisol, comprising the step of administering a composition comprising capromorelin to an animal in need thereof, is described. The method may further comprise the step of determining the concentration of the plasma marker in the blood of the animal and monitoring the concentration of the plasma marker in the blood stream of the animal over time. Preferably, the method further includes the step of administering the capromorelin composition to the animal until a point where the concentration of the plasma markers in the blood increase relative to the initial concentration of the plasma marker in the animal.

[0020] The compositions of the present invention provided for the management of inappetence-induced weight loss include capromorelin, which includes any racemates, polymorphs, enantiomers, salts, and any other suitable pharmaceutically acceptable derivative of capromorelin. For example, in some aspects, the composition can include any active ingredient disclosed in U.S. Patent Nos. 6,482,825, 6,852,722, or 6,306,875. In particular, capromorelin is also known as 2-amino-N-[2-(3aR-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-yl-1R-benzyloxymethyl-2-oxo-ethyl]-isobutyramid-L-tartate. In addition, capromorelin has the following chemical structure.



[0021] In some companion animals and livestock, ghrelin is a hormone that is produced predominantly in the stomach and other portions of the alimentary canal and is the endogenous ligand of the ghrelin receptor, which is also known as the growth hormone secretagogue receptor (GHS-R). GHS-Rs can be expressed in multiple tissues, including neurological tissues, such as, but not limited to the pituitary gland and the hypothalamus. Ghrelin exhibits a relatively short half-life (e.g., approximately ten minutes) in the blood of animals, including companion animals and livestock, and begins accumulating in the blood shortly after completion of a meal. Accordingly, the longer the period of time since the last meal of the animal, the greater the concentration of ghrelin will be in the animal's blood. Moreover, once sufficient amounts of ghrelin bind the GHS-Rs in the hypothalamus, the animals begin feeling hunger, which stimulates food intake.

[0022] In addition to binding GHS-Rs in the hypothalamus, circulating ghrelin can also bind GHS-Rs in the pituitary gland to stimulate the release of GH. Furthermore, in addition to the release of GH originating from ghrelin binding the GHS-Rs in the pituitary gland, animals naturally secrete GH throughout the circadian rhythm cycle. Although this natural release remains constant throughout the life of the animal, the magnitude of the releases of GH diminishes over the course of the life of the animal. The released GH can circulate through the companion animal, which can induce the production and secretion of IGF-1 into circulation. The increase in circulating IGF-1 levels can induce lean muscle growth, which can be correlated with increased strength, stamina, and well-being. Moreover, in addition to inducing GH production, ghrelin can also induce production of cortisol, which has been shown to increase the likelihood of adipose deposition of adipose tissue.

[0023] When administered to an animal, such as a companion animal or livestock, capromorelin can function as a GHS-R agonist to control inappetence, weight loss, anorexia, and/or cachexia. Specifically, the administration of capromorelin can induce appetite stimulation and secretion of GH. Unlike endogenous ghrelin, capromorelin typically exhibits a longer half-life in circulation and unlike exogenous ghrelin, capromorelin can be orally administered. Capromorelin compositions are orally administered to the animals. However, as discussed in greater detail below, capromorelin compositions can also be administered via other routes, including, but not limited to, (e.g., intravenous, intraperitoneal, intramuscular, intrathecal, subcutaneous, and any other suitable route of administration).

[0024] The pharmacologic mechanism of action of capromorelin operates similar to the mechanism of ghrelin. For example, after administration, capromorelin binds to GHS-R, a G-protein-coupled receptor that can activate protein kinase C and stimulate GH release from the pituitary gland, which can result in the elevation of circulating GH. GH can then cause the release of IGF-1, which may induce negative feedback to the pituitary gland, thereby reducing or inhibiting GH release. As previously mentioned, IGF-1 also acts to increase lean body mass. Moreover, the administration of capromorelin can supplement the diminishing natural release of GH over the life of the animal. In addition, the negative feedback arising from the circulating IGF-1 can also reduce levels of circulating cortisol, thereby at least partially reducing the likelihood of increased adipose deposition.

[0025] In some embodiments, capromorelin is included within the inappetence-controlling composition in one or more concentrations. In some of the following embodiments, the capromorelin is at least partially dissolved in an aqueous solvent (e.g., deionized and/or purified water). In some embodiments, the concentration of capromorelin is preferably at least one of 3.0 mg/kg, 4.0 mg/kg, and any concentrations there between. In addition, in some embodiments, as described in further detail below, capromorelin can be at least partially dissolved in an aqueous solvent and the pharmaceutical composition can comprise other non-active ingredients, such as preservatives, emulsifying and/or viscosifying agents, sweeteners, flavoring agents, flavor-masking agents, and/or other carrier materials.

[0026] Moreover, in some embodiments, the concentration of capromorelin within the inappetence-controlling composition is at least partially dependent upon the route of administration and/or the number of times in a pre-determined time period the composition is administered to companion animals or livestock. The inappetence-controlling composition is orally administered one or more times per day. For example, the composition can be administered as a solution, a solid, or a preferred viscous liquid formulation. Correspondingly, the greater number of times per day the composition is administered to the companion animals, the lesser the amount of capromorelin is needed to produce desired results.

[0027] By way of example only, in some embodiments, dosing of the animals can be divided into multiple treatment regimens, depending on severity of the indications of the animal. In some embodiments, an animal may receive a 3 mg/kg, 3.5 mg/kg, 4 mg/kg or 4.5 mg/kg dosing regimen. Moreover, some of these dosing regimens may be in the form of solid or liquid formulations. For example, some animals (e.g., dogs) can receive one or more solid oral formulations, such as inappetence-controlling composition formulated for administration via capsules, gel caps, gel-like liquids (i.e., viscous liquids), pills, caplets, tablets, or other solid, liquid, or nebulized forms. For example, the capsules or other forms can include different concentrations of capromorelin to enable dosing of animals of a plurality of weights (i.e., because the capromorelin dosing is at least partially dependent on the weight of the animal). By way of example only, in some embodiments, capsules can be manufactured with a capromorelin concentration of 20 mg per capsule, 35 mg per capsule, and 75 mg per capsule. As a result, different combinations of capsules can be administered to the animals in need of treatment to provide the necessary dose of capromorelin to the animal. By way of example only, an animal weighing approximately 15 kg and placed on a 3 mg/kg treatment regimen would require about 45 mg of capromorelin per dose. Accordingly, the animal can receive two 20 mg capsules to provide a dose of capromorelin that is close to 45 mg (i.e., with between 5 and 10 milligrams of the desired dose based on animal weight or within a dosing band). Other animals of other sizes and placed on other treatment regimens can be similarly treated to provide an efficacious amount of capromorelin.

[0028] In a preferred embodiment, the dose of capromorelin comprises a sufficient amount to achieve a Cmax of around 150 nanograms of capromorelin or a metabolite thereof per milliliter of plasma at a Tmax of around 2 hours. In an alternate embodiment, the dose of capromorelin comprises a sufficient amount to achieve a Cmax of around 905 nanograms of capromorelin or a metabolite thereof per milliliter of plasma at a Tmax of around twenty-five minutes. The Tmax can occur in individual animals preferably at a 30 minute, 1 hour or 2 hour time interval, with the range being from about 30 minutes to 2 hours to reach Tmax. Preferably, the Cmax is between 100 ng/mL to 1000 ng/, however, this varies in different animals, therefore the Cmax could be even higher. Preferably, the Cmax is about 100 ng/mL, about 200 ng/mL, about 300 ng/mL, about 400 ng/mL, about 500 ng/mL, about 600 ng/mL, about 700 ng/mL, about 800 ng/mL, about 900 ng/mL, and about 100 ng/mL.

[0029] In addition, some embodiments of the inappetence-controlling composition comprise liquid oral formulations that can be used in a manner similar to the above solid oral formulation. Additionally, the liquid formulations can be administered in a syringe or sprayed on animal food, treats, or chews. For example, the liquid formulations can be prepared to comprise the following concentrations of capromorelin within the liquid formulation: 20 mg/mL, 30 mg/mL, 40 mg/mL, or 60 mg/mL. Similar to the solid formulations discussed above, the different concentrations of the liquid formulation can be used to enable dosing of animals of a plurality of weights (i.e., because the capromorelin dosing is at least partially dependent on the weight of the animal). As a result, different volumes of the different solutions can be administered to the animals to provide the required dose of capromorelin. By way of example only, an animal weighing approximately 15 kg and placed on a 3 mg/kg treatment regimen would require about 45 mg of capromorelin per dose. Accordingly, the animal can receive about 2.3 mL of the 20 mg/mL solution or 1.1 mL of the 40 mg/mL solution to provide a dose of capromorelin that is close to 45 mg. Similarly, if the same animal was placed on a 4.5 mg/kg treatment regimen, the animal could receive 2.3 mL of the 30 mg/mL solution or 1.1 mL of the 60 mg/mL solution to provide a dose of capromorelin close to 67.5 mg (i.e., the dose a 15 kg animal should receive on this treatment regimen). Other animals of other sizes and placed on other treatment regimens can be similarly treated to provide an efficacious amount of capromorelin.

[0030] The inappetence-controlling composition is orally administered. Optionally, the inappetence-controlling composition is additionally parenterally and/or topically administered. For example, in some embodiments, the inappetence-controlling composition can be orally formulated in a liquid and/or a solid formulation so that the composition can be administered using at least one of a spray, a syringe, a pill, a tablet, a caplet, a gel-cap, or an otherwise liquid-based administration scheme.

[0031] In some embodiments, the composition can be administered to the animal as a part of a daily feeding regimen. For example, the composition can be formulated to be mixed with the feed or other food product intended to be consumed by the animal such that, as the animal consumes its daily food intake (e.g., kibble or soft food), the animal is also consuming the composition. In particular, the composition can be formulated as a liquid or a powder so that prior to feeding the animal, the formulation can be applied (e.g., sprayed) to the food for consumption by the animal. Moreover, in some embodiments, the food provided to the animals (e.g., companion animals) can be provided with the pharmaceutical composition already admixed with the food product such that the animal's caretaker need only provide the medicated food to the animal.

[0032] In some embodiments, other food products provided to the animal (e.g., companion animals) can be supplemented with the capromorelin composition. For example, soft or hard treats or chews (e.g., rawhide or other animal-based products given to animals for enjoyment and/or enrichment) can be supplemented with the capromorelin composition, where the capromorelin composition is either incorporated into the treat or chew or sprayed onto the treat or chew. In some aspects, the treats or chews can be purchased in a form that already includes the capromorelin composition. In other aspects, the capromorelin composition can be later added to the treats or chews by the individual feeding the animal.

[0033] The composition may be produced and delivered in the form of a kit. The kit preferably includes a syringe, one or more vessels, and directions that instruct the user to withdraw about one done from the vessels and administer the dose to the animals. By way of example only, in some embodiments, the composition can be stored in one or more vessels (e.g., a sterile bottle) from which an individual (e.g., a veterinarian and/or a caretaker/owner of the animal) can access the inappetence-controlling composition. For instance, using a syringe, the individual can withdraw about one dose of the composition (e.g., about five milliliters) from the vessel for administration to the animal. In some embodiments, the individual can secure the animal and place the syringe within the mouth of the animal (e.g., a back corner of the mouth near the back of the tongue. Once prepared, the individual can depress the plunger of the syringe to release the composition into the mouth/oral cavity of the animal so that the animal swallows the composition. As a result of placing the syringe near the rear of the mouth, the animal will nearly involuntarily swallow the composition so that some or all of the composition is received within the alimentary canal of the animal. In yet other embodiments, the inappetence-inducing composition can comprise a solid-dosage formulation so that the composition can be given in other forms (e.g., pills, caplets, tablets, etc.) with or without food.

[0034] In some embodiments, the inappetence-controlling composition is provided to the individual in a "ready-to-use" formulation. For example, the composition can be provided in the vessel so that the individual is not required to make any further additions to the vessel or treat the composition in any way to prepare the composition for administration to the animal. In other embodiments, the inappetence-controlling composition can be provided in an emulsified liquid formulation or suspension so that one or more additional compounds, excipients, other materials or preparatory steps may need to be added or carried out to ready the composition for administration to the animal.

[0035] The composition includes one or more pharmaceutically acceptable excipients or carriers. For example, some examples of possible excipients or carriers include, but are not limited to, diluents, binders, fillers, buffering agents, pH modifying agents, disintegrants, dispersing agents, stabilizers, preservatives, salt solutions, and/or coloring agents. The amount and types of excipients may be selected according to known principles of pharmaceutical science.

[0036] In some embodiments, the composition includes one or more flavoring agents and/or flavor-masking agents. Particularly, the composition may have an unpleasant or undesirable flavor so that one or more additional compounds may be added to increase palatability. In some embodiments, the flavoring agents and/or flavor masking agents may comprise one or more of a sweetening agent, a savory agent (i.e., an agent that imbues the composition with a salty flavor), a bittering agent, and a souring agent. In some embodiments, the inappetence-controlling composition that may be formulated for oral administration can include one or more of the following flavoring agents and/or flavor-masking agents (e.g., sweetening agents): sucralose, MagnaSweet®, Di-Pac® compressible sugar (i.e., a 97% : 3% mixture of sucrose and maltodextrin), Thaumatin T200X, Talin-Pure, OptisweetSD, stevia extract rebaudioside A, and/or neotame. In particular, some sugar-containing sweeteners (e.g., saccharose-containing materials) may at least partially degrade the capromorelin within the composition. Accordingly, large concentrations of some sugar-containing sweeteners should be avoided. In addition, in some embodiments, the flavoring agents and/or flavor-masking agents can comprise a vanilla-comprising composition, such as, but not limited to ethyl vanillin, vanillin-RHD, vanillin-Merck, vanilla-TG-old and suitable solvents (e.g., ethanol and/or water). In other aspects, other flavoring agents and/or flavor-masking agents can be added that confer other flavors on the composition, such as banana, pork liver, beef, etc.

[0037] In some embodiments, the flavoring agents and/or flavor-masking agents preferably comprise a percent weight per final volume of the inappetence-controlling composition of between about 50% to about 0.001%, depending on the agent selected. Preferably, the flavoring agents and/or flavor-masking agents can comprise a percent weight per final volume of the inappetence-controlling composition of between about 40% to about 0.01%, depending on the agent selected. More preferably, the flavoring agents and/or flavor-masking agents can comprise a percent weight per final volume of the inappetence-controlling composition of between about 30% to about 0.01%, depending on the agent selected. As previously mentioned, in some embodiments, the inappetence-controlling composition can include more than one flavoring agent and/or flavor-masking agent.

[0038] In some embodiments, the inappetence-controlling composition includes one or more inactive ingredients (i.e., carriers) that can function to stabilize or buffer the composition, function as an emulsifier or viscosifying agent for at least one or more of the constituents of the composition, function as a vehicle, function as a replacement material for sucrose, function as a solvent, and can function to serve any other desirable role. For example, the inappetence-controlling composition can include one or more of the following substances: citric acid, sodium citrate, sodium chloride, methyl 4-hydroxybenzoate salt, propyl 4-hydroxybenzoate salt, neosorb sorbitol, maltitol, propylene glycol, vegetable glycerin, Kollidon 90F, xanthan gum, Pluriol-E3350®, polyvinylpyrrolidone, polyethylene glycol and/or purified/deionized water. In some embodiments, the inactive ingredients can comprise a percent weight per final volume of the inappetence-controlling composition of between about 80% to about 0.001%, depending on the agent selected. Preferably, the inactive ingredients can comprise a percent weight per final volume or weight of the inappetence-controlling composition of between about 40% to about 0.01%, depending on the agent selected. More preferably, the inactive ingredients can comprise a percent weight per final volume of the inappetence-controlling composition of between about 25% to about 0.01%, depending on the agent selected. As previously mentioned, in some embodiments, the inappetence-controlling composition can include more than one inactive ingredient.

[0039] The inappetence-controlling composition may include the following base formulation in a solution:

Ingredient	% weight per volume
Capromorelin	2.10, 3.10, or 4.10
Methyl 4-Hydroxybenzoate S. Salt	0.045 - 0.115
Propyl 4-Hydroxybenzoate S. Salt	0.005 - 0.015

Ingredient	% weight per volume
Citric Acid (Anhydrous)	0.5 - 0.7
Sodium Citrate	0.5
Sodium Chloride	0.7 - 1.0
Neosorb sorbitol 70%	30 - 31
Maltitol Solution	25
Vegetable-based Glycerin	17 - 21
Purified Water	q.s.

However, this formulation is exemplary, with the amounts of each components and combination of ingredients is subject to variation.

[0040] Moreover, the following combinations of materials, solutions, compositions, and/or compounds can be added to the base formulation disclosed above to form one or more inappetence-controlling compositions for administration to treat inappetence-induced weight loss. In a preferred embodiment, the composition of the present invention comprises capromorelin, a viscosifying agent, and a flavoring agent and/or flavor-masking agent. The flavoring agent and/or flavor-masking agent is preferably a sweetener. In addition, one or more of the constituents can be omitted from the base formulation when preparing the inappetence-controlling compositions. The formulations shown below are exemplary and are not intended to be limiting.

Formulation Number	Concentration of Capromorelin Composition (in mg/mL)	Viscosifying Agent (in % weight per volume)	Sweetener	Flavoring Agent and/or Flavor-Masking Agent
1	21	Kollidon 90F (1.5%)	Thaumatin T200X (0.4%); Stevia Rebaudioside A (0.4%); and MagnaSweet® (0.5%)	Ethyl Vanillin (0.1%) and Ethanol (0.25%)
2	21	Kollidon 90F (1.4%-1.5%)	Sucralose (0.7%) and MagnaSweet® (0.5%)	Vanillin (0.1%) and optionally Ethanol (0.25%)
3	21	Kollidon 90F (1.5%)	Talin-Pure (0.3%) and MagnaSweet® (0.5%)	Ethyl Vanillin (0.1%) and Ethanol (0.25%)
4	21	Kollidon 90F (1.5%)	OptisweetSD	Ethyl

Formulation Number	Concentration of Capromorelin Composition (in mg/mL)	Viscosifying Agent (in % weight per volume)	Sweetener	Flavoring Agent and/or Flavor-Masking Agent
			(0.5%) and MagnaSweet® (0.5%)	Vanillin (0.1%) and Ethanol (0.25%)
5	21	Xanthan-Gum (0.05%)	Thaumatin T200X (0.4%); Stevia Rebaudioside A (0.4%); and MagnaSweet® (0.5%)	Vanillin-RHD (0.1%) and water
6	21	Pluriol-E3350® (7.5%)	Thaumatin T200X (0.4%); Stevia Rebaudioside A (0.4%); and MagnaSweet® (0.5%)	Ethyl Vanillin (0.13%) and Ethanol (0.3%)
7	21	None	Thaumatin T200X (0.4%); Stevia Rebaudioside A (0.4%); and MagnaSweet® (0.5%)	Vanillin-Merck (0.13%) and Ethanol (0.3%)
8	21	Kollidon 90F (1.5%)	Thaumatin T200X (0.10 - 0.4%); Stevia Rebaudioside A (0.1 - 0.4%); and MagnaSweet® (0.3 - 0.5%)	Vanillin-Merck (0.13%) and Ethanol (0.3%)
9	31	Kollidon 90F (1.5%)	Thaumatin T200X (0.6% - 0.7%); Stevia Rebaudioside A (0.7%); and MagnaSweet® (0.5%)	Vanillin (0.10 - 0.20%) and Ethanol (0.3 - 0.5%)
10	41	Kollidon 90F (1.5%)	Thaumatin T200X (0.7%); Stevia Rebaudioside A (0.7%); and	Ethyl Vanillin (0.13%) and

Formulation Number	Concentration of Capromorelin Composition (in mg/mL)	Viscosifying Agent (in % weight per volume)	Sweetener	Flavoring Agent and/or Flavor-Masking Agent
			MagnaSweet® (0.5%)	Ethanol (0.3%)
11	21	Polyvinylpyrrolidone K-90 (1.5%)	Thaumatin T200X (0.4%); Stevia Rebaudioside A (0.4%); and MagnaSweet® (0.5%)	Vanilla-TG-Old (0.4%) and water
12	21	Polyvinylpyrrolidone K-90 (1.5%)	Sucralose (0.5%) and MagnaSweet® (0.3%)	Vanilla-TG-old (0.25%) and water

[0041] In some embodiments, the compositions can be used in conjunction with another treatment regimen that may induce inappetence. For example, in some embodiments, the compositions can be administered to animals (e.g., companion animals) as a part of a chemotherapeutic or radiation treatment regimen. Those skilled in the art will recognize that chemotherapeutic or radiation treatment regimens may cause significant weight loss, wasting, muscle loss, cachexia, or other negative side effects that can be at least partially improved or abrogated by additional food consumption and/or increases in lean muscle mass. Accordingly, administration of therapeutically effective amounts of the compositions comprising capromorelin can induce food intake, thereby leading to weight gain and increased lean muscle mass. As a result, the animals can have more energy for activities and coping with the treatment regimens.

[0042] Moreover, in some embodiments, the compositions are administered to animals suffering from other conditions requiring unappetizing food. For example, some animals diagnosed with chronic kidney disease are placed on a specialized diet to improve this condition. However, some animals do not find the specialized diet food to be appetizing, and, as a result, do not consume enough of the specialized diet food for treatment of the chronic kidney disease or for sustenance. Accordingly, some animals can receive therapeutically effective amounts of the inappetence-controlling composition comprising capromorelin to stimulate hunger and induce consumption of the specialized diet food. As a result, the chronic kidney disease can be better controlled by the specialized diet food and the animal can consume sufficient calories for a pleasant existence.

[0043] In some embodiments, the compositions can be used to treat a general state of inappetence-induced weight loss. For example, some animals, for unknown reasons, experience inappetence, which, as previously mentioned, can lead to weigh loss, wasting, cachexia, lethargy, and other unpleasant results. After diagnosis of inappetence-induced weight loss by one skilled in the art, such as a veterinarian, the animals can receive one or more therapeutically effective doses of the composition comprising capromorelin to increase food consumption and lean muscle mass. As result, the companion animals can experience healthy weight gain leading to an improved quality of life.

[0044] The composition can be used to increase lean muscle mass. In a preferred embodiment, the capromorelin-containing composition comprises a sufficient amount of capromorelin to achieve a Cmax of around 150 nanograms of capromorelin or a metabolite thereof per milliliter of plasma at a Tmax of around two hours. However, the Tmax is preferably from about twenty-five minutes to 2 hours, where intervals are envisioned at about 30 minutes, about an hour, and about 2 hours. Additionally, the Tmax is preferably from about 100 ng/mL to about 1,000 ng/mL.

[0045] The treatment regimen of the inappetence-controlling composition of the present invention can be at least partially adjusted during the course of treatment. For example, after the animal is diagnosed as experiencing inappetence-induced weight loss (e.g., regardless of cause), an amount of the composition believed to be therapeutically effective can be orally administered to the animal. After a pre-determined time period, (e.g., about eight hours after the first administration of the composition and about seven days later), a technician, a veterinarian, or any other suitable individual can extract a sample (e.g., a serum sample) from the animal to measure amounts of one or more plasma markers within the sample. The samples may be taken at any other suitable time points known to those skilled in the art that would be appropriate for measuring the one or more plasma markers. For example, the plasma markers are preferably selected from the group consisting of, but not limited to, IGF-1, cortisol, capromorelin, and combinations thereof. In an alternate embodiment, an indicator is used. The indicator is preferably selected from, but not limited to, weight gain, weight loss, an increase in food consumption, a decrease in food consumption, an increase in muscle mass, a decrease in muscle mass, and combinations thereof. As a result of knowing the amounts of one or more of these plasma markers and/or indictors, the dose of the composition can be adjusted in light of the amounts of the plasma markers or indicators within the sample. In one embodiment, a minimum concentration of one or more of the plasma markers is determined at a first time point, a minimum concentration of one or more of the plasma markers is determined at a second time point, and so on. Preferably, the minimum concentration of one or more of the plasma markers is determined at a first time point, a first and a second time point, or a first, a second, and a third time point. Preferably, the concentration of the plasma markers can be compared to determine if the plasma marker is increasing or decreasing over time. Further, the concentration of the plasma markers may be compared to a predetermined value such that the dose of the pharmaceutical composition can be increased or decreased depending on the concentration of the plasma marker. A method of determining the effectiveness of the composition can be determined using the steps above and is preferably adjusted during the course of treatment. For example, if the amount or concentration of IGF-1 within the sample is low, the dose of the composition is increased in either concentration of capromorelin or amount of capromorelin administered to the companion animal. Conversely, if the amount of cortisol within the sample is too great, which can lead to increased adipose deposition, the dose of the composition can be decreased in either concentration of capromorelin or amount of capromorelin administered to the companion animal.

[0046] Also described is a method for determining the effectiveness of the pharmaceutical composition. The method preferably comprises the steps of determining that an animal is experiencing inappetence, measuring one or more plasma markers, administering a composition comprising capromorelin to the animal, taking a further measurement of one or more plasma markers, and determining if the dose is appropriate or needs to be adjusted. The plasma markers are preferably selected from the group consisting of, but not limited to, IGF-1, cortisol, capromorelin, and combinations thereof

[0047] The above treatment regimen may be carried out without extracting a sample. For example, after administering one or more of the therapeutically effective doses to the animal, other indicators of weight loss can be measured to assess the effectiveness of the treatment regimen. These indicators can include a change in weight (e.g., continued weight loss, weigh gain, weight loss stabilization), a change in food intake (e.g., increase in food intake relative to the pre-treatment time period), and/or a measurement of a change in lean muscle (e.g., scoring a value of the lean muscle index of the animal to assess lean muscle growth). As a result, the animal does not experience the invasive extraction of a serum sample and the individuals monitoring the treatment regimen can accordingly adjust the dose of the treatment regimen.

[0048] One or more of the above-described treatment regimens may be carried out until a satisfactory result is achieved. In particular, the capromorelin composition can be administered to an animal in need thereof until the animal is no longer in need thereof. For example, the capromorelin composition can be administered to an animal suffering from inappetence-induced weight loss until the animal regains a sufficient amount of weight. Specifically, the veterinarian or caretaker can continue to administer the composition (e.g., daily etc.) until the weight of the animal increases a sufficient amount. For example, the sufficient amount of weight gain may be a 5% increase in body weight compared to the body weight of the animal prior to receiving the initial dose of the composition. In other embodiments, the sufficient amount of weight gain may be more than 5% (e.g., 10%, 20%, 25%, etc.), as determined by the needs of the animal.

[0049] There is disclosed a method of treating inappetence comprising the steps of determining that an animal has inappetence, administering at least one dose of a capromorelin-containing composition, assessing a plasma marker or indicator value in the animal, and continuing to administer the capromorelin-containing composition until the value of the plasma marker or indicator is appropriate for the animal.

DEFINITIONS

[0050] As used herein, the terms "about" and "approximately" designate that a value is within a statistically meaningful range. Such a range can be typically within 20%, more typically still within 10%, and even more typically within 5% of a given value or range. The allowable variation encompassed by the terms "about" and "approximately" depends on the particular system under study and can be readily appreciated by one of ordinary skill in the art.

[0051] As used herein, the term "animal" designates non-human animals, such as "livestock" and "companion animals."

[0052] As used herein, the term "livestock" includes cattle, sheep, pigs, poultry (e.g., chickens, turkeys, quail, etc.) goats, llamas, and other similar animals.

[0053] As used herein, the term "h" designates hours.

[0054] As used herein, the term "composition" applies to any solid object, semi-solid, or liquid composition designed to contain a specific pre-determined amount (dose) of a certain ingredient, for example, an active pharmaceutical ingredient, as previously mentioned and as discussed below. Suitable compositions may be pharmaceutical drug delivery systems, including those for oral administration, buccal administration, rectal administration, topical or mucosal administration, or subcutaneous implants, or other implanted drug delivery systems; or compositions for delivery minerals, vitamins and other nutraceuticals, oral care agents, flavorants, flavor-masking agents, and the like. In one embodiment of the invention, the compositions are generally liquid, however they may contain solid or semi-solid components. Generally, the dosage form is an orally administered system for delivering a pharmaceutical active ingredient to the alimentary canal of a companion animal.

[0055] As used herein, the term "mg/kg" designates milligrams of composition per kilogram of body weight.

[0056] As used herein, the term "treatment" or "treating" of a condition, such as inappetence, includes inhibiting an existing condition or arresting its development; or ameliorating or causing regression of the condition. The term "preventing" or "prevention" of a condition, such as inappetence, weight loss, or cachexia, includes substantially blocking or inhibiting the development or growth of a condition before it starts.

[0057] As used herein, the term "animal" refers to a mammal, specifically a companion animal, including but not limited to dogs, cats, rabbits, ferrets, horses, and hamsters.

[0058] As used herein, the phrase "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of capromorelin may be determined by a person skilled in the art (e.g., a veterinarian) and may vary according to factors such as the clinical state, age, sex, and weight of the companion animal, bioavailability of capromorelin, and the ability of the active agent(s) to elicit a desired response in the companion animal. A therapeutically effective amount is also one in which any toxic or detrimental effects of the active agent(s), are outweighed by the therapeutically beneficial effects. A therapeutically effective amount also encompasses an amount that is effective, at dosages and for periods of time necessary, to achieve the desired result (e.g., weight gain through the addition of lean muscle mass).

[0059] As used herein, the term "q.s." means to add a quantity (e.g., volume or mass) of an ingredient until the final amount (e.g., volume or mass) is reached.

[0060] As used herein, the term "w/v" designates a concentration of a substance as measured in weight of the substance per volume of a solution or composition.

ILLUSTRATIVE EXAMPLES

EXAMPLE 1 - Defining a Dosing Regimen of an Inappetence-Controlling Compound Containing Capromorelin for Inducing Food Intake and Lean Muscle Increases in Companion Animals

[0061] A controlled, seven-day study was performed to assess the impact of different capromorelin-dosing regimens on the production of insulin-like growth factor 1 (hereinafter "IGF-1"), growth hormone (hereinafter "GH"), and cortisol. The different capromorelin-dosing regimens were also assessed for the impact on food intake and changes in body mass.

[0062] Eighteen adult non-naive Beagle dogs (nine males and nine females) were divided into one of three treatment groups. Each of the three treatment groups included three males and three females. Group A, which was the control group, was dosed twice per day, via oral gavage, with a vehicle (deionized water alone) and was used as a baseline data point for comparison against the active treatment regimens. Group B comprised an active treatment group that received two treatments per day, via oral gavage, with a capromorelin-containing composition with a concentration of 3 mg/kg capromorelin per treatment. Finally, Group C comprised an active treatment group that received one treatment per day, via oral gavage, with a capromorelin-containing composition with a concentration of 6 mg/kg capromorelin per treatment.

[0063] During the ten day study period, on an at least once-daily basis, each of the dogs was monitored for clinical observations, mortality, morbidity, body mass, and food consumption. Serum samples were taken to measure capromorelin concentration, GH concentration, IGF-1 concentration, and cortisol concentration. Serum samples were taken on days 1, 2, 4, and 7 at -15 minutes (pre-dose), immediately prior to dosing (0 minutes) and 30, 45, 60, 90, 120, 240, 360, and/or 480 minutes post dosing. Additional blood samples were taken at 8 AM on Day 10 of the study to assess long-term impact of the active treatments.

[0064] As indicated in FIGS. 1-7, dogs in the active treatment groups (i.e., Groups B and C) consumed greater amounts of food and put on more weight compared to dogs in the control group (i.e., Group A). As shown in FIGS. 1-3, overall, dogs treated with a once-daily 6 mg/kg or a twice-daily 3mg/kg dose of capromorelin consumed more food relative to dogs receiving deionized water only. Furthermore, referring to FIGS. 2 and 3, although males treated with the once-daily 6 mg/kg or the twice-daily 3 mg/kg dose of capromorelin tended to consume more food, females treated with the once-daily 6 mg/kg tended to consume more food relative to females in the other groups.

[0065] Similarly, as shown in FIGS. 4-7, dogs treated with the once-daily 6 mg/kg or the twice-daily 3mg/kg dose of capromorelin gained more weight relative to dogs receiving deionized water only. The male dogs in these treatment groups experienced a 4-5% increase in weight over the course of the seven day treatment period (FIG. 6); however body weight changes in female dogs (FIG. 7) were not as clearly defined. The increase in body weight appears to be correlated with the increase in food consumption. More specifically, as discussed above, male dogs tended to consume more food (FIG. 2), and, correspondingly, male dogs also gained more body weight (FIG. 6).

[0066] Referring now to FIGS. 8-10, dogs in both Groups B and C exhibited elevated concentrations of capromorelin in their serum. Using data from serum samples taken on Days 1 and 7 of the study, capromorelin concentrations tended to spike at approximately 0.5 h after dosing and, in general, decreased to near undetectable levels by eight hours after dosing (i.e., 480 minutes). The amount of capromorelin detected in the serum of the dogs correlates with the dosing regimen. Particularly, dogs receiving a 6 mg/kg dose exhibited higher capromorelin concentrations in their serum (about 2.3-fold higher) relative to dogs receiving the twice-daily 3 mg/kg dose, as shown in FIGS. 8-10. In addition, as shown in FIGS. 9 and 10, female dogs receiving with a 3 mg/kg dose exhibited a slightly higher capromorelin concentration in the serum relative to male dogs receiving the same dose.

[0067] As reflected in FIGS. 11-24, dogs in Groups B and C both experienced changes in serum concentrations of IGF-1, GH, and cortisol, which are likely attributable to the capromorelin administration.

[0068] First, as shown in FIGS. 11-15, treatment with capromorelin induced IGF-1 levels within the serum of the dogs. Specifically, as shown in FIG. 11, approximately one to four hours after initially dosing the dogs with capromorelin, IGF-1 levels exhibited an increase in the serum, relative to the dogs receiving only deionized water. Moreover, as shown in FIGS. 12-14, on days 2, 4, and 7 of the treatment course, serum IGF-1 levels remained consistently higher in dogs receiving both doses of capromorelin. As shown in FIG. 15, three days after terminating treatment (Day 10), levels of serum IGF-1 in the dogs receiving capromorelin treatment were not significantly different than the levels of serum IGF-1 in the dogs receiving deionized water alone. In addition, the general elevation of IGF-1 during the treatment regimen was similarly observed dogs treated with the once-daily 6 mg/kg or the twice-daily 3 mg/kg dose of capromorelin.

[0069] Like serum IGF-1 levels, during the study, serum levels of GH appeared to be dependent upon capromorelin administration, as shown in FIGS. 16-20. Specifically, on days 1, 2, 4, and 7, GH levels increased approximately 0.5h after the dogs received their capromorelin dosing. Prior to treatment, all dogs exhibited nearly undetectable levels of GH in the serum; however, after receiving either the once-daily 6 mg/kg or the twice-daily 3 mg/kg dose of capromorelin, dogs in Groups B and C exhibited a marked increase in GH levels in the serum that continued to be elevated relative to the dogs in Group A, which received only deionized water. As shown in FIG. 20, three days after terminating treatment (Day 10), levels of GH in the serum in the dogs receiving capromorelin treatment were not significantly different than the levels of GH in the serum in the dogs receiving deionized water alone. In addition, with the exception of Day 1 (FIG. 11), the levels of GH in the serum appear to correlated with the dose received by the dogs. Specifically, as shown in FIGS. 12-14, on days 2, 4, and 7, dogs receiving the once-daily 6 mg/kg dose exhibit greater concentrations of GH in the serum relative to dogs receiving the twice-daily 3 mg/kg dose.

[0070] Referring now to FIGS. 21-24, similar to GH, cortisol concentrations in the serum appear to correlate with administration of capromorelin. Specifically, on days 1, 2, and 7 (FIGS. 21-23, respectively), after approximately 0.5h post treatment, cortisol concentrations in the serum of dogs treated with capromorelin increased relative to dogs receiving only deionized water. Moreover, the amount of increase in cortisol concentration in the serum correlates with the dosing regimen used. Particularly, dogs that received the once-daily 6 mg/kg dose exhibited greater concentrations of cortisol in the serum relative to dogs that received the twice-daily 3 mg/kg dose of capromorelin. Moreover, as shown in FIG. 24, three days after terminating treatment (Day 10), levels of cortisol in the serum in the dogs receiving capromorelin treatment were not significantly different than the levels of cortisol in the serum in the dogs receiving deionized water alone.

[0071] Overall, both dosing regimens produced discernible impacts on the dogs of Groups B and C, relative to the negative control dogs of Group A. Moreover, no toxicological responses were noted. Pharmacological effects were noted, including increased body weight and food consumption, as well as increased levels of serum GH, IGF-1, cortisol, and capromorelin. In general, the increases in serum concentrations of GH, IGF-1, and cortisol were more pronounced in animals receiving the once-daily 6 mg/kg dosing regimen. Moreover, although both dosing regimens induced GH, IGF-1, and cortisol, the twice-daily 3 mg/kg dosing regimen induced sufficient amounts of IGF-1 to promote lean muscle growth within the dogs, but also did not induce increases in GH and cortisol concentrations to the same extent as the once-daily 6 mg/kg dosing regimen. As a result of the lower concentrations of GH and cortisol, the dogs are less likely experience an increase in adipose deposition, meaning that the increase in body weight is more likely to be lean muscle.

EXAMPLE 2 - Assessing the Pharmacokinetic Profile of Capromorelin and Dog

Acceptability/Palatability

[0072] After selecting the 3 mg/kg dosing regimen, a controlled, eight-hour study was performed to assess the pharmacokinetic profile and acceptability/palatability of different capromorelin formulations. Briefly, twelve Beagle dogs (six males and six females) were randomized into three groups, with four dogs per group (two males and two females). Each of the dogs received a test formulation of capromorelin via a single oral gavage or intravenous ("IV") administration. This testing included two iterations with the same three groups of dogs with a seven-day washout period between iterations. Serum was collected prior to administration (time 0) and 0.5h and 1, 2, 4, and 8 hours after capromorelin administration. Serum was tested for capromorelin and IGF-1 concentrations and dogs were observed for clinical changes.

[0073] In addition, the same dogs were used to assess acceptability/palatability. The acceptability/palatability testing was conducted the first two days after the pharmacokinetic analysis. Briefly, at the same time on Days 1 and 2 after the pharmacokinetic analysis, dogs were orally dosed in the corner of the mouth with the capromorelin formulations used in the pharmacokinetic analysis. The dogs' responses to the different formulations were recorded.

[0074] As shown in FIGS. 25-27, all formulations tested in the pharmacokinetic analysis produced detectable levels of capromorelin and increased levels of IGF-1 in the serum of the dogs over an eight-hour period. Specifically, in the first iteration (FIG. 25), which includes the IV formulation and test formulations 2 and 3, all three formulations produced an increase in capromorelin concentration in the serum within 0.5h of administration, which dropped over the course of the eight-hour study. Similarly, in the second iteration, which includes formulations 4, 5, and 6, all three formulations produced an increased capromorelin serum concentration, with peak concentrations occurring between 0.5h and 2h post administration. As shown in FIG. 27, IGF-1 levels at eight hours post administration were also increased by all formulations administered to the dogs. In general, no adverse clinical side effects were detected in any of the dogs during the trial, with the exception of excessive salivation in the dogs receiving the IV formulation.

[0075] Although no data is shown for the acceptability/palatability analysis, formulation administration in the corner of the mouth via syringe was accepted by the dogs, but not well accepted. It did not appear that the dogs liked the taste of the formulations, with formulation 5 being the most accepted and formulation 1 being the least accepted.

[0076] Overall, each of the tested formulations produced adequate serum concentrations of capromorelin. Moreover, the administration of all of the formulations produced increased levels of IGF-1 in the serum. However, formulation 4 will be used in future experimentation because it produced the most consistent capromorelin serum profile. As discussed in greater detail below, further refinement of formulation four will be needed in order to improve the palatability, which can improve the ease with which owners of the companion animals can administer the composition.

[0077] Specifically, formulation 4 includes the following constituents at the following concentrations, as measured in weight of the constituent per total volume of the solution:

Ingredient	% weight per volume
Capromorelin	2.10
Methyl 4-Hydroxybenzoate Salt	0.14
Propyl 4-Hydroxybenzoate Salt	0.02
Ethyl Vanillin	0.32
Sucralose	1.27
Purified Water	36.00
Propylene Glycol	q.s.

EXAMPLE 3 - Refining Dog Acceptability/Palatability of the Capromorelin Composition

[0078] After selecting formulation 4, a controlled, eight-hour study was performed to refine formulation 4 to improve acceptability/palatability of this capromorelin formulation. Particularly, formulation 4 (as shown above) was mixed with a plurality of different sweeteners, flavors, and/or masking agents to improve dog acceptability/palatability of this formulation. Briefly, twenty Beagle dogs (ten males and ten females) were randomized into five groups, with four dogs per group (two males and two females). Each of the dogs received a test formulation of capromorelin via a single oral dose in the corner of the mouth. This testing included two iterations with the same groups of dogs on consecutive days. However, on the second day, only four groups were necessary because a total of nine formulations were tested (i.e., five formulations tested on the first day and four formulations tested on the second day).

[0079] During testing, nine new formulations of formulation 4 were tested at the 3 mg/kg dose. Moreover, during administration of the test formulations, dogs were observed to determine whether the test formulations were "well-accepted" by assessing a lack of clinical observations and an apparent acceptance or willingness to orally receive the formulations. Moreover, during testing, if at least three of the four dogs in a test group displayed a "well-accepted" response to a test formulation (as determined by testing personal), serum samples were collected a times 0, 0.5h, 1h, 2h, 4h, and 8h post administration. Serum samples were tested for capromorelin and IGF-1 concentrations.

[0080] Data reflecting "well-accepted" formulations is shown in FIGS. 28 and 29. Specifically, of the nine test formulations, formulations 1, 3, 7, and 8 were determined to be "well-accepted" by the dogs. In addition to being "well-accepted," each of these formulations resulted in detectable levels of capromorelin in the serum and increases in IGF-1 at eight hours after administration.

It was determined that formulation 8 produced the most consistent capromorelin serum profile, however, the present invention is not limited to the embodiment of formulation 8.

[0081] Specifically, the "well-accepted" formulations include the following constituents at the following concentrations, as measured in weight of the constituent per total volume of the solution:

Formulation 1	
Ingredient	% weight per volume
Capromorelin	2.10
Citric Acid	0.50
Sodium Citrate	0.50
Sodium Chloride	1.00
Methyl 4-Hydroxybenzoate Salt	0.11
Propyl 4-Hydroxybenzoate Salt	0.01
Sucralose	0.50
MagnaSweet	0.50
Natural Vanilla Flavor	0.40
Di-Pac® Compressible sugar (97% Sucrose and 3% Maltodextrin)	30.00
Propylene Glycol	25.00
Vegetable Glycerin	17.00
Purified Water	q.s.

Formulation 3	
Ingredient	% weight per volume
Capromorelin	2.10
Citric Acid	0.50
Sodium Citrate	0.50
Sodium Chloride	1.00
Methyl 4-Hydroxybenzoate Salt	0.11
Propyl 4-Hydroxybenzoate Salt	0.01
Sucralose	0.50
MagnaSweet	0.50
Macorogolglycerol Hydroxysterarate	0.16
Natural Vanilla Flavor	0.40
Di-Pac® Compressible sugar (97% Sucrose and 3% Maltodextrin)	30.00
Propylene Glycol	25.00

Formulation 3	
Ingredient	% weight per volume
Vegetable Glycerin	17.00
Purified Water	q.s.
Formulation 7	
Ingredient	% weight per volume
Capromorelin	2.10
Citric Acid	0.50
Sodium Citrate	0.50
Sodium Chloride	1.00
Methyl 4-Hydroxybenzoate Salt	0.11
Propyl 4-Hydroxybenzoate Salt	0.01
Neotame	0.15
MagnaSweet	0.35
Natural Vanilla Flavor	0.40
Di-Pac® Compressible sugar (97% Sucrose and 3% Maltodextrin)	30.00
Propylene Glycol	25.00
Vegetable Glycerin	17.00
Purified Water	q.s.
Formulation 8	
Ingredient	% weight per volume
Capromorelin	2.10
Citric Acid	0.50
Sodium Citrate	0.50
Sodium Chloride	1.00
Methyl 4-Hydroxybenzoate Salt	0.11
Propyl 4-Hydroxybenzoate Salt	0.01
Thaumatin	0.18
Stevia Extract Rebaudioside A	0.13
MagnaSweet	0.30
Natural Vanilla Flavor	0.40
Di-Pac® Compressible sugar (97% Sucrose and 3% Maltodextrin)	30.00
Propylene Glycol	25.00
Vegetable Glycerin	17.00

Formulation 8	
Ingredient	% weight per volume
Purified Water	q.s.

EXAMPLE 4 - Refining the Dosing Regimen of the Inappetence-Controlling Compound Containing Capromorelin

[0082] Although the twice-daily 3 mg/kg dosing regimen was previously selected for further formulation analysis, an additional analysis of the dosing regimen was conducted to refine the concentrations and numbers of daily administrations of the capromorelin composition. Specifically, an analysis was conducted to determine if a less frequent dosing regimen of the capromorelin composition was a viable alternative to the twice-daily 3 mg/kg dosing regimen.

[0083] A controlled, seven-day study was performed to assess the impact of different capromorelin-dosing regimens on the production of IGF-1, GH, and cortisol. The different capromorelin-dosing regimens were also assessed for the impact on food intake and changes in body mass.

[0084] Twenty-four adult non-naive Beagle dogs (twelve males and twelve females) were divided into one of three treatment groups, with one negative control group and two active treatment groups. Each of the three treatment groups included three males and three females. The first group received a placebo formulation (i.e., deionized water) twice per day, via oral gavage. The second group received a once-daily dose of the capromorelin composition at a concentration of 3 mg/kg, via oral gavage. The third group received a twice-daily dose of the capromorelin composition at a concentration of 3 mg/kg, via oral gavage.

[0085] During the ten day study period, on an at least once-daily basis, each of the dogs was monitored for clinical observations, mortality, moribundity, body mass, acceptability/palatability, and food consumption. Serum samples were taken to measure capromorelin concentration, GH concentration, IGF-1 concentration, and cortisol concentration. Serum samples were taken on days 1, 2, 4, and 7 at -15 minutes (pre-dose), immediately prior to dosing (0 minutes) and 30, 45, 60, 90, 120, 240, 360, and/or 480 minutes post dosing. Additional serum samples were taken at 8 AM on Day 10 of the study to assess long-term impact of the active treatments.

[0086] As indicated in FIGS. 30-32, dogs in the active treatment groups (i.e., the second and third treatment groups) consumed greater amounts of food and did not lose weight during the experiment, compared to dogs in the control group (i.e., the first group). Specifically, as shown in FIGS. 30 and 31, dogs receiving the active treatment, regardless of dose, consumed more food than did dogs in the negative control group. For example, dogs receiving the once-daily and the twice-daily 3 mg/kg dose of capromorelin consumed an average of approximately 34% more food consumed daily, relative to the negative control. Correspondingly, as shown in FIG.

32, the dogs receiving the active treatments did not experience the same weight loss exhibited by the dogs in the negative treatment group. Although the dogs in the active treatment groups did not experience significant weight gain, over the course of the experiment, the dogs receiving only deionized water exhibited an average weight loss of 3.73% body weight. Conversely, the dogs receiving the once-daily administration of capromorelin did not experience weight loss or did not experience as great a weight loss as the negative control.

[0087] Referring now to FIGS. 33 and 34, dogs in the active treatment groups exhibited elevated concentrations of capromorelin in their serum. Using data from serum samples taken on Days 1 and 7 of the study, capromorelin concentrations tended to begin rising at approximately 0.5 h after dosing and, in general, decreased to near undetectable levels by eight hours after administration. The results confirmed that the capromorelin composition was correctly administered.

[0088] As reflected in FIGS. 35-46, dogs in the active treatment groups experienced changes in serum concentrations of IGF-1, GH, and cortisol, which are likely attributable to the capromorelin administration.

[0089] First, as shown in FIGS. 35-38, treatment with capromorelin induced IGF-1 levels within the serum of the dogs. Specifically, as shown in FIG. 35, approximately one to four hours after initially dosing the dogs with capromorelin, IGF-1 levels exhibited an increase in the serum, relative to the dogs receiving only deionized water. Moreover, as shown in FIGS. 36 and 37, on days 4 and 7 of the treatment experiment, serum IGF-1 levels remained consistently higher in dogs receiving capromorelin. As shown in FIG. 38, three days after terminating treatment (Day 10), levels of serum IGF-1 in the dogs receiving capromorelin treatment were not significantly different than the levels of serum IGF-1 in the dogs receiving deionized water alone.

[0090] In an additional analysis of the same data discussed above, relative to time 0 (i.e., prior to administration of the capromorelin composition), the dogs in the active treatment group exhibit increased IGF-1 levels in the serum. For example, on day 1, at eight hours post administration, the dogs receiving the once-daily treatment exhibit an approximately 83.9% increase in serum IGF-1 concentration, relative to time 0 on day 1. The dogs receiving the twice-daily treatment exhibit an approximately 50.6% increase in serum IGF-1 concentration, relative to time 0 on day 1. On days 4 and 7, at eight hours post administration, the once-daily treatment induces approximately 39.5% and 36.8% increases in serum IGF-1 concentration, relatively to time 0 on days 4 and 7, respectively. Similarly, on days 4 and 7, at eight hours post administration, the twice-daily treatment induces approximately 15.4% and 13.3% increases in serum IGF-1 concentration, relatively to time 0 on days 4 and 7, respectively. It is possible that the dogs receiving the twice-daily administration of the capromorelin composition exhibit increases of a lesser magnitude because serum concentrations of IGF-1 are already at higher concentrations than are IGF-1 levels in dogs receiving the once-daily administration of capromorelin.

[0091] Like serum IGF-1 levels, during the study, serum levels of GH appeared to be dependent upon capromorelin administration, as shown in FIGS. 39-42. Specifically, on days 1, 4, and 7, GH levels increased at approximately 0.5h after the dogs received the capromorelin composition. Prior to treatment, all dogs exhibited nearly undetectable levels of GH in the serum; however, after receiving either the once-daily 3 mg/kg or the twice-daily 3 mg/kg dose of capromorelin, dogs in active treatment groups exhibited a marked increase in GH levels in the serum that continued to be elevated relative to the dogs in negative control group, which received only deionized water. As shown in FIG. 42, three days after terminating treatment (Day 10), levels of GH in the serum in the dogs receiving capromorelin treatment were not significantly different than the levels of GH in the serum in the dogs receiving deionized water alone.

[0092] Referring now to FIGS. 43-46, similar to GH, cortisol concentrations in the serum appear to correlate with administration of capromorelin. Specifically, on days 1, 4, and 7 (FIGS. 43-45, respectively), at approximately 0.5h post treatment, cortisol concentrations in the serum of dogs treated with capromorelin increased relative to dogs receiving only deionized water. In addition, increases in cortisol serum levels were mitigated on days 4 and 7, and even more so with the twice-daily treatment of capromorelin. Moreover, as shown in FIG. 46, three days after terminating treatment (Day 10), levels of cortisol in the serum in the dogs receiving capromorelin treatment were not significantly different than the levels of cortisol in the serum in the dogs receiving deionized water alone.

[0093] Overall, both dosing regimens produced discernible impacts on the dogs of the active treatment groups, relative to the negative control dogs. Moreover, no toxicological responses were noted. Pharmacological effects were noted, including no significant decreases in body weight and increased food consumption, as well as increased levels of serum GH, IGF-1, cortisol, and capromorelin. In general, the more pronounced increases in serum concentrations of IGF-1 and mitigated expression of cortisol was noted in the dogs receiving the twice-daily administrations. Because of this noted benefit, the twice-daily administration of the capromorelin composition (at a concentration of 3 mg/kg) will be further explored, along with other dosing regimens to determine the most efficacious dose in an optimal volume.

EXAMPLE 5 - Further Refinements of the Dosing Regimen of the Inappetence-Controlling Compound Containing Capromorelin

[0094] In order to further refine the dosing regimen that would provide an appropriate blood profile of capromorelin and desired results from the perspective of increased food intake and weight gain, an additional series of experiments were conducted. In these experiments, twenty-four adult (male and female) Beagle dogs weighing approximately 9 to 13 kilograms were randomly divided into four groups. Group 1 received a placebo formulation, without any active compound, two times per day; Group 2 received a composition comprising 3 mg/kg of body weight of capromorelin one time per day; Group 3 received a composition comprising 4.5 mg/kg of body weight of capromorelin one time per day; and Group 4 received a composition comprising 3 mg/kg of body weight of capromorelin two times per day.

[0095] In particular, on the first day of dosing, Day 1, through the last day of dosing, Day 7, the compositions were orally administered (i.e., using a syringe) to the animals in a flavored formulation of the following composition:

Formulation 9	
Ingredient	% weight per volume
Capromorelin (not present in Group 1 composition)	3.10
Citric Acid	0.70
Sodium Citrate	0.50
Sodium Chloride	0.70
Methyl 4-Hydroxybenzoate Salt	0.045
Propyl 4-Hydroxybenzoate Salt	0.005
Thaumatin T200X	0.60
Stevia Extract Rebaudioside A 99%	0.70
MagnaSweet	0.50
Vanillin	0.20
Neosorb Sorbitol 70%	30.30
Maltitol Solution (Lycasin 80/55)	25.00
Glycerol Anhydrous	20.20
Kollidon 90F (PVP)	1.5
Ethanol (ABS)	0.50
Purified Water	q.s.

[0096] In these experiments, the animals were orally administered the flavored formulation at approximately 8:00 AM and, for Group 4 only, again at 6:00 PM. The animals were fed at 10:00 AM beginning seven days prior to Day 1 and continuing for the duration of the study. The animals were offered twice the normal amount of food. Approximately two hours after the food offering, the remainder was removed and weighed to assess food intake. This restricted feeding regime was started at Day -7 to allow the animals to transition to a normal feed intake before the study was initiated. Food consumption was calculated and recorded on Days -7 through Day 7. Baseline food consumption was calculated for each individual dog as the average number of grams of food consumed on Days -3, -2, and -1. The study period food consumption was calculated for each individual dog as the average of Days 1 through 7. Body weights were collected on Days -1, 3, and 7. Blood was collected for measurements of capromorelin, growth hormone, cortisol, and IGF-1 concentrations on Days 1, 4, and 7 at about 15 minutes pre-administration, immediately prior to dosing (0 minutes), 30, 45, 60, 90, 120, 240, 360, and/or 480 minutes post dosing via the jugular or other accessible vessel. As reflected by the data in FIGS. 61-74, the animals' response to the capromorelin-containing composition is largely in accord with the results discussed above.

[0097] First, as shown in FIG. 61 and in Table 1 below, the animals that received the experimental compositions consumed greater amounts of food and gained more weight than the animals in Group 1 (*i.e.*, the placebo group). In particular, as shown in FIG. 61, the animals of Groups 2-4, (*i.e.*, those that received the capromorelin-containing composition), consumed greater amounts of food relative to the animals in the control group. Specifically, when comparing the food consumed on Days -1 and Day 7, the control animals consumed nearly 16% less food, with the Group 2 animals consuming 42.7% more food, the Group 3 animals consuming 34.5% more food, and the Group 4 animals consuming 31.5% more food. Moreover, as shown in Table 1 below, the increased food consumption corresponded to an increase in body weight.

Table 1: Weight Change

Group	Treatment	Comparison of Weight on Day -1 to Weight on Day 7 (X ± SD, %)
1	Placebo - 2x per day	-1.17 ± 1.51%
2	Capromorelin - 3mg/kg 1x per day	4.52 ± 1.67 %
3	Capromorelin - 4.5 mg/kg 1x per day	3.78 ± 2.93 %
4	Capromorelin - 3 mg/kg 2x per day	4.17 ± 1.35 %

[0098] Correspondingly, as shown in FIGS. 62 and 63, the concentrations of capromorelin within the serum were as expected. In particular, the serum concentration of capromorelin initially spiked at 30 minutes post administration and, by 8 hours was back to baseline levels. Moreover, as expected, the animals in Group 3, which received the highest dose of capromorelin, exhibited greater serum concentrations of capromorelin. In addition, this data also shows that there was no evidence of capromorelin accumulation in these animals, as the concentration dropped to below detectable levels by 8 hours post administration.

[0099] Similarly, as shown in FIGS. 64A-74, the levels of IGF-1, growth hormone, and cortisol increased as a result of capromorelin administration. In particular, as shown in FIGS. 64A-66, the IGF-1 levels in the control animals remained near baseline throughout the study. However, the animals in Groups 2-4 experienced increases in the amounts of IGF-1 present in the serum on Days 1, 4, and 7. Moreover, the IGF-1 levels exhibited a sustained increase over a twenty-four hour period in the treated animals by Day 4 (FIG. 64B) and remained elevated on Day 7. Furthermore, the animals receiving the twice-daily administrations (Group 4) exhibited the highest sustained increase, but it appeared that there was little difference in the sustained levels of IGF-1 between Groups 2 and 3. Finally, the data in FIG. 66 shows that the IGF-1 levels remained slightly elevated after the treatment had been ceased for 2 days (*i.e.*, on Day 9).

[0100] As shown in FIGS. 67-70, Groups 2-4 experienced initial increases in the serum concentration of growth hormone. In particular, the level of growth hormone in the Group 1 animals remained near baseline for the duration of the experiment. However, the animals that received capromorelin experienced an increase in growth hormone in the serum on Day 1 (FIG. 67), which was mitigated by Day 4 (FIG. 68), further reduced by Day 7 (FIG. 69), and not detected after the conclusion of the experiment (Day 9; FIG. 70).

[0101] Finally, as shown in FIGS. 71-74, treatment with capromorelin also resulted in initially increased levels of cortisol. In particular, the level of cortisol in the Group 1 animals remained near baseline for the duration of the experiment. However, the animals that received capromorelin experienced an initial increase in cortisol in the serum on Day 1 (FIG. 71), which was mitigated by Day 4 (FIG. 72), further reduced by Day 7 (FIG. 73), and not detected after the conclusion of the experiment (Day 9; FIG. 74). Interestingly, it appears that the cortisol profile was best mitigated in the Group 4 animals, but there was no significant difference between the Group 2 and Group 3 animals.

[0102] Overall, based on the results discussed above, the experimental formulations were well-accepted by the animals. These results demonstrate that administration of the capromorelin-containing compositions in dogs resulted in a measurable serum profile of capromorelin at all doses tested. Moreover, although the number of animals was small and the duration was short, there was a trend in Groups 2-4 of increased body weight and food intake. In addition, there did not appear to be differences in groups dosed once or twice per day in Groups 2-4. Accordingly, based on these experiments and the data presented in prior examples, it appears that a single dose of capromorelin between about 3 and about 4 mg per kg of body weight could be an effective dosage.

EXAMPLE 6 - Refining Dog Acceptability/Palatability of the Capromorelin Composition

[0103] After some of the aforementioned experiments and data not shown, additional experiments were conducted to further refine the formulation based on animal acceptability / palatability. In particular, experiments were conducted using the following formulations:

Formulation 2	
Ingredient	% weight per volume
Capromorelin	3.10
Citric Acid (Anhydrous)	0.70
Sodium Citrate	0.50
Sodium Chloride	0.70
Methyl 4-Hydroxybenzoate Salt	0.045
Propyl 4-Hydroxybenzoate Salt	0.005
Sucralose	0.70

Formulation 2	
Ingredient	% weight per volume
MagnaSweet Plus Liquid	0.50
Vanillin	0.10
Neosorb Sorbitol 70%	30.00
Maltitol Solution (Lycasin 80/55)	25.00
Glycerol Anhydrous	20.50
Kollidon 90F (PVP)	1.5
Purified Water	q.s.

Formulation 9	
Ingredient	% weight per volume
Capromorelin	3.10
Citric Acid (Anhydrous)	0.70
Sodium Citrate	0.50
Sodium Chloride	0.70
Methyl 4-Hydroxybenzoate Salt	0.045
Propyl 4-Hydroxybenzoate Salt	0.005
Thaumatin T200X	0.60
Stevia Extract Rebaudioside A 99%	0.70
MagnaSweet Plus Liquid	0.50
Vanillin	0.20
Neosorb Sorbitol 70%	30.30
Maltitol Solution (Lycasin 80/55)	25.00
Glycerol Anhydrous	20.20
Kollidon 90F (PVP)	1.5
Ethanol (ABS)	0.50
Purified Water	q.s.

[0104] In these experiments, testing was conducted to evaluate Formulation 2 versus Formulation 9 at a 4 mg/kg of body weight, once-per-day treatment regimen. In particular, this study was conducted to measure capromorelin concentrations in the serum, as well as measurements of food intake and weight change. In these experiments, sixteen adult (male and female) Beagle dogs weighing approximately 9 to 13 kgs were randomly divided into two treatment groups, Group 1 received Formulation 9 once per day and Group 2 received Formulation 2 once per day.

[0105] In these experiments, the animals were orally administered the different formulations at approximately 8:00 AM. The animals were fed at 10:00 AM beginning seven days prior to Day 1 and continuing for the duration of the study (5 days). The animals were offered twice the normal amount of food. Approximately two hours after the food offering, the remainder was removed and weighed to assess food intake. This restricted feeding regime was started at Day -7 to allow the animals to transition to a normal feed intake before the study was initiated. Food consumption was calculated and recorded on Days -7 through Day 5. Baseline food consumption was calculated for each individual dog as the average number of grams of food consumed on Days -3, -2, and -1. The study period food consumption was calculated for each individual dog as the average of Days 1 through 5. Body weights were collected on Days -1 and 5. Blood was collected for measurements of capromorelin and IGF-1 concentrations on Day 5 at about 15 minutes pre-administration, immediately prior to dosing (0 minutes), 30, 60, 120, 240, and/or 480 minutes post dosing. As reflected by the data in FIGS. 75-78, the animals' response showed positive signs when administered both compositions.

[0106] In particular, as shown in FIGS. 75 and 76, both formulations induced weight gain and increased food consumption over the course of the study. First, as shown in FIG. 75, although throughout the experiment the body weights of the animals were greater in the group receiving Formulation 9, a greater increase in body weight was seen in animals receiving Formulation 2. Specifically, animals receiving Formulation 2 exhibited an approximately 7.84% increase in body weight on Day 5, relative to Day -1, while animals receiving Formulation 9 exhibited an approximately 6.5% increase in body weight over the same time period. Similarly, as shown in FIG. 76, both groups of animals also consumed increased amounts of food over the course of the five-day experiment. In particular, relative to Days -3 to -1, over the course of the five day experiment, the dogs that received Formulation 9 consumed 73.5% more food and the dogs that received Formulation 2 consumed 56.9% more food. In addition, as shown in FIGS. 77 and 78, capromorelin and increased IGF-1 concentrations were detectable in the sera of the animals. Overall, based on the data discussed above, it appears that either Formulation 2 or 9 could function as vehicle to deliver the capromorelin-containing composition.

EXAMPLE 7 - Dog Dose Titration Study

[0107] Additional experiments were performed in order to further refine the dosage administered to the dogs to provide the desired response (*i.e.*, increased body weight and increased food consumption). In particular, the dogs received either Formulation 2 from Example 6 above or a placebo form of the same Formulation. In these experiments, the dogs were divided into five groups, with each group having three males and three females. The groups were divided by dosing concentration. Specifically, the first group received the placebo formulation once per day, the second group received Formulation 2 that was administered at a dose of 0.33 mg/kg once per day, the third group received Formulation 2 that was administered at a dose of 2.0 mg/kg once per day, the fourth group received Formulation 2 that was administered at a dose of 3.0 mg/kg once per day, and the fifth group received Formulation 2 that was administered at a dose of 4.0 mg/kg once per day.

[0108] In these experiments, the animals were orally administered the formulation at approximately 8:00 AM. The animals were fed at 10:00 AM beginning 10 days prior to Day 1 and continuing for the duration of the study (7 days). Approximately two hours after the food offering, the remainder was removed and weighed to assess food intake. This feeding regime was started at Day -10 to allow the animals to transition to a normal feed intake before the study was initiated. Food consumption was calculated and recorded on Days -3 through Day 7. Baseline food consumption was calculated for each group of dogs as the average number of grams of food consumed on Days -3, -2, and -1. The study period food consumption was calculated for each group of dogs as the average of study Days 1 through 7. Body weights were collected on Days 1 (immediately prior to dosing) and 8 (following an overnight fast). No blood was collected for during this experiment.

[0109] As reflected by the data in FIGS. 89 and 90, the animals' response showed positive signs when administered nearly all of the doses. In particular, as best seen in FIG. 89, the body weights increased in all of groups of dogs that received Formulation 2. Interestingly, the body weights of the animals in the placebo group slightly decreased. As viewed a different way, the percent change in body weights went up in all animals that received Formulation 2, as seen in Table 2. In addition, using statistical analyses, it was shown that, relative to placebo, all treatments except for the 0.33 mg/kg, produced statistically significant increases in body weight values.

Table 2: Weight Change

Treatment	Comparison of Weight on Day 1 to Weight on Day 8
Placebo - 1x per day	-0.26%
Formulation 2 - 0.33 mg/kg 1x per day	1.88%
Formulation 2 - 2.0 mg/kg 1x per day	4.91%
Formulation 2 - 3 mg/kg 1x per day	5.29%
Formulation 2 - 4 mg/kg 1x per day	4.54%

[0110] In addition, as shown in FIG. 91 and in Table 3 below, the average food consumption increased in the non-placebo groups when compared to baseline. Specifically, the baseline average was calculated by averaging the food consumed by the dogs on each of Days -3 to -1. Then, the food consumption average was calculated by taking the daily food consumption during the study period on Days 1 to 7. In particular, FIG. 91 generally shows an increase in the amount of food consumed by the animals receiving the non-placebo formulation. In addition, using statistical analyses, it was shown that, relative to placebo, the 4 mg/kg group consumed significantly more food. Moreover, referring to FIG. 92, the Pearson correlation coefficient for the percent change in food consumption versus the percent change in body weight was 0.585, which corresponds to a slope of 5.9%. As such, the increase in body weight was directly proportional to the increased food intake.

Table 3: Food Intake Change

Treatment	Day -3 to -1 (Baseline Period) Average Food Consumption (Grams)	Day 1 to Day 7 (Study Period) Average Food Consumption (Grams)	Difference	% Food Consumption Change over Baseline
Placebo - 1x per day	159.89	161.76	1.87	1.17
Formulation 2 - 0.33 mg/kg 1x per day	193.33	244.55	51.22	26.49
Formulation 2 - 2.0 mg/kg 1x per day	178.89	242.83	63.94	35.74
Formulation 2 - 3 mg/kg 1x per day	205.83	266.48	60.65	29.47
Formulation 2 - 4 mg/kg 1x per day	136.72	210.93	74.21	54.28

EXAMPLE 8 - Cat Probe Formulation Study

[0111] Similar to the previously mentioned pharmacokinetic analysis conducted in dogs, a pharmacokinetic study was conducted in cats to assess capromorelin and IGF-1 concentrations in the serum after administration of different formulations. Briefly, twelve cats were randomized into Group A (six cats) and Group B (six cats). Group A received an IV formulation that included 0.75 mg/kg of capromorelin and Group B received the previously tested formulation 4 via oral gavage. Formulation 4 includes capromorelin at a concentration of 3 mg/kg. Serum samples were taken after administration of the two test formulations to assess capromorelin and IGF-1 concentrations. Samples were taken a time 0 (pre-administration) and 5 minutes, 10 minutes, 30 minutes, 1h, 2h, 4h, 6h, 8h, and 12h post administration.

[0112] As shown in FIGS. 47 and 48, capromorelin compositions in cats do not exhibit the same pharmacokinetic profile as these compositions exhibit in dogs. In particular, as shown in FIG. 48, formulation 4, which was administered via oral gavage, produced a relatively low serum concentration of capromorelin, with the peak concentration occurring two hours after administration. The IV formulation, however, produced a serum concentration of capromorelin similar to what was observed in dogs. Specifically, the serum concentration of capromorelin increased relatively soon after administration (i.e., 5 minutes) and proceeded to decrease until the final samples were taken twelve hours after administration. In spite of the relatively low levels of oral bioavailability (formulation 4), IGF-1 is still induced eight hours after administration, as shown in FIG. 49. This disparity in bioavailability and IGF-1 expression could indicate a relatively large efficacy window for capromorelin to trigger an IGF-1-induced lean muscle response.

EXAMPLE 9 - Refining the Dosing Regimen of the Inappetence-Controlling Compound Containing Capromorelin for Cats

[0113] A four-day study was performed to further assess the pharmacokinetics of formulation 8 from Example 3 (i.e., the most "well-accepted" formulation) in cats. Moreover, the administration of formulation 8 was also analyzed to determine if administration of this formulation could induce sustained production of IGF-1 and relatively depressed, mitigated, or lower levels of cortisol. The different capromorelin-dosing regimens were also assessed for the impact on food intake and changes in body mass.

[0114] Twenty-four adult cats were divided into one of four treatment groups, with all four groups as active treatment groups. Each of the active treatment groups included 6 cats. The first group received a sterile injection of a capromorelin composition containing a 0.75 mg/kg concentration of capromorelin once per day during the four-day experiment. The second group received a once-daily sterile injection of a capromorelin composition at a concentration of 2 mg/kg. The third group received a once-daily dose of a capromorelin composition at a concentration of 2 mg/kg, via oral gavage. The fourth group received a once-daily dose of a capromorelin composition containing capromorelin at a concentration of 4 mg/kg, via oral gavage.

[0115] During the seven day study period, on an at least once-daily basis, each of the cats was monitored for clinical observations, mortality, moribundity, body mass, acceptability/palatability, and food consumption. Serum samples were taken to measure capromorelin concentration, IGF-1 concentration, and cortisol concentration. Serum samples were taken on days 1 and 4 immediately prior to dosing (0 minutes) and 30, 60, 90, 120, 240, 360, and/or 480 minutes post dosing. Additional serum samples were taken at 8 AM on Day 7 of the study to assess long-term impact of the active treatments.

[0116] As indicated in FIGS. 50 and 51, over the course of the experiment, most of the cats consumed greater amounts of food and did not lose weight during the experiment. Specifically, as shown in FIG. 50, cats receiving the sterile injectable formulations or the 4 mg/kg oral gavage administration, consumed more food on day 4 of the experiment relative to prior days of the experiment. Similarly, as shown in FIG. 51, in general, the cats gained weight during the course of the experiment. For example, cats receiving the 0.75 mg/kg and the 2 mg/kg sterile injections of capromorelin exhibited a 1.33% and a 2.37% increase in body weight, respectively, relative to baseline measurements. Similarly, cats receiving the 2 mg/kg and 4 mg/kg oral administrations of capromorelin exhibited a 0.70% and a 1.47% increase in body weight, respectively, relative to baseline measurements.

[0117] Referring now to FIGS. 52-54, cats receiving the sterile injectable formulations exhibited a different pharmacokinetic profile, relative to the cats receiving the oral formulation. The cats receiving sterile injectable formulation displayed a pharmacokinetic profile similar to the previous examples with dogs. Specifically, the capromorelin concentration in the serum peaked at about 0.5h post administration and decreased until reaching near undetectable levels by around eight hours after administration. Additionally, the serum concentrations of capromorelin in the groups receiving the sterile injectable formulation appear to correspond to the concentration of capromorelin administered, as shown in FIGS. 51-53. More specifically, the maximum concentrations of capromorelin in the serum are approximately 2.5 to 3 times greater in the group of cats receiving the 2 mg/kg sterile injection relative to the cats receiving the 0.75 mg/kg dose.

[0118] Conversely, cats receiving the oral formulations exhibited relatively low levels of capromorelin in the serum. Specifically, the 2 mg/kg oral formulation in the active treatment groups exhibited elevated concentrations of capromorelin in their serum, but lower than the cats receiving the sterile injectable formulations. Using data from serum samples taken on days 1 and 4 of the study, capromorelin concentrations tended to begin rising at approximately 0.5 h after dosing and, in general, decreased to near undetectable levels by eight hours after administration. These results confirm that the capromorelin composition was correctly administered.

[0119] As reflected in FIGS. 55-60, cats receiving both the sterile injectable and the oral formulations experienced changes in serum concentrations of IGF-1 and cortisol, which are likely attributable to the capromorelin administration.

[0120] First, as shown in FIGS. 55-57, treatment with capromorelin induced IGF-1 levels within the serum of the cats. Specifically, as shown in FIG. 55, approximately two to four hours after initially dosing the cats with most of the capromorelin formulations, IGF-1 levels exhibited an increase in the serum. However, one treatment group, the cats receiving the 2 mg/kg oral formulation, experienced only moderately increased concentrations of IGF-1 at eight hours post administration, relative to pre-treatment levels. Similarly, on day 4, cats receiving the sterile injectable formulations and the 4 mg/kg oral formulation exhibited sustained increased IGF-1 levels, similar to the IGF-1 profile observed in dogs. On day 4, the cats dosed with the 2 mg/kg oral formulation did not exhibit further increases of IGF-1, as shown in FIG. 56. As shown in FIG. 57, three days after terminating treatment (Day 7), levels of serum IGF-1 in the cats receiving capromorelin treatment were similar in all treatment groups.

[0121] More specifically, in data not shown, relative to time 0 (i.e., prior to administration of the capromorelin composition), the cats in at least some of the treatment groups exhibit increased IGF-1 levels in the serum. For example, on day 1, at eight hours post administration, the cats receiving the 0.75 mg/kg and 2 mg/kg sterile injectable formulations exhibit approximately 39.8% and 43.1% increases in serum IGF-1 concentration, respectively, relative to time 0 on day 1. The cats receiving the 2 mg/kg and 4 mg/kg oral formulations exhibit approximately 26.6% and 30.8% increases in serum IGF-1 concentration, respectively, relative to time 0 on day 1. On day 4, at eight hours post administration, the 0.75 mg/kg and 2 mg/kg sterile injectable formulations induce approximately 12.2% and 10.8% increases in serum IGF-1 concentration, relatively to time 0 on day 4, respectively. Similarly, on day 4, at eight hours post administration, the 2 mg/kg and 4 mg/kg oral formulations induce approximately 7.6% and 0.7% increases in serum IGF-1 concentration, relatively to time 0 on day 4, respectively. It is possible that the cats receiving the sterile injectable and 4 mg/kg oral formulations exhibit increases of a lesser magnitude because serum concentrations of IGF-1 are already at a higher level than are IGF-1 levels in cats receiving theses dosing regimens of capromorelin.

[0122] Referring now to FIGS. 58-60, cortisol concentrations in the serum appear to correlate with administration of capromorelin. Specifically, on days 1 and 4 (FIGS. 58 and 59, respectively), at approximately 0.5h post treatment, cortisol concentrations in the serum of dogs treated with capromorelin begin increasing. Moreover, in all treatment groups other than the 2 mg/kg oral formulation group, the cortisol concentrations continued to increase until between 90 and 120 minutes, where the concentrations began to decrease until reaching near undetectable levels at 480 minutes. In addition, increases in cortisol serum levels were mitigated on day 4, relative to the levels detected during day 1. Moreover, as shown in FIG. 60, three days after terminating treatment (Day 7), levels of serum cortisol in the cats receiving capromorelin treatment were similar in all treatment groups.

[0123] Overall, most of the dosing regimens produced discernible impacts on the cats. Moreover, no toxicological responses were noted. Pharmacological effects were noted, including no increases in body weight and food consumption, as well as increased levels of serum IGF-1, cortisol, and capromorelin. In general, it appeared as through the sterile injectable formulation induced more desirable profiles of serum IGF-1, cortisol, and capromorelin.

EXAMPLE 10 - Further Refinement of the Dosing Regimen of the Inappetence-Controlling Compound Containing Capromorelin for Cats

[0124] Next, additional experiments were conducted to further refine the formulation intended for use with the inappetence-controlling compound containing capromorelin, to confirm the capromorelin serum profile and the IGF-1 response, and to confirm that treatment with a capromorelin-containing composition results in weight gain and increased food consumption. In particular, following an acclimation period of seven days, a total of 20 cats (10 neutered males and 10 intact females) were randomly divided between four treatment groups, with five animals assigned to each group. Specifically, Group 1 received Formulation 1 (referred to as PRT2-81 in corresponding Figures; described below) once per day at a dose of 4 mg/kg of body weight of capromorelin; Group 2 received Formulation 2 (referred to as New Form in corresponding

Figures; described below) once per day at a dose of 4 mg/kg of body weight of capromorelin; Group 3 received Formulation 3 (referred to as PERT2-86 in corresponding Figures; described below) once per day at a dose of 4 mg/kg of body weight of capromorelin; and Group 4 received Formulation 4 (referred to as PRT3-99I in corresponding Figures; described below) once per day at a dose of 4 mg/kg of body weight of capromorelin.

Formulation 1 - PRT2-81	
Ingredient	% weight per volume
Capromorelin	2.10
Citric Acid	0.70
Sodium Citrate	0.50
Sodium Chloride	0.70
Methyl 4-Hydroxybenzoate Salt	0.112
Propyl 4-Hydroxybenzoate Salt	0.013
Thaumatin T200X	0.40
S Rebaudioside A	0.40
MagnaSweet Plus Liquid	0.50
Ethyl Vanillin	0.10
Ethanol	0.25
Neosorb Sorbitol 70%	30.00
Maltitol Solution (Lycasin 80/55)	25.00
Glycerin	20.00
Kollidon 90F (PVP)	1.5
Purified Water	q.s.

Formulation 2 - New Form	
Ingredient	% weight per volume
Capromorelin	3.10
Citric Acid	0.70
Sodium Citrate	0.50
Sodium Chloride	0.70
Methyl 4-Hydroxybenzoate Salt	0.045
Propyl 4-Hydroxybenzoate Salt	0.005
Thaumatin T200X	0.60
MagnaSweet Plus Liquid	0.50
S Rebaudioside A	0.7
Vanillin	0.20
Neosorb Sorbitol 70%	30.00

Formulation 2 - New Form	
Ingredient	% weight per volume
Maltitol Solution (Lycasin 80/55)	25.00
Glycerol Anhydrous	20.00
Kollidon 90F (PVP)	1.5
Purified Water	q.s.
Formulation 3 - PERT2-86	
Ingredient	% weight per volume
Capromorelin	2.10
Citric Acid	0.70
Sodium Citrate	0.50
Sodium Chloride	0.70
Methyl 4-Hydroxybenzoate Salt	0.112
Propyl 4-Hydroxybenzoate Salt	0.013
Thaumatin T200X	0.40
S Rebaudioside A	0.40
MagnaSweet Plus Liquid	0.50
Ethyl Vanillin	0.13
Ethanol	0.30
Neosorb Sorbitol 70%	30.00
Maltitol Solution (Lycasin 80/55)	25.00
Glycerol Anhydrous	20.50
Pluriol-E3350 (PEG)	7.5
Purified Water	q.s.
Formulation 4- PRT3-99I	
Ingredient	% weight per volume
Capromorelin	3.10
Citric Acid (Anhydrous)	0.70
Sodium Citrate	0.50
Sodium Chloride	0.70
Methyl 4-Hydroxybenzoate Salt	0.045
Propyl 4-Hydroxybenzoate Salt	0.005
Thaumatin T200X	0.60
Stevia Extract Rebaudioside A 99%	0.70
MagnaSweet Plus Liquid	0.50

Formulation 4- PRT3-99I	
Ingredient	% weight per volume
Vanillin	0.20
Neosorb Sorbitol 70%	30.30
Maltitol Solution (Lycasin 80/55)	25.00
Glycerol Anhydrous	20.20
Kollidon 90F (PVP)	1.5
Ethanol (ABS)	0.50
Purified Water	q.s.

[0125] In these experiments, on Days 1 through 6, all animals were orally administered the appropriate formulation of capromorelin by syringe in the corner of the right side of the mouth. On Day 6, blood samples were taken from each cat at multiple time points for measurements of capromorelin and IGF-1 in the serum. In particular, blood samples were taken at pre-dose (0 minutes), 30, 60, 90, 120, 240, and 480 minutes post dose. Moreover, IGF-1 was measured at 0 minutes and 480 minutes, and capromorelin was measured at each time period. In addition, on Days 1, 2, 3, 4, and 5, dose acceptability and palatability observations were performed.

[0126] As summarized in FIGS. 79-82, the cats did not appear to have significant issues with any of the formulations, although the cats appeared to generally dislike the dosing procedure. In general, none of the formulations were "well accepted" by the cats; however most of the formulations were still accepted with some adverse clinical observation projected by some of the cats (i.e., licking, smacking of the mouth/lips, and salivation). Overall, the formulations were generally accepted at similar levels by the cats.

[0127] Next, as shown in FIG. 83 and Table 2 below, the cats all gained weight as a result of receiving the test formulations. On average, all of the groups experienced between a 2% and 4% increase in weight.

Table 4: weight Change

Group	**Day -1 Weights (mean ± SD, kg)**	**Day 6 Weights (mean ± SD, kg)**	**Average Increase in Weight on Day 6 v. Day -1**
1 - PRT2-81	5.1±1.4	5.2±1.4	2.0%
2 - New Form	5.0±2.5	5.2±2.4	4.0%
3 - PERT2-86	5.0±1.6	5.2±1.6	4.0%
4 - PRT3-99I	4.9±2.1	5.0±2.0	2.0%

Group	Day -1 Weights (mean ± SD, kg)	Day 6 Weights (mean ± SD, kg)	Average Increase in Weight on Day 6 v. Day -1

[0128] As illustrated in FIGS. 84-86 and Table 3 below, the increase seen in the weights of the cats was due, at least in part, to an increase in food consumption. In particular, during the experiment, food consumption was calculated for all animals, including during the acclimation period during Days -3 to -1. Specifically, during the acclimation period, mean individual food consumption ranged from 19 to 60 grams per day for all made study cats and 23 to 50 grams per day for all female study cats. The acclimation mean individual daily food consumed, based on Day -1 body weight, was calculated to be 3.6 to 8.8 g/kg for all male study animals and 6.1 to 14.0 g/kg for all female study animals. As shown in FIGS. 84-86, all study animals were observed with an increased appetite, which resulted in increased mean food consumption, when comparing the acclimation period to the post-dosing period. Significantly, food consumption likely decreased on Day 6 due to the numerous blood samples collected that day. As highlighted in Table 3, each of the different formulations induced large increases in food consumption.

Table 5: Food Intake Increase

Group	Day -3 to -1 Mean (g)	Day 1 to 6 Mean (g)	Difference (g)	Percent Food Intake Increase
1 - PRT2-81	36.20	67.23	31.03	85.72
2 - New Form	38.21	75.93	37.72	98.72
3 - PERT2-86	45.33	69.73	24.40	53.83
4 - PRT3-99I	44.13	63.33	19.20	43.51

[0129] Next, as shown in FIG. 87, similar to prior results in both cats and dogs, each of the test formulations induced an initial spike in capromorelin concentration in the test animals within 30 minutes of administration. After the initial spike and over the course of the next eight hours, the serum concentrations of capromorelin decreased to levels below detection limitations of the assay. Interestingly, animals in Group 1, on average, exhibited a higher initial spike in capromorelin concentration in the serum, but eventually cleared the composition by eight hours post dosing. In addition, as shown in FIG. 88 and Table 4 below, all four tested formulations induced some level of increase in serum concentration of IGF-1. As discussed in previous experiments, these daily increases may not be as significant as expected due to the fact that by Day 6, it would be expected to have sustained amounts of IGF-1 circulating through the animals as a result of treatment with a capromorelin-containing composition.

Table 6: Percent Increase of Serum IGF-1 levels on Day 6

Group	Serum IFG-1 levels at T=0 min (ng/mL)	Serum IFG-1 levels at T=480 min (ng/mL)	Percent Food Intake Increase
1 - PRT2-81	714.0	859.1	20.3
2 - New Form	833.7	922.6	10.7
3 - PERT2-86	952.7	1023.9	7.5
4 - PRT3-99I	1047.6	1085.4	3.6

EXAMPLE 11 - Additional Refinement of the Dosing Regimen of the Inappetence-Controlling Compound Comprising Capromorelin for Cats

[0130] In order to determine a dosing scheme for cats that provides the desired profile of IGF-1 and cortisol levels to support the positive effects associated with the inappetence-controlling composition (*i.e.*, increased appetite and muscle mass), additional experiments were conducted. In particular, all of the cats in this experiment received different doses of Formulation 4 from Example 10 discussed above. In particular, a total of 30 cats were divided into five groups, with three males and three females included in each group: Group 1 received the placebo formulation once per day; Group 2 received Formulation 4 at a dose of 1 mg/kg once per day; Group 3 received Formulation 4 at a dose of 2 mg/kg once per day; Group 4 received Formulation 4 at a dose of 3 mg/kg once per day; and Group 5 received Formulation 4 at a dose of 4 mg/kg once per day. All animals were orally dosed.

[0131] The experiment proceeded after an acclimation period of seven days, with this period intended to allow the cats to adapt to the feeding regimen associated with the experiments. Starting with Day -7, 300 grams of food was offered to each of the animals for a period of approximately 4 hours, starting at 11:00 AM and ending at 3:00 PM. After removal, the food was weighed each day to assess consumption. In these experiments, on Days 1 through 10, all animals were orally administered in the corner of the mouth with the appropriate dose of Formulation 4. On Days 1 and 10, blood samples were taken from each cat at multiple time points for measurements of capromorelin, IGF-1, and/or cortisol in the serum. In particular, blood samples were taken at pre-dose (0 minutes), 30, 60, 90, 120, 240, and 480 minutes post dose. Blood samples were also taken on Days 12 and 15 to assess "washout" of the capromorelin composition. Moreover, body weights of the individual animals were measured on Days -7, -1, 5, and 10. In addition, appropriate dosing of Formulation 4 was based on the weight data gathered on Day -1.

[0132] As shown in FIG. 93 and Table 7, administration of the inappetence-controlling composition resulted in an overall daily increase in food consumption, relative to the baseline amounts. In particular, the baseline values were calculated by averaging the food consumed for each group on Days -3 to -1 and the study period average was calculated for Days 1 through 10. Although food consumption generally increased during the study, on Day 10, one of the two days on which there was extensive blood sampling, the amount of food consumed was slightly reduced, which is likely attributable to the stress induced by the blood sampling. As shown in Table 7 and generally illustrated in FIG. 93, treatment with all different doses of Formulation 4 resulted in increased food consumption.

Table 7: Food Intake Increase

Group	Day -3 to -1 (Baseline) (g)	Day 1 to 10 (Study Period) (g)	Difference (g)	Percent Food Consumption Change Over Baseline
1 - Placebo	43.06	47.25	4.20	9.75
2 - 1 mg/kg	48.33	58.43	10.10	20.90
3 - 2 mg/kg	43.89	62.83	18.95	43.17
4 - 3 mg/kg	45.94	68.78	22.84	49.71
5 - 4 mg/kg	27.67	56.62	28.95	104.62

[0133] Next, as shown in FIG. 94 and Table 8 below, treatment with different doses of Formulation 4 of the inappetence-controlling composition also resulted in generally increased body weights of the cats. In addition, the animals that received the placebo formulation did not have any change in body weight between Days -1 and 10. Overall, the cats in all of the experimental groups gained weight as a result of the treatment, with the animals that received the 3 mg/kg and 4 mg/kg doses exhibiting significant increases in body weight, relative to the placebo control animals.

Table 8: Change in Body Weight

Group	Mean - Change from Baseline to Day 10 (kg)	Mean - Change from Baseline to Day 10 (%)
1 - Placebo	0.00	0.00
2 - 1 mg/kg	0.15	3.07
3 - 2 mg/kg	0.16	3.04
4 - 3 mg/kg	0.27	5.38
5 - 4 mg/kg	0.21	4.43

[0134] Referring now to FIGS. 95 and 96, treatment with different doses of Formulation 4 of the inappetence-controlling composition resulted in corresponding increases in capromorelin concentration in the serum. In particular, the greater doses of capromorelin administered to the cats were correlated with greater concentrations of capromorelin detected in the serum during the eight hours after administration on both Days 1 and 10. Moreover, there was no evidence of capromorelin accumulation within the animals, as the concentration of capromorelin returned to undetectable levels by eight hours after administration on both Days 1 and 10.

[0135] As illustrated in FIGS. 97-100 and Tables 9 and 10 below, treatment with different doses of Formulation 4 of the inappetence-controlling composition resulted in initial increases in IGF-1 levels in the serum of the cats. Initially, as shown in FIG. 97 and Table 9, after administration on Day 1, the serum levels of IGF-1 began to rise in the experimental groups around 120 minute post administration and were all higher by 480 minutes post administration, relative to the pre-dose time point. Moreover, as shown in FIG. 98 and Table 10, by Day 10, the animals receiving the non-placebo formulation all exhibited sustained increases in IGF-1 concentration in the serum over the entire sampling time frame. This sustained increase in IGF-1 after receiving multiple consecutive daily or twice daily doses of a capromorelin-comprising composition is consistent with the previously discussed examples. Overall, based on a review of the data, it appears that the animals in Group 4 (3 mg/kg) exhibited the highest sustained increase of IGF-1 over the study period. In particular, as shown in Table 10, the percent increase in IGF-1 for Group 4 at the 480 minute time point relative to the pre-dose time point was actually negative because of the highly sustained IGF-1 levels over the previous 24 hours. Further, as shown in FIGS. 99 and 100, two days after ceasing treatments (Day 12 - FIG. 99), the serum IGF-1 levels began to decrease, and by five days after treatments (Day 15 - FIG. 100), the serum IGF-1 levels had returned to baseline.

Table 9: IGF-1 Serum Concentrations: Day 1

Group	Percent Increase in IGF-1 at 480 Minutes relative to Pre-Dose Levels (0 Minutes)
1 - Placebo	12.79
2 - 1 mg/kg	44.69
3 - 2 mg/kg	34.35
4 - 3 mg/kg	45.02
5 - 4 mg/kg	56.83

Table 10: IGF-1 Serum Concentrations: Day 10

Group	Percent Increase in IGF-1 at 480 Minutes relative to Pre-Dose Levels (0 Minutes)
1 - Placebo	5.23
2 - 1 mg/kg	8.51
3 - 2 mg/kg	10.41
4 - 3 mg/kg	-3.45

Group	Percent Increase in IGF-1 at 480 Minutes relative to Pre-Dose Levels (0 Minutes)
5 - 4 mg/kg	11.26

[0136] As illustrated in FIGS. 101 and 102, treatment with different doses of Formulation 4 of the inappetence-controlling composition resulted in initial increases in cortisol levels in the serum of the cats. In particular, as shown in FIG. 101, on Day 1, each of the animals in the experimental groups showed an initial increase in serum cortisol concentration, which eventually returned to baseline levels by 480 minutes after administration. Moreover, this increase seen on Day 1 in the experimental groups was mitigated by Day 10. Specifically, as shown in FIG. 102, the increase in serum cortisol concentration was abrogated, relative to the serum concentrations spikes detected on Day 1, which is consistent with the other Examples discussed above. In addition, as shown in FIGS. 103 and 104, after the experimental period, on Days 12 and 15, there was no sustained increase in serum cortisol concentrations detected in the experimental or control animals.

EXAMPLE 12 - Cat Probe Formulation Study and Pharmacokinetic Analysis

[0137] Similar to some of the other pharmacokinetic analyses conducted in dogs and cats, an additional pharmacokinetic study was conducted in cats to assess capromorelin formulations that allow sufficient drug to circulate to produce appetite stimulation and to define the capromorelin pharmacokinetic profile in cats. Briefly, twelve cats were randomized into Group 1 (six cats) and Group 2 (six cats). Group 1 received an intravenous formulation that included 0.75 mg/kg of capromorelin dissolved in sterile water and Group 2 received a previously tested formulation via oral gavage. Food consumption was determined daily for all cats. Specifically, animals were offered feed at approximately 11:00 AM, with the removal of feed at approximately 3:00 PM. Upon removal of feed, the amount consumed was calculated. As an initial matter, the observed food consumption did not reveal any significant increases in food consumption (data not shown), but the length of the treatment regimen was shorter than traditional treatment regimens.

[0138] Initially, the cats were given a seven day acclimation period to adjust to the experimental conditions and feed provided. After the acclimation period, on Day 0, all animals in Group 1 received an intravenous injection of the composition containing a dose of 0.75 mg/kg of capromorelin. On Day 0, the animals in Group 2 received an oral administration of the formulation via gavage at a dose of 3 mg/kg of capromorelin. On Day 0, serum samples were taken from the Group 1 animals at time 0 (pre-administration) and 5 minutes, 10 minutes, 30 minutes, 1h, 2h, 4h, 6h, 8h, and 12h post administration and serum samples were also taken from the Group 2 animals at time 0 (per-administration) and 15 minutes, 30 minutes, 45 minutes, 1h, 2h, 4h, 6h, 8h, and 12h post administration. Thereafter, on Day 1, the animals in Group 2 received a second dose of the test formulation at a dose of 1 mg/kg to assess palatability and acceptability, which revealed general acceptability and palatability of the formulation (data now shown).

[0139] Referring to FIGS. 105 and 106, the serum profile of the concentration of capromorelin differed between Groups 1 and 2. In particular, as one would expect, the serum concentration of the Group 1 animals increased at a much faster rate and reached a much greater level, compared to the Group 2. Specifically, the Group 2 animals, which received an oral administration of the capromorelin composition, experienced a small peak in serum concentration at around 2 hours post administration of around 150 ng/mL. Conversely, the Group 1 animals, which received an intravenous injection of the composition, experienced a greater peak (around 625 ng/mL) at around 5 minutes post administration. Referring now to FIG. 107, the animals in Group 1 also experienced a greater increased in IGF-1 levels in the serum compared to the animals in Group 2.

[0140] In addition to testing the aforementioned plasma levels of capromorelin and IGF-1, additional pharmacokinetic analysis was also completed. In particular, it was determined that the plasma profile of the capromorelin in the Group 1 animals was biphasic, which included both a distribution and an elimination component. Moreover, this analysis also revealed that the clearance of capromorelin in the Group 1 animals was rapid, (approximately 30 mL/min/kg), which is substantially similar to hepatic blood flow in cats. As a result of this relatively rapid clearance rate, it is suggestive that the oral bioavailability will be generally low and variable in cats. In addition, the pharmacokinetic data also suggests that the terminal half-life of capromorelin in cats is about 0.9 hours. The overall pharmacokinetic data for the Group 1 animals is illustrated in FIG. 108.

[0141] The plasma profile of the Group 2 animals consisted of an absorption phase, plateau or double peak at the T_{max}, and a rapid terminal phase. In particular, the pharmacokinetic data for the Group 2 animals is illustrated in FIG. 109. For example, the mean C_{max} was 148.9 ng/mL and occurred at 2 hours. The plateau or double peak of the profile could be due to the enterohepatic recycling, which occurs when a drug is eliminated as a drug-conjugate complex in the bile such that the complex is broken down in the distal intestinal track so that the drug is reabsorbed. The plateau or double peak could also be due to absorption at different points in the intestinal track. In addition, the mean-terminal half-life was 1.04 hours.

EXAMPLE 13 - Cat Compromised Kidney Study

[0142] The following study was undertaken to assess multiple points. First, the following experiments were conducted to determine if a formulation of capromorelin, when administered either intravenously or subcutaneously, can stimulate appetite in cats with compromised kidney function. Second, the following experiments were conducted to assess the pharmacokinetic profile of capromorelin in the serum of cats with compromised kidney function. Finally, the following experiments were conducted to determine if capromorelin accumulates in the serum after 14 days of treatment that is subcutaneously administered.

[0143] Sixteen cats with compromised kidney function were acclimatized for the following study. Animals assigned to Group 1 (n=6) received an intravenous administration of a capromorelin formulation (i.e., capromorelin in sterile water) at a dose of 0.75 mg/kg on Day 0 of the experiment. Animals assigned to Group 2 (n=6) received a subcutaneous administration of a capromorelin formulation (2.1% w/v capromorelin, 1% w/v benzyl alcohol, and citrate buffer) daily for 14 days at a dose of 2 mg/kg. Animals assigned to Group 3 (n=4) served as untreated controls. During the study, blood samples were taken from the Group 1 animals at time points 0 (pre-administration), 5 minutes, 10 minutes, 30 minutes, 1 h, 2h, 4h, 6h, 8h, and 12h post administration on Day 0. Blood samples were taken from the Group 2 animals at time points 0 (pre-administration), 15 minutes, 30 minutes, 45 minutes, 1 h, 2h, 4h, 6h, 8h, and 12h post administration on Day 0 and time points 0, 30 minutes, 1h, 2h, 4h, and 8h post administration on Day 13. In addition, body weights were collected on study days -7, -1, and 13 (for Groups 2 and 3 only). Diet consumption was also monitored on study days -7 until day 13 for the animals in Groups 2 and 3 only.

[0144] Referring to FIG. 110, there were no significant differences found in the body weights of animals in Groups 2 and 3 over the course of the study. In particular, during the study, animals in both Groups 2 and 3 lost weight, which suggests that the loss of weight in the Group 2 animals is likely not due to the treatment. Similarly, as shown in FIG. 111, there is no significant difference in the amount of food consumed between the animals in Groups 2 and 3, although it appears that the raw means of food consumed by the Group 2 animals are greater than the means of the amount of food consumed by the Group 3 animals.

[0145] Referring to FIG. 112, after administration of the capromorelin compositions to the animals in Groups 1 and 2, an initial increase was immediately seen in the serum concentration of capromorelin. In particular, in the Group 1 animals that received an intravenous administration of the composition, the serum concentration of capromorelin initially spiked at about 5 minutes post-administration (about 397 ng/mL) and then gradually returned to baseline by about 8 hours after administration. Similarly, on Day 0 in the Group 2 animals that received a subcutaneous injection of the composition, the serum concentration of capromorelin also initially spiked at about 15 minutes post-administration (about 833 ng/mL) and then returned to baseline levels by about 8 hours after administration. Moreover, as shown in FIG. 113, on Day 13 of the study (i.e., after having received 13 previous administrations), the animals in Group 2 exhibited a spike in serum capromorelin concentration at 30 minutes post administration (about 950 ng/mL) and then returned to baseline levels by about 8 hours post administration. As such, it appears that capromorelin does not accumulate in the serum of animals after 14 days of treatment because the levels of capromorelin in the Group 2 animals were at a baseline at both times 0 and 8 hours post administration on Day 13.

[0146] Referring now to FIGS. 114 and 115, the animals in Groups 1 and 2 both experienced an increased in serum concentration of IGF-1 as a result of the treatment with capromorelin. In particular, after 8 hours post administration on Day 0, the animals in Group 1 experienced an increase in IGF-1 (FIG. 114), which was also seen on Days 0 and 13 in the Group 2 animals (FIG. 115).

[0147] Furthermore, additional pharmacokinetic analyses were also conducted on the serum samples from the Groups 1 and 2 animals. Referring to FIGS. 116 and 117, the pharmacokinetics of capromorelin in the Group 1 animals was similar to what was previously observed regarding a rapid clearance (20 mL/min/kg) in several of the test animals. Moreover, the terminal half-life of the capromorelin was estimated to be between 0.67 and 0.9 hours. All together, the pharmacokinetics are substantially similar to non-kidney compromised cats, with respect to administration via intravenous injection.

[0148] Referring to FIGS. 116 and 118, the pharmacokinetics of subcutaneously administered capromorelin were also determined. In particular, the geometric Cmax was 893 ng/mL and was noted at 0.42 hours. In addition, the mean fraction of the dose absorbed was determined by dividing the mean area under the curve (AUC)/dose of the animals in Group 2, which was divided by AUC/dose of the animals in Group 1. In this case, the mean fraction of the dose (F) absorbed is 1.37. The mean absorption time was rapid (0.4 hr), which suggests rapid absorption of capromorelin via subcutaneous administration, which is shorter than oral administration times of absorption. Taken together, this pharmacokinetic data suggests that capromorelin that is subcutaneously administered to cats is well absorbed.

REFERENCES CITED IN THE DESCRIPTION

Cited references

Patent documents cited in the description

- US2009170757A [0003]
- US2010249228A [0003]
- US6482825B [0020]
- US6852722B [0020]
- US6306875B [0020]

Non-patent literature cited in the description

- **WHITE, J.**Clin. Endocrin Metabolism, 2009, vol. 94, 41198-1206 [0003]

PATENTKRAV

1. Farmaceutisk sammensætning til anvendelse i behandling af manglende appetit hos en hund eller kat, hvor sammensætningen er beregnet til oral administration, hvilken sammensætning omfatter:

en terapeutisk virksom mængde capromorelin omfattende en koncentration på mellem ca. 3,0 milligram og ca. 4,5 milligram capromorelin pr. kilogram af hundens eller kattens kropsvægt;

et eller flere farmaceutisk acceptable hjælpestoffer eller bærestoffer;

hvor sammensætningen er formuleret til administration mindst én gang dagligt; og

hvor, efter administration til hunden eller katten, hunden eller katten øger foderindtagelsen med mindst 50 % sammenlignet med ingen administration, og den magre muskelmasse øges med mindst 5 % af hunden eller katten sammenlignet med ingen administration.

2. Farmaceutisk sammensætning til anvendelse ifølge krav 1, hvor capromorelinsammensætningen omfatter en mængde capromorelin, der er tilstrækkelig til at opnå en C_{max} på ca. 150 nanogram capromorelin eller en metabolit deraf pr. milliliter plasma ved en T_{max} på ca. to timer.

3. Farmaceutisk sammensætning til anvendelse ifølge krav 1 eller krav 2, videre omfattende en bestanddel valgt fra gruppen bestående af et emulgeringsmiddel og et viskositetsforbedrende middel.

4. Farmaceutisk sammensætning til anvendelse ifølge et hvilket som helst foregående krav, videre omfattende en bestanddel fra gruppen bestående af et smagsstof, et maskeringsmiddel og kombinationer deraf.

5. Farmaceutisk sammensætning til anvendelse ifølge krav 4, hvor smagsstoffet eller maskeringsmidlet vælges fra gruppen bestående af et sødemiddel, et saltsmagsmiddel, et bitterstof, et syrningsmiddel og kombinationer deraf.

6. Farmaceutisk sammensætning til anvendelse ifølge krav 5, hvor sødemidlet vælges fra gruppen bestående af sucralose, neotam, steviaekstrakt, rebaudiosid A, 97 %: 3 % blanding af saccharose og maltodextrin, en vaniljeholdig sammensætning og kombinationer deraf.

7. Farmaceutisk sammensætning til anvendelse ifølge et hvilket som helst foregående krav, hvor hjælpestoffet vælges fra en gruppes bestående af fortyndingsmidler, bindemidler, fyldstoffer, buffermidler, pH-modificerende midler, sprængmidler, dispergeringsmidler, stabilisatorer, konserveringsmidler og farvestoffer.

8. Farmaceutisk sammensætning til anvendelse ifølge et hvilket som helst foregående krav, hvor den farmaceutiske sammensætning er indeholdt i en injektionssprøjte.

9. Farmaceutisk sammensætning til anvendelse ifølge et hvilket som helst foregående krav, hvor sammensætningen er i form af en opløsning eller en suspension.

10. Farmaceutisk sammensætning til anvendelse ifølge et hvilket som helst foregående krav, hvor bærestoffet omfatter en saltopløsning.

DRAWINGS

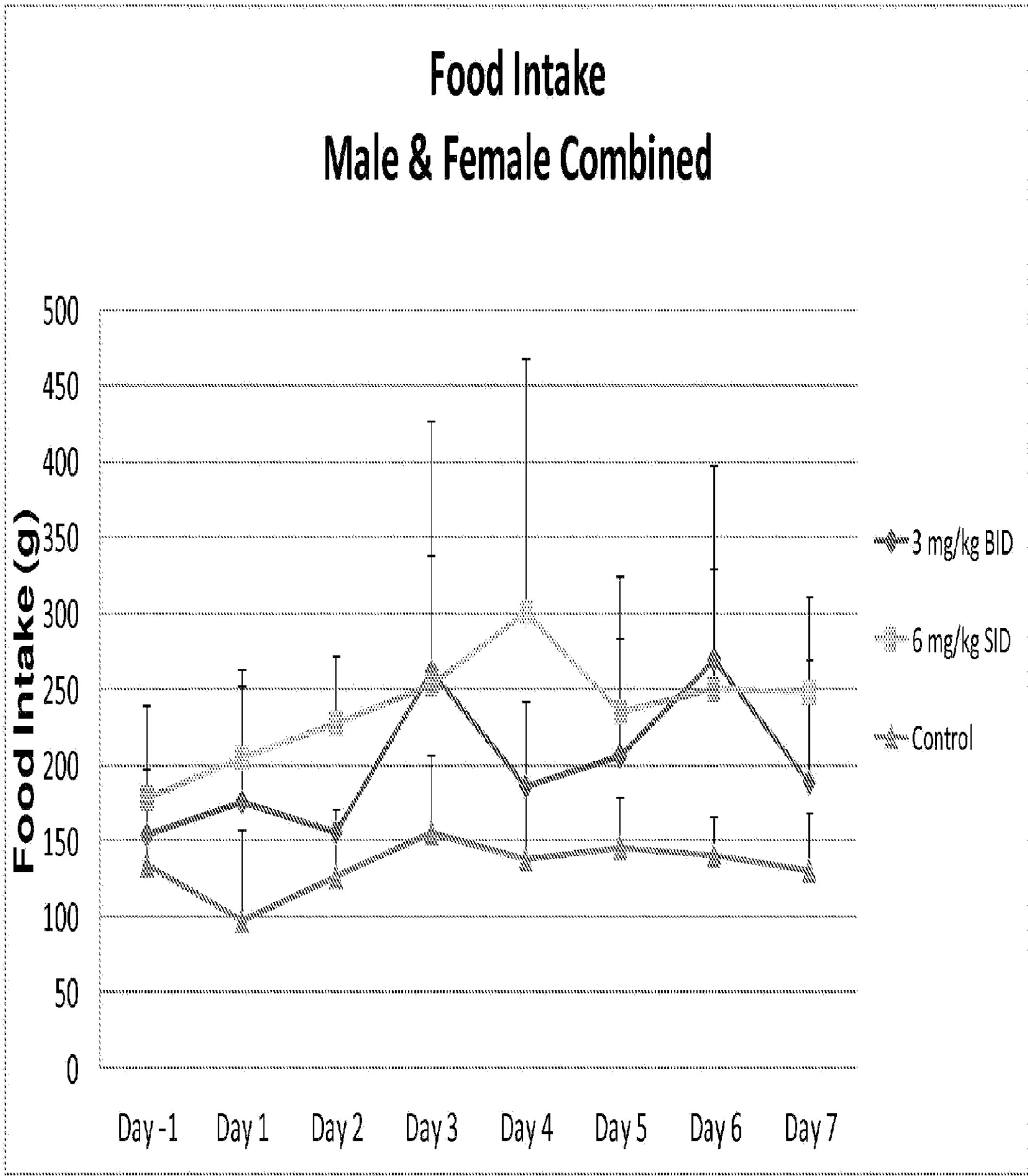
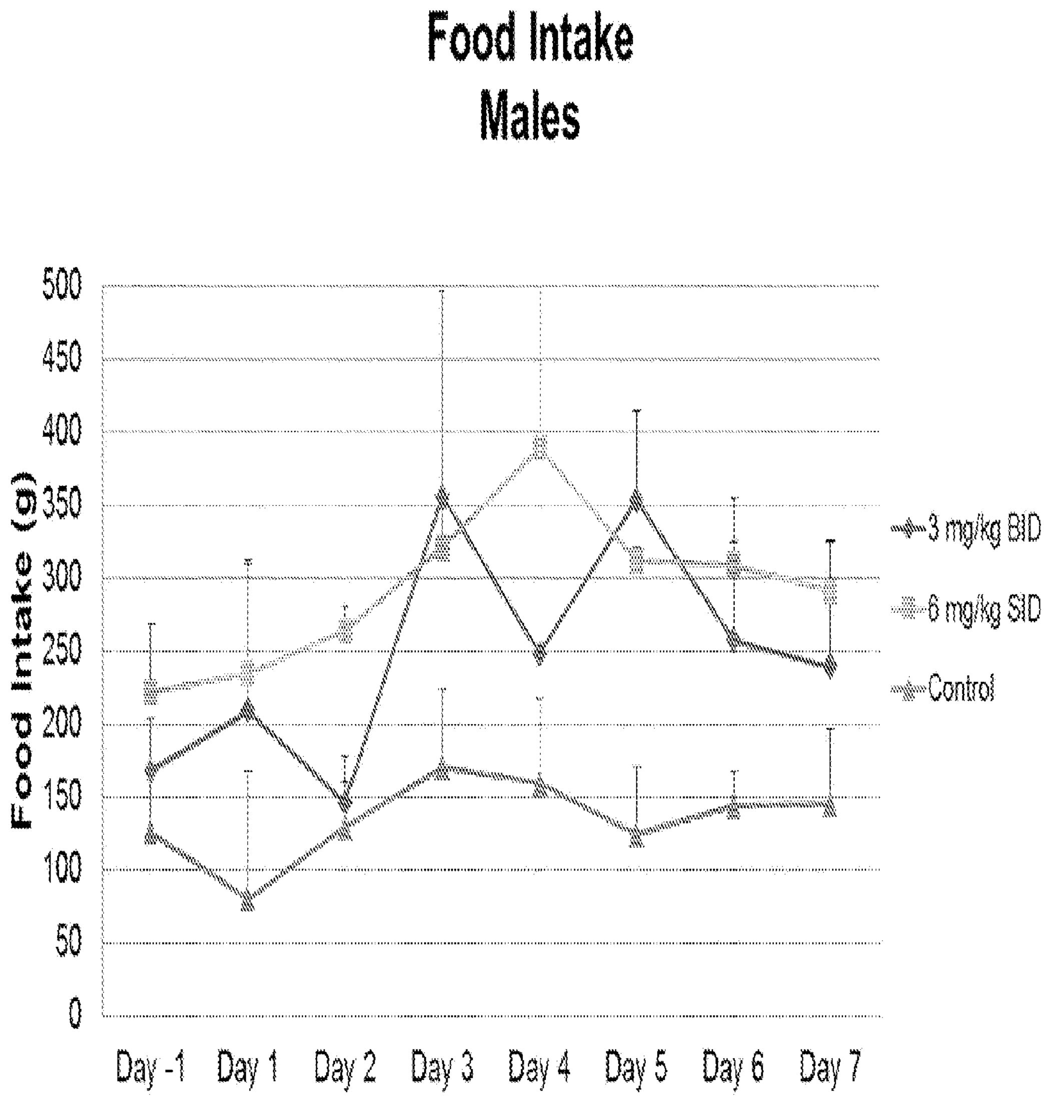


FIGURE 1



Food Intake
Males
Food Intake (g)
500
450
400
350
300
250
200
150
100
50
0
Day -1
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
3 mg/kg BID
6 mg/kg SID
Control

FIGURE 2

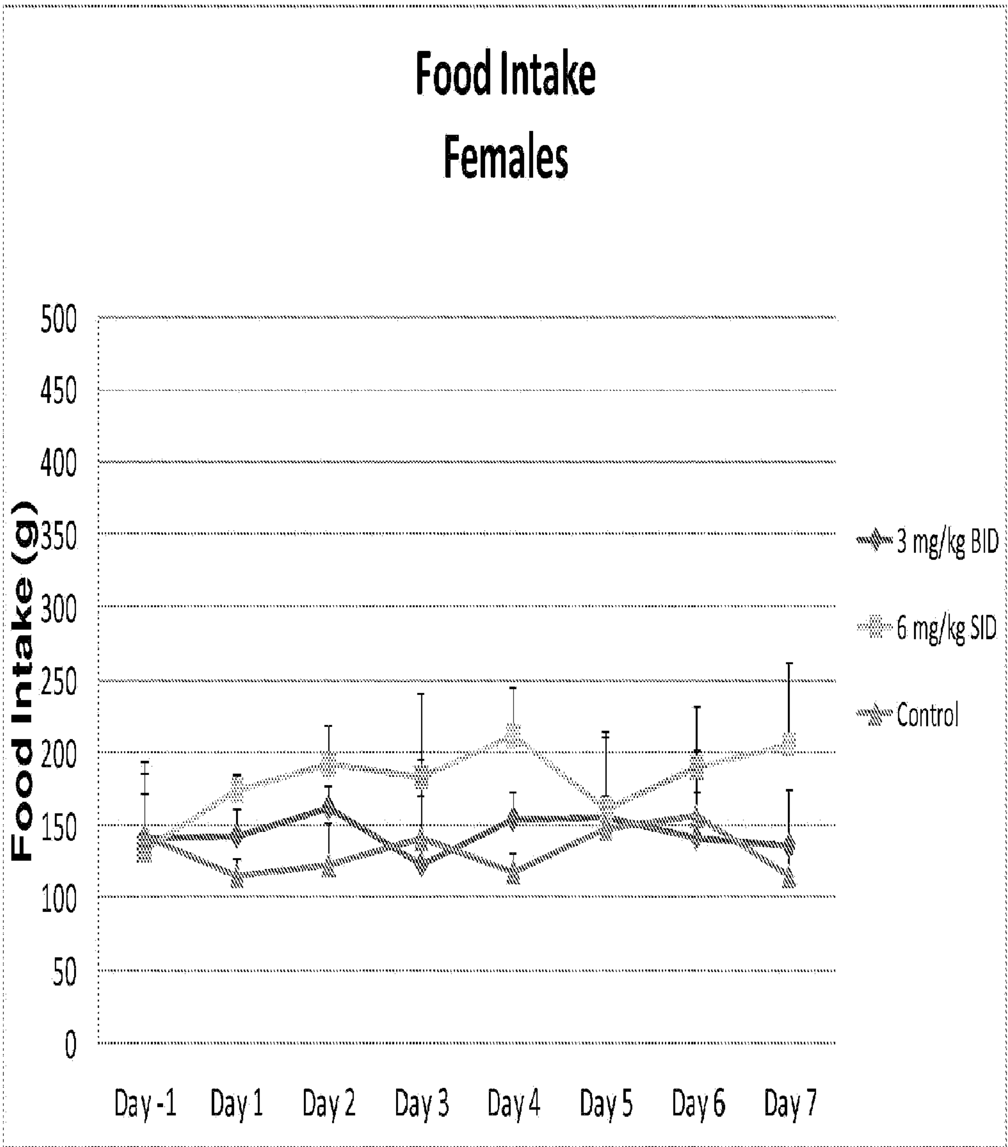

Food Intake
Females
Food Intake (g)
500
450
400
350
300
250
200
150
100
50
0
Day -1
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
3 mg/kg BID
6 mg/kg SID
Control

FIGURE 3

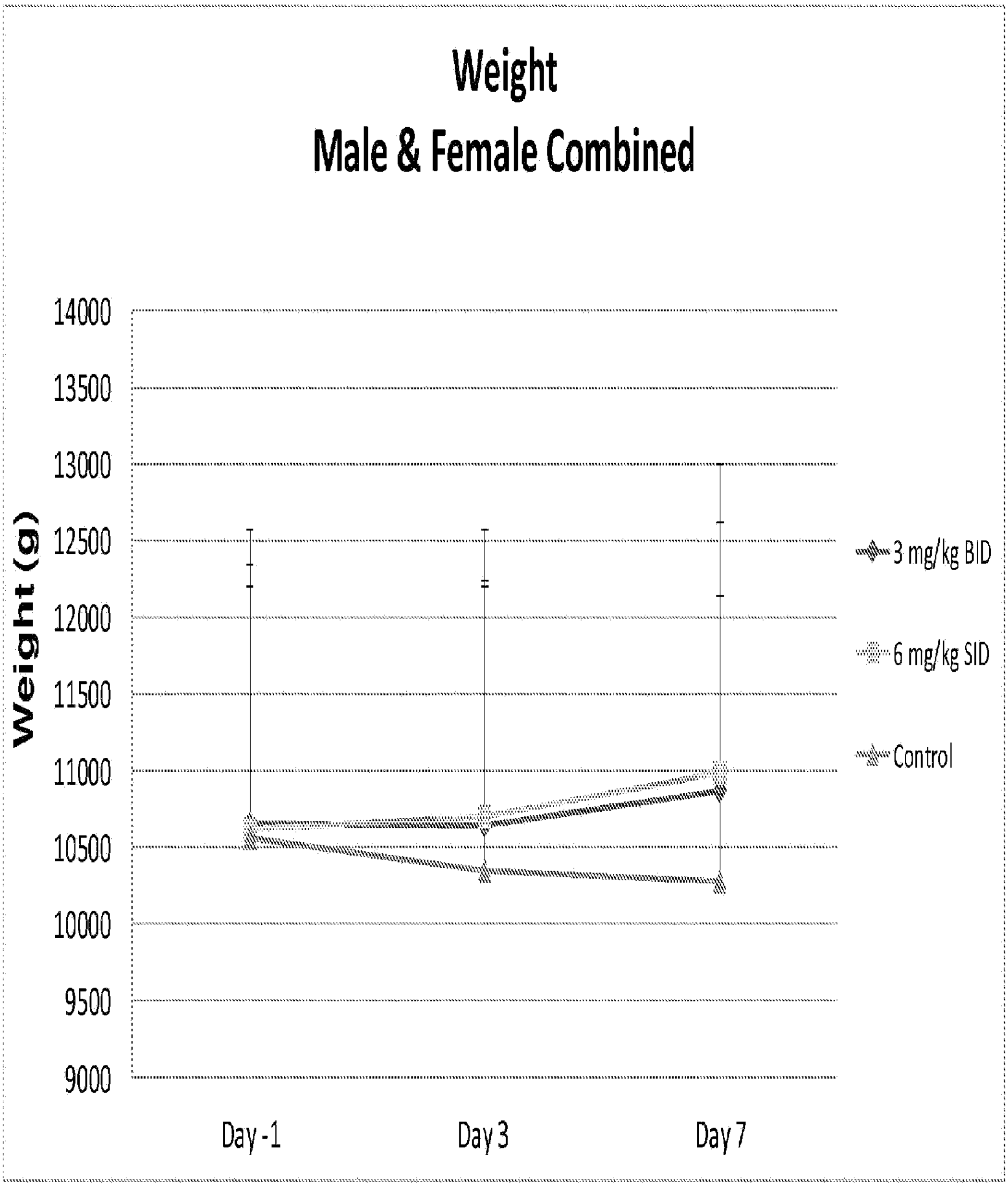

Weight
Male & Female Combined
Weight (g)
14000
13500
13000
12500
12000
11500
11000
10500
10000
9500
9000
Day -1
Day 3
Day 7
3 mg/kg BID
6 mg/kg SID
Control

FIGURE 4

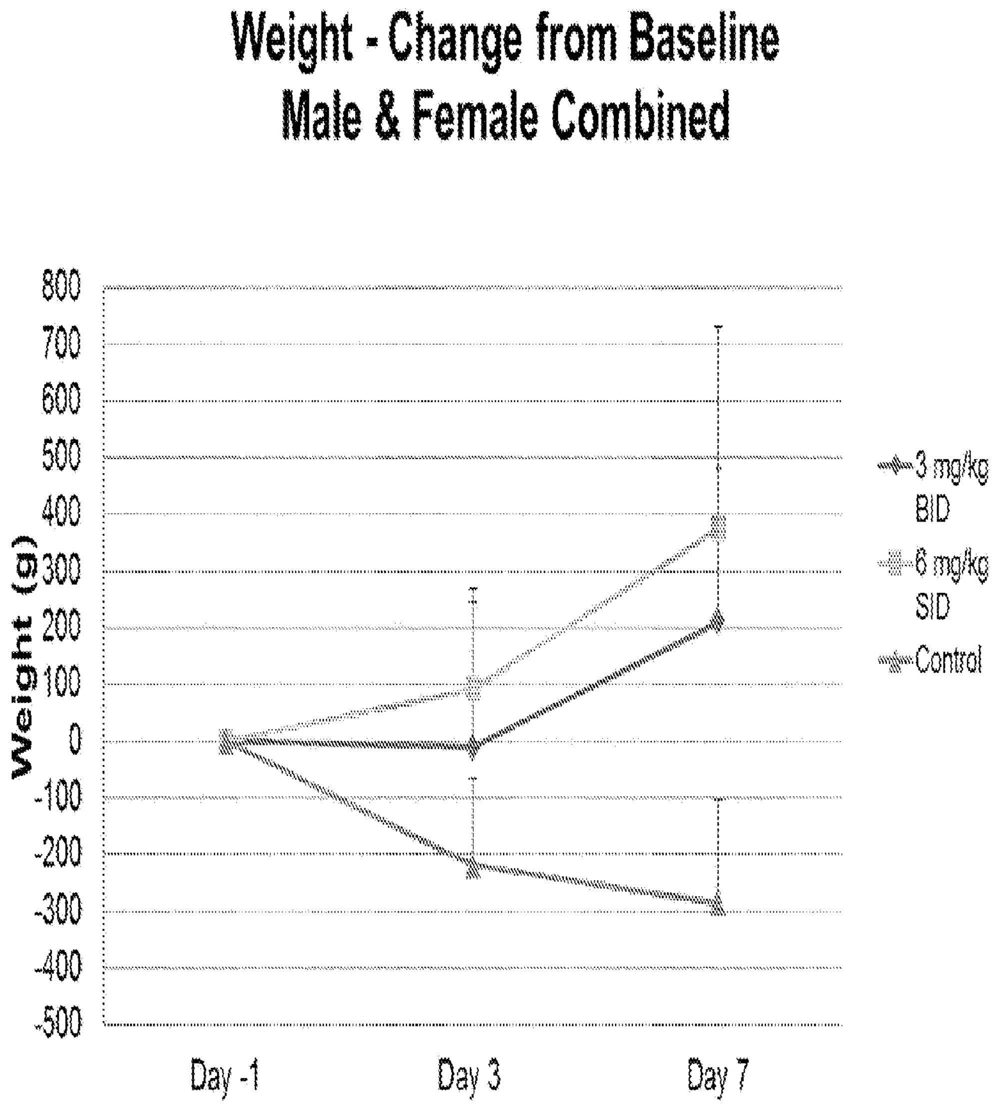

Weight - Change from Baseline
Male & Female Combined
Weight (g)
800
700
600
500
400
300
200
100
0
-100
-200
-300
-400
-500
Day -1
Day 3
Day 7
3 mg/kg BID
6 mg/kg SID
Control

FIGURE 5

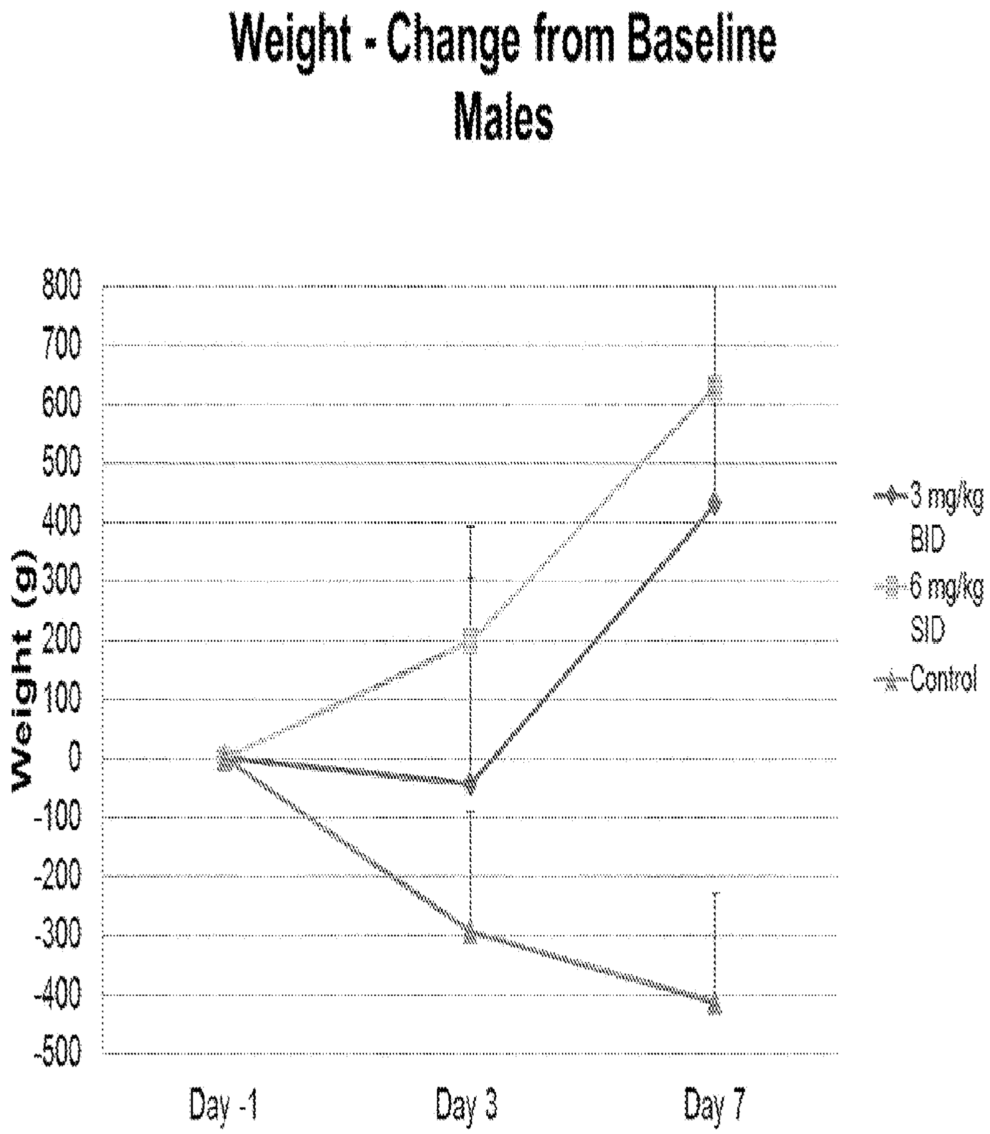

Weight - Change from Baseline
Males
Weight (g)
800
700
600
500
400
300
200
100
0
-100
-200
-300
-400
-500
Day -1
Day 3
Day 7
3 mg/kg BID
6 mg/kg SID
Control

FIGURE 6

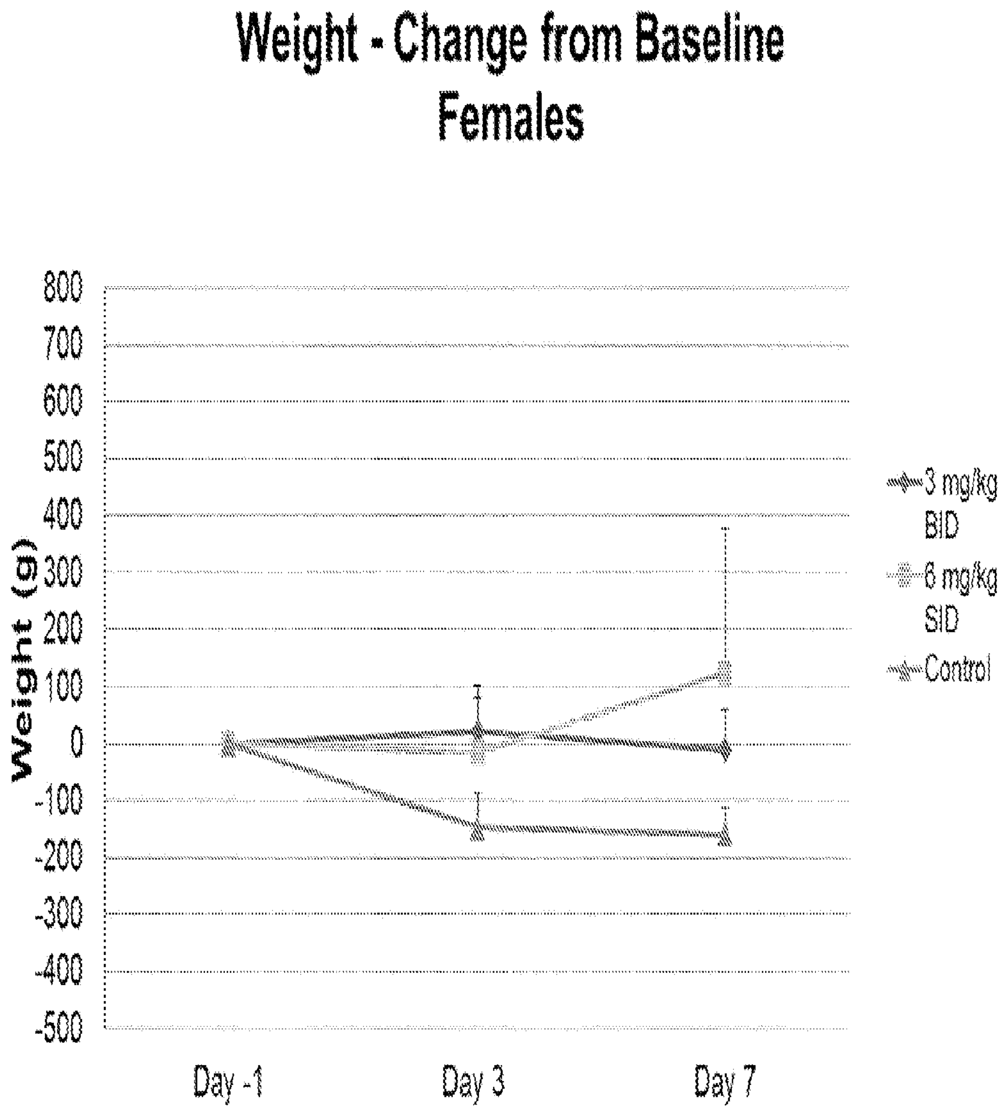

Weight - Change from Baseline
Females
800
700
600
500
400
300
200
100
0
-100
-200
-300
-400
-500
Weight (g)
Day -1
Day 3
Day 7
3 mg/kg BID
6 mg/kg SID
Control

FIGURE 7

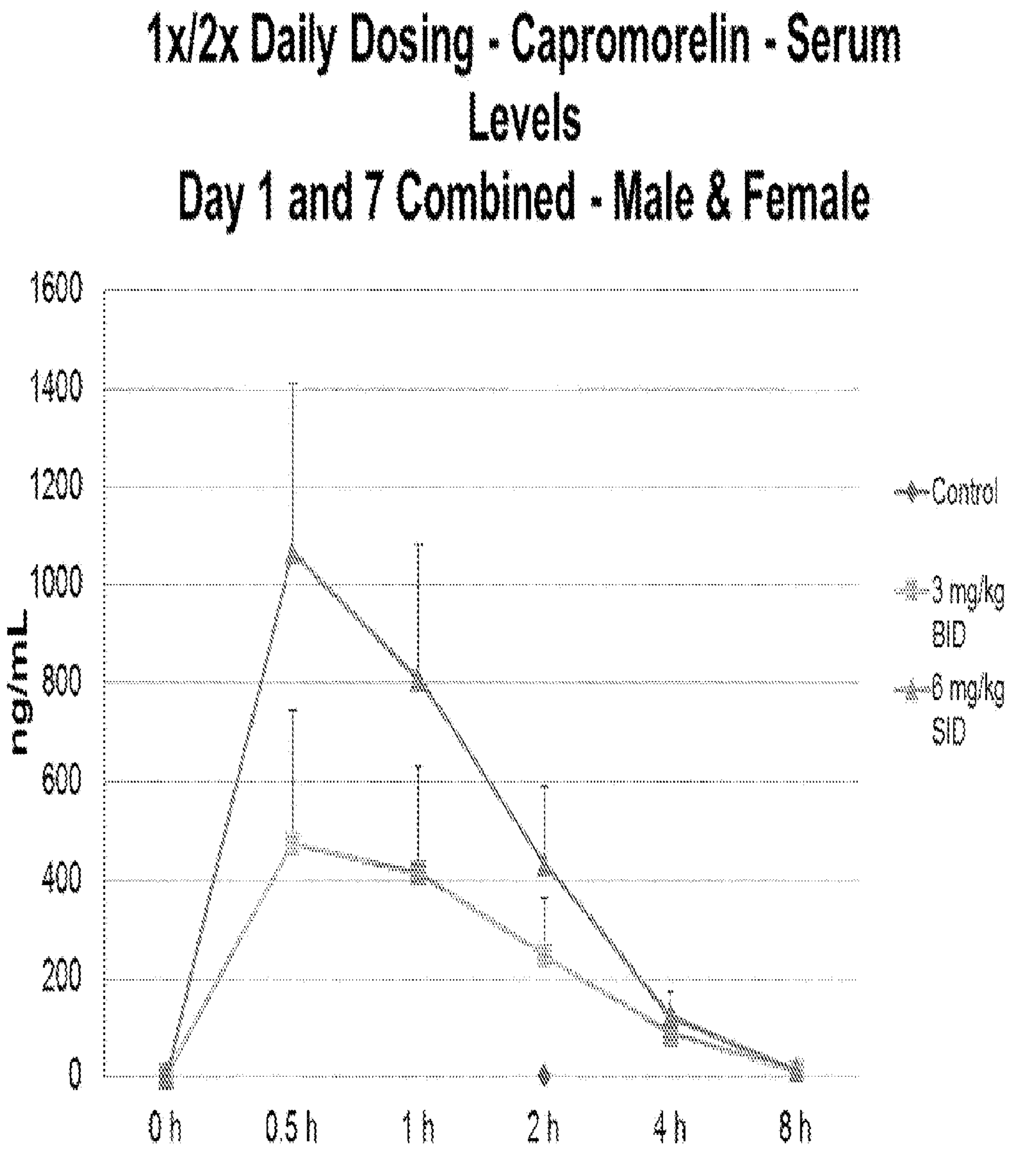

1x/2x Daily Dosing - Capromorelin - Serum Levels
Day 1 and 7 Combined - Male & Female
1600
1400
1200
1000
800
600
400
200
0
ng/mL
0 h
0.5 h
1 h
2 h
4 h
8 h
Control
3 mg/kg BID
6 mg/kg SID

FIGURE 8

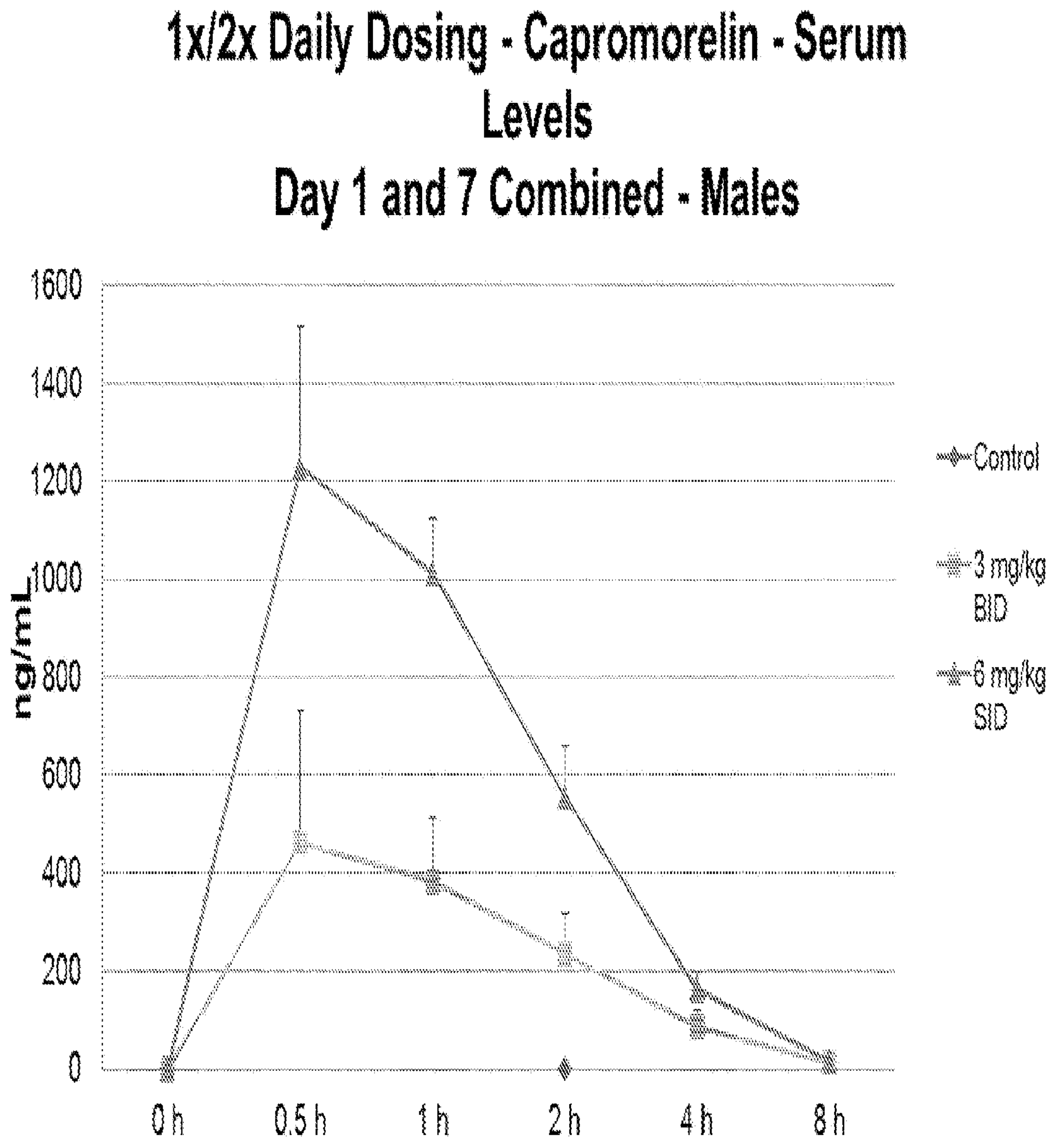

1x/2x Daily Dosing - Capromorelin - Serum Levels
Day 1 and 7 Combined - Males
ng/mL
1600
1400
1200
1000
800
600
400
200
0
0 h
0.5 h
1 h
2 h
4 h
8 h
Control
3 mg/kg BID
6 mg/kg SID

FIGURE 9

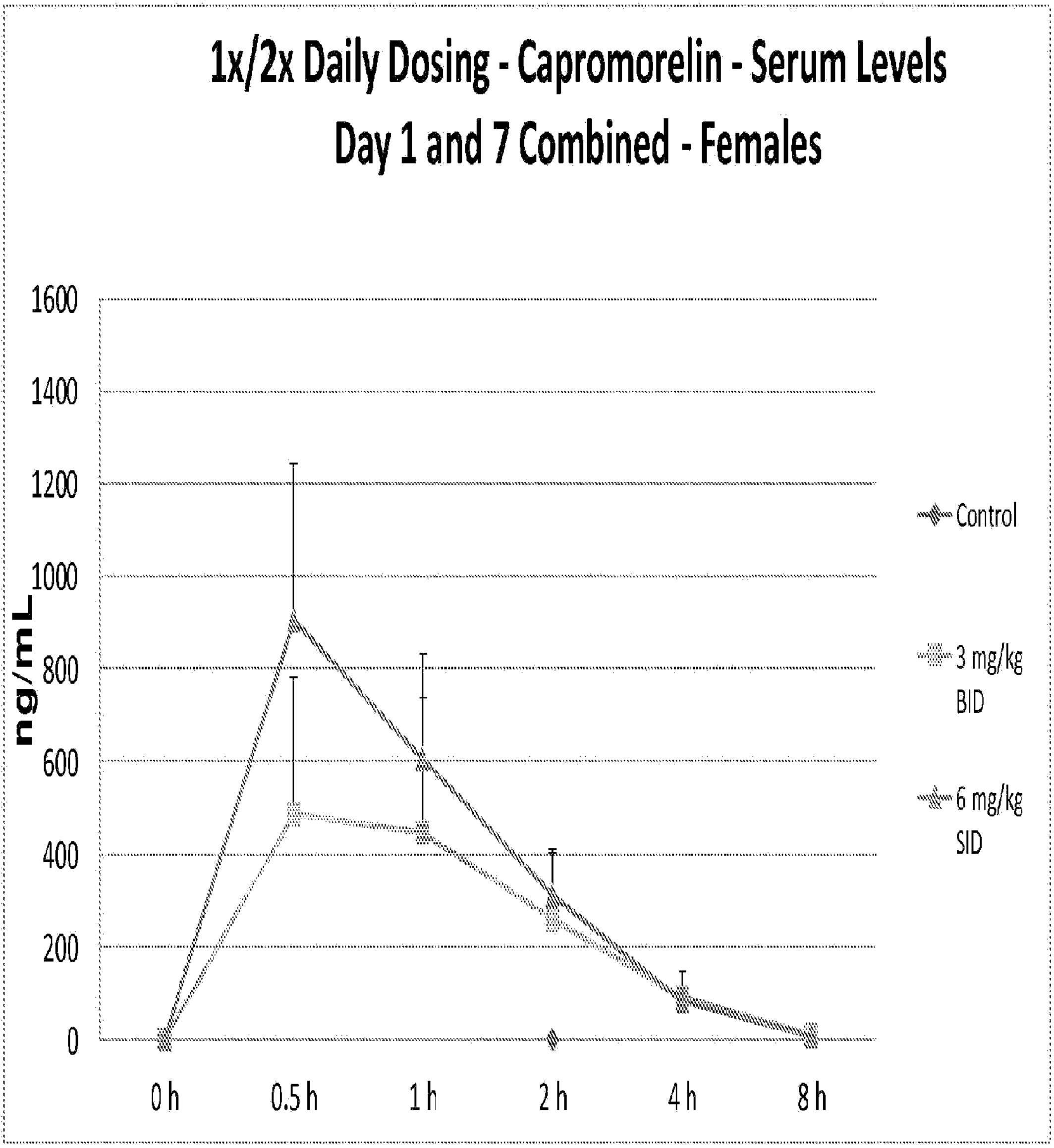

1x/2x Daily Dosing - Capromorelin - Serum Levels
Day 1 and 7 Combined - Females
ng/mL
1600
1400
1200
1000
800
600
400
200
0
0 h
0.5 h
1 h
2 h
4 h
8 h
Control
3 mg/kg BID
6 mg/kg SID

FIGURE 10

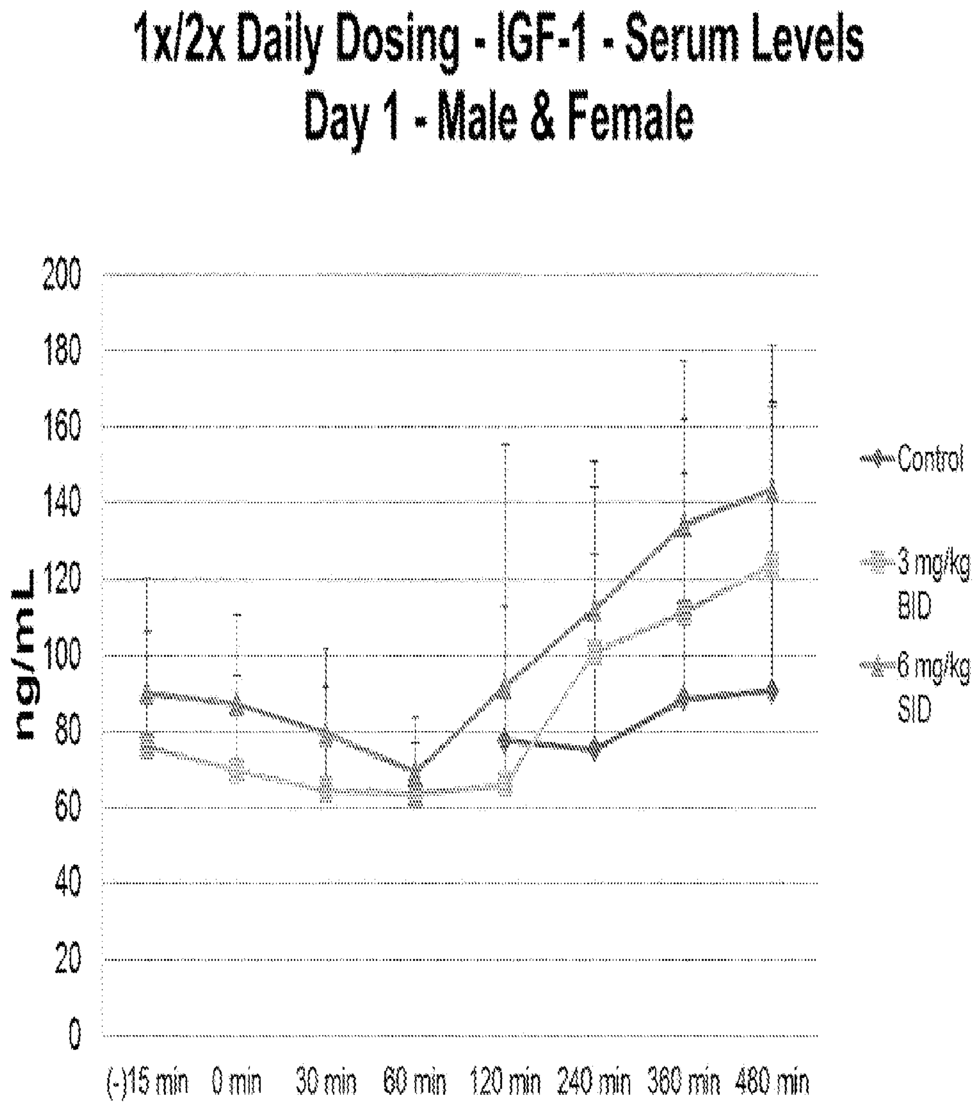

1x/2x Daily Dosing - IGF-1 - Serum Levels
Day 1 - Male & Female
ng/mL
200
180
160
140
120
100
80
60
40
20
0
(-)15 min
0 min
30 min
60 min
120 min
240 min
360 min
480 min
Control
3 mg/kg BID
6 mg/kg SID

FIGURE 11

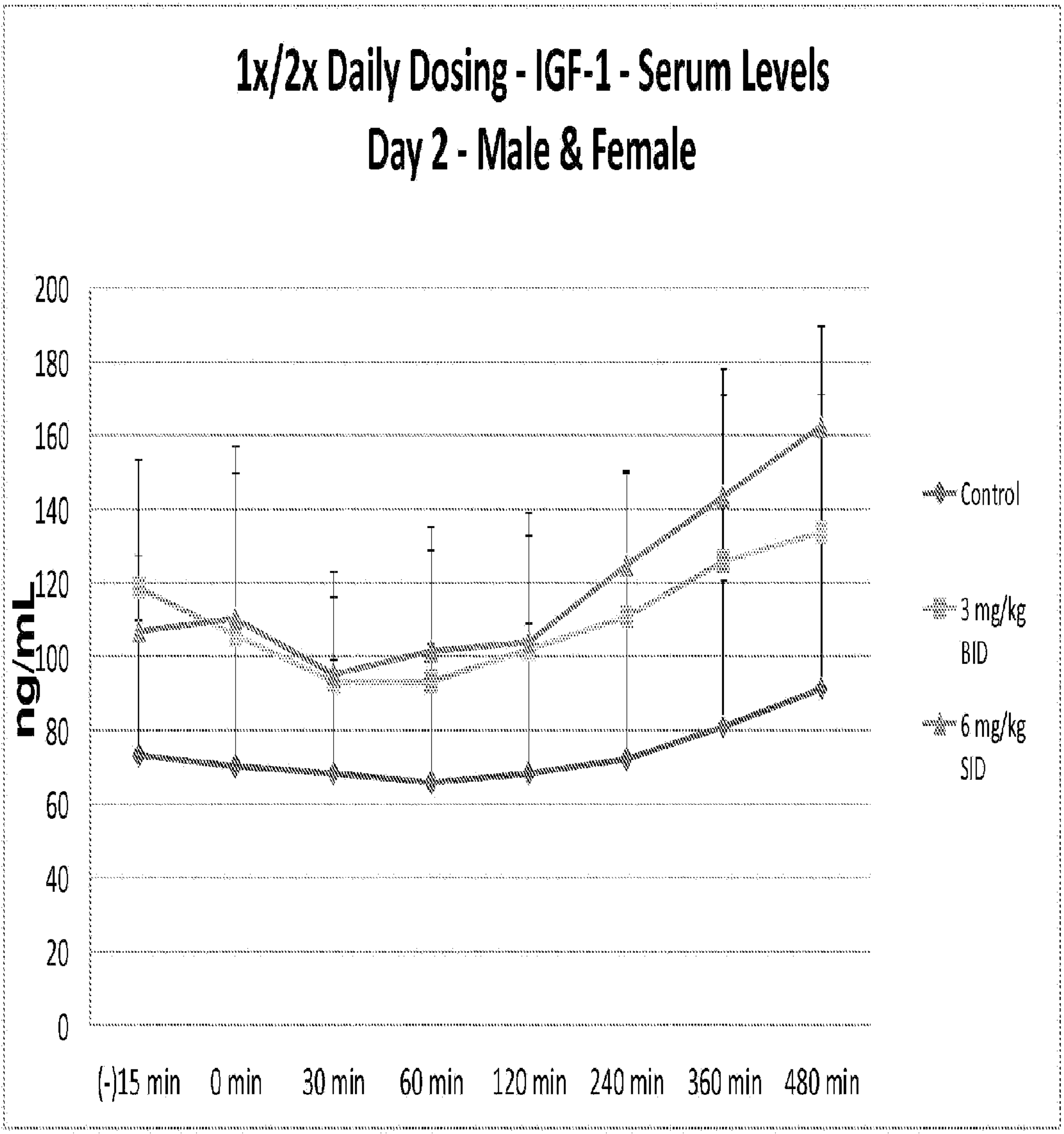

1x/2x Daily Dosing - IGF-1 - Serum Levels
Day 2 - Male & Female
ng/mL
200
180
160
140
120
100
80
60
40
20
0
(-)15 min
0 min
30 min
60 min
120 min
240 min
360 min
480 min
Control
3 mg/kg BID
6 mg/kg SID

FIGURE 12

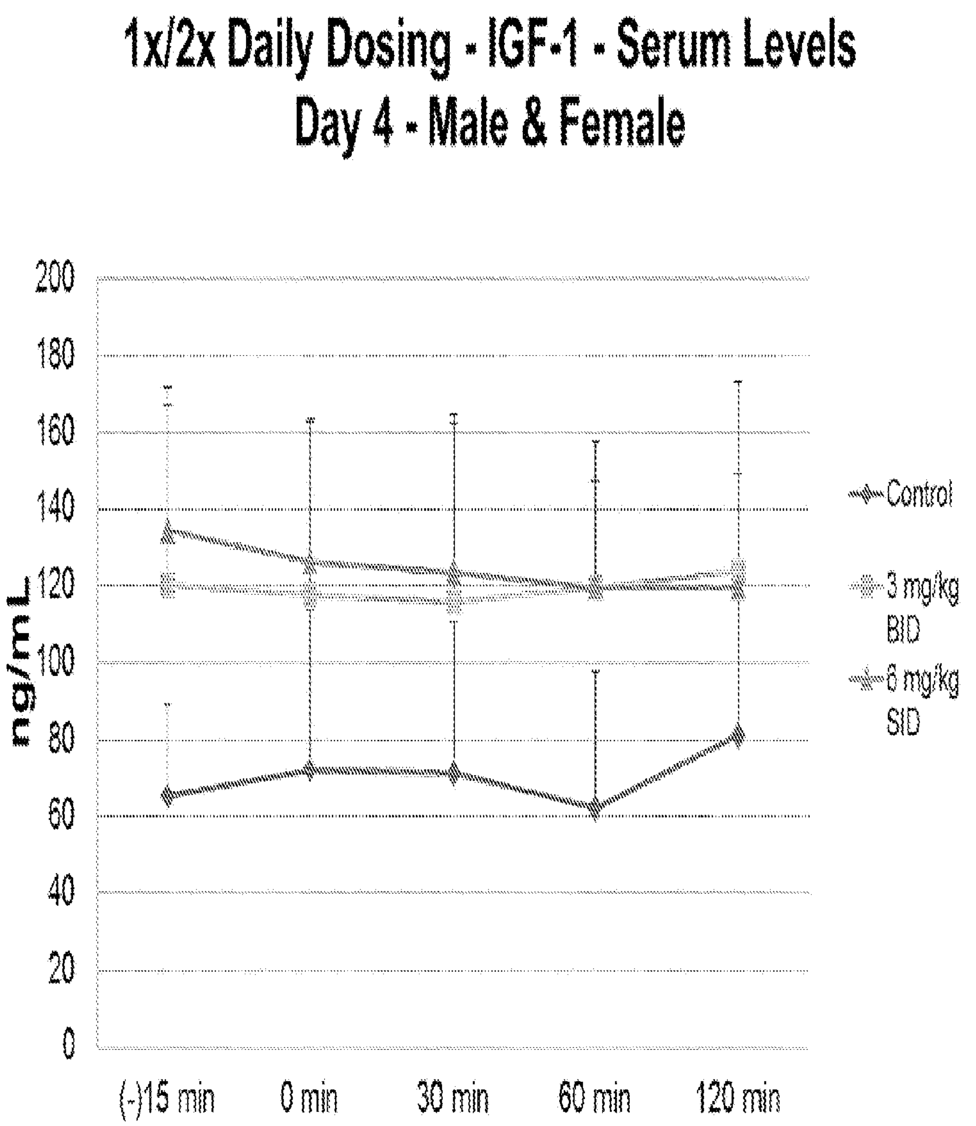

1x/2x Daily Dosing - IGF-1 - Serum Levels
Day 4 - Male & Female
200
180
160
140
120
100
80
60
40
20
0
ng/mL
(-)15 min
0 min
30 min
60 min
120 min
Control
3 mg/kg BID
6 mg/kg SID

FIGURE 13

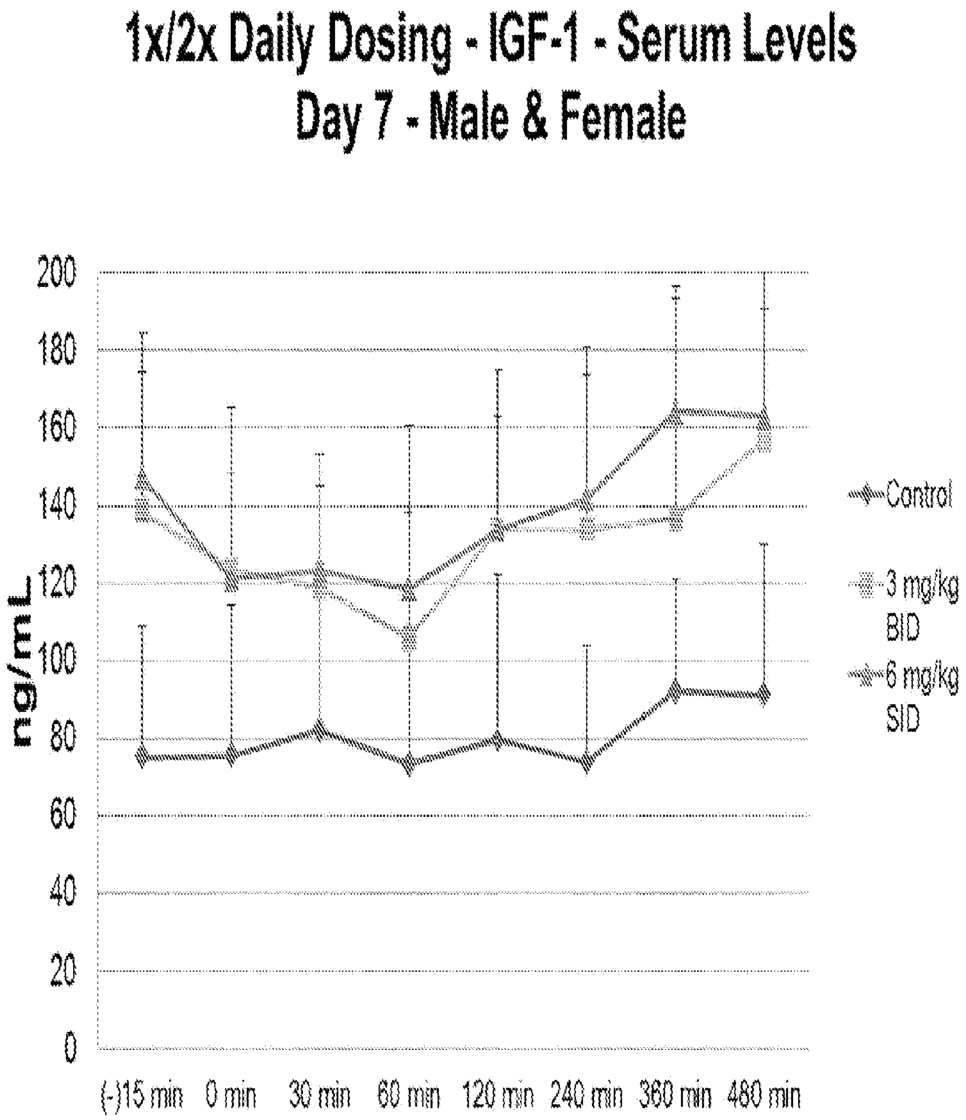

1x/2x Daily Dosing - IGF-1 - Serum Levels
Day 7 - Male & Female
200
180
160
140
120
100
80
60
40
20
0
ng/mL
(-)15 min
0 min
30 min
60 min
120 min
240 min
360 min
480 min
Control
3 mg/kg BID
6 mg/kg SID

FIGURE 14

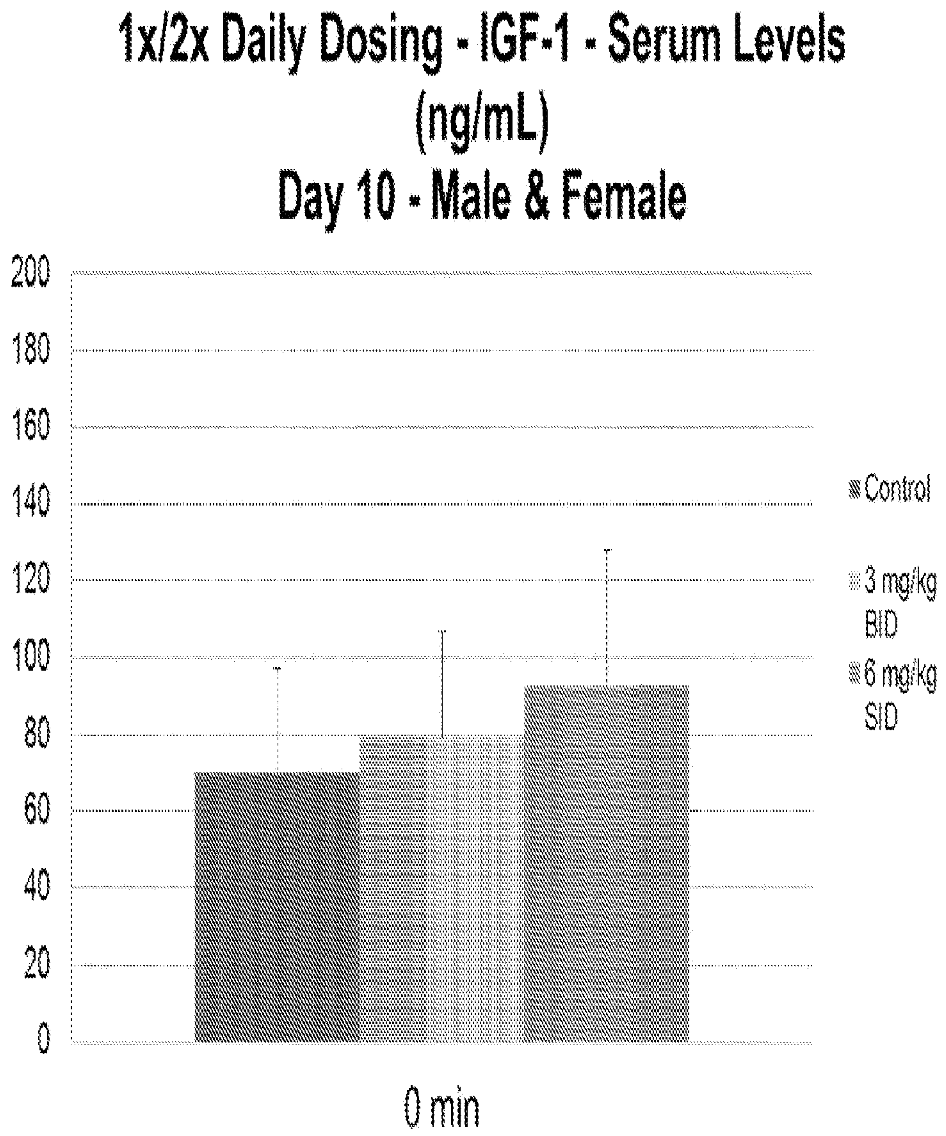

1x/2x Daily Dosing - IGF-1 - Serum Levels (ng/mL)
Day 10 - Male & Female
200
180
160
140
120
100
80
60
40
20
0
0 min
Control
3 mg/kg BID
6 mg/kg SID

FIGURE 15

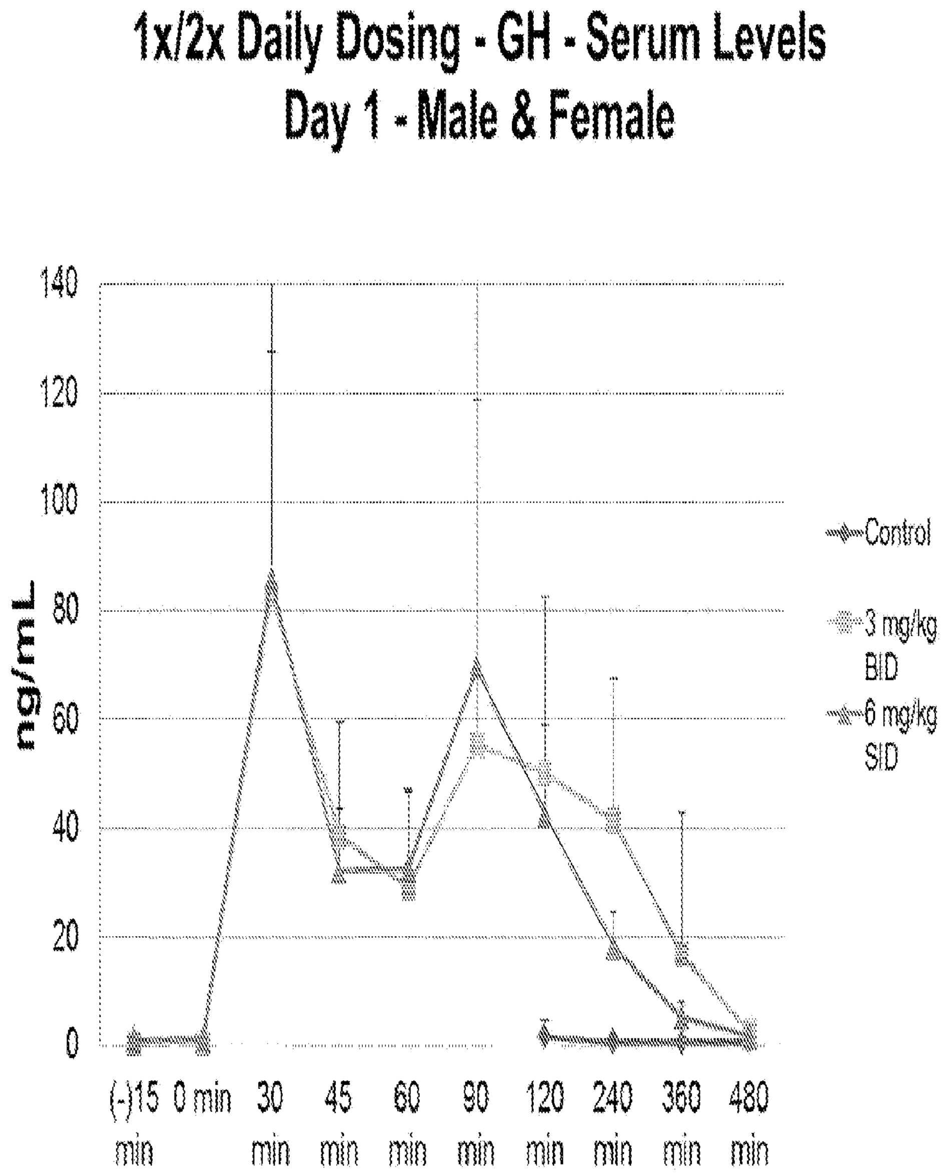

1x/2x Daily Dosing - GH - Serum Levels
Day 1 - Male & Female
ng/mL
140
120
100
80
60
40
20
0
(-)15 min
0 min
30 min
45 min
60 min
90 min
120 min
240 min
360 min
480 min
Control
3 mg/kg BID
6 mg/kg SID

FIGURE 16

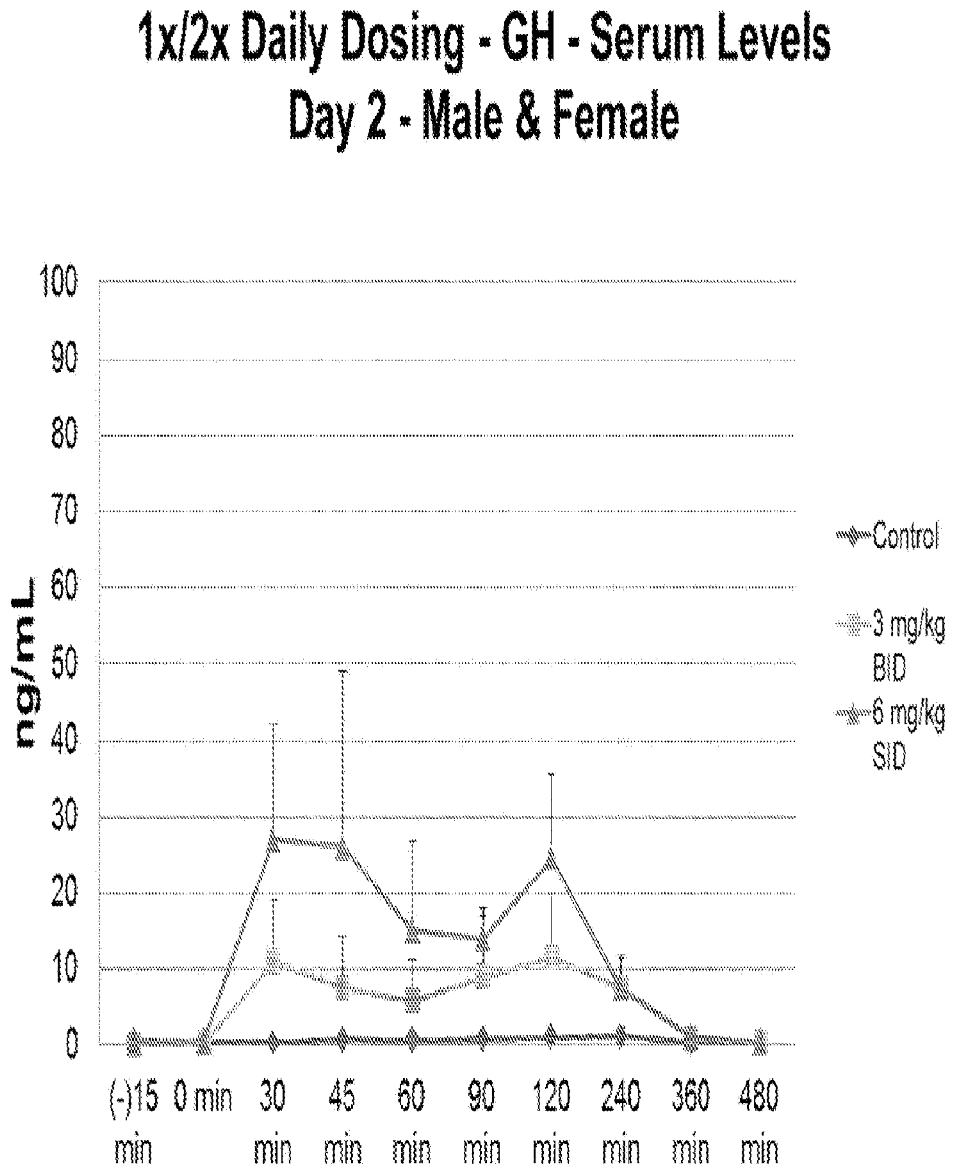

1x/2x Daily Dosing - GH - Serum Levels
Day 2 - Male & Female
ng/mL
100
90
80
70
60
50
40
30
20
10
0
(-)15 min
0 min
30 min
45 min
60 min
90 min
120 min
240 min
360 min
480 min
Control
3 mg/kg BID
6 mg/kg SID

FIGURE 17

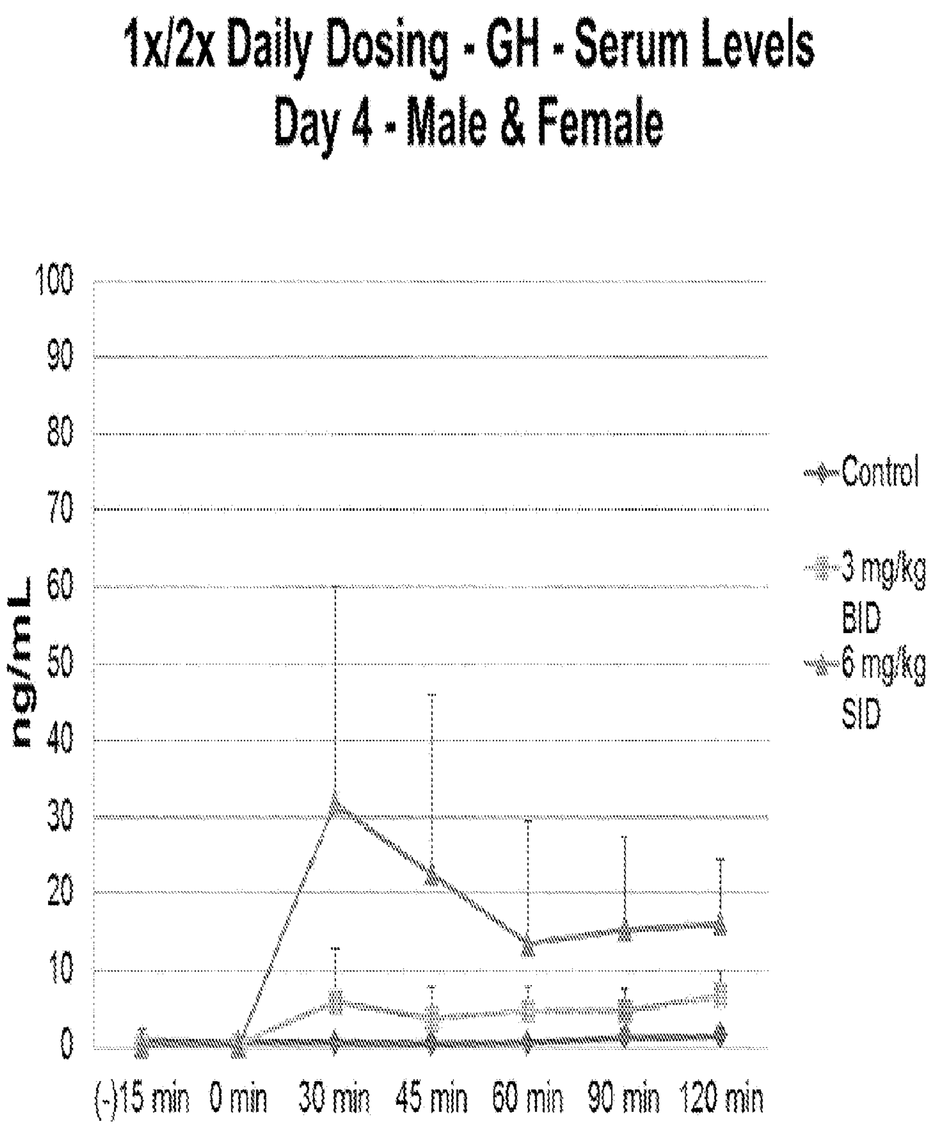

1x/2x Daily Dosing - GH - Serum Levels
Day 4 - Male & Female
ng/mL
100
90
80
70
60
50
40
30
20
10
0
(-)15 min
0 min
30 min
45 min
60 min
90 min
120 min
Control
3 mg/kg BID
6 mg/kg SID

FIGURE 18

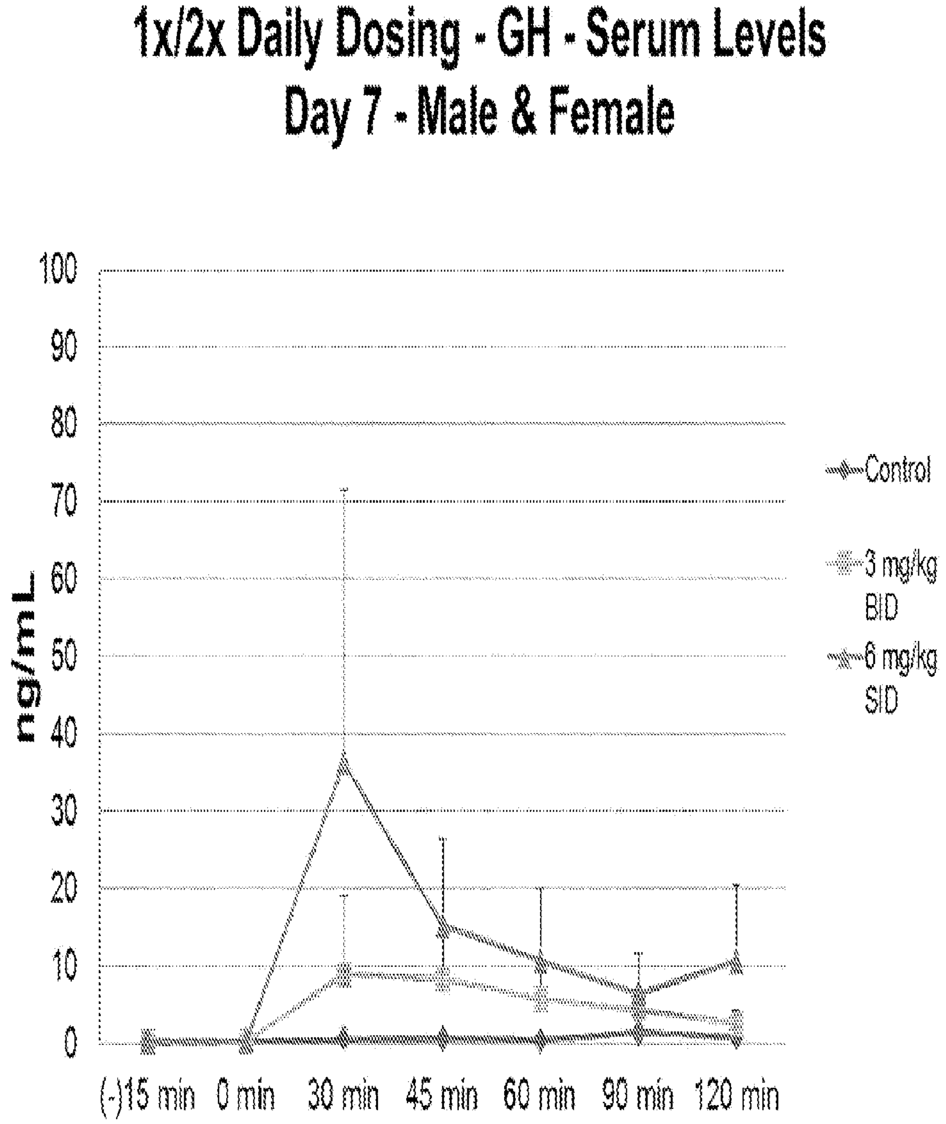
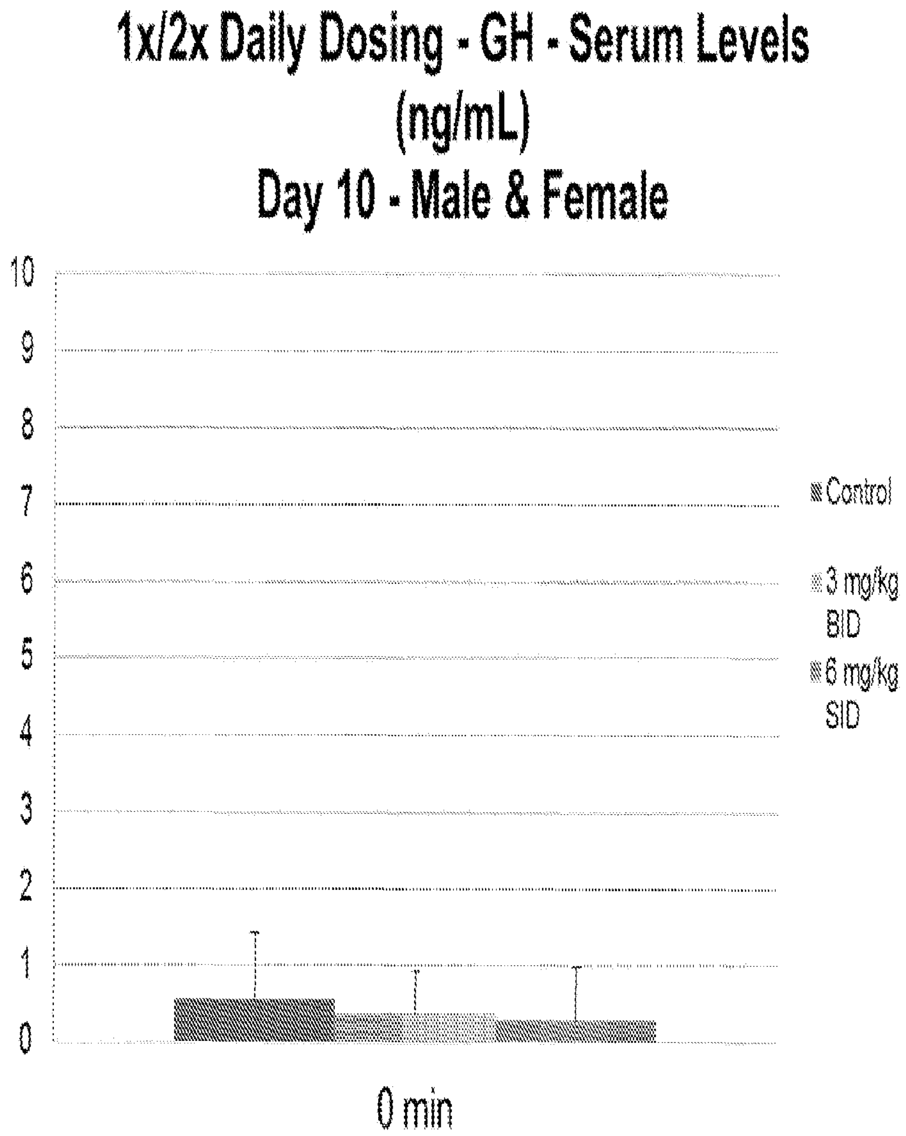

1x/2x Daily Dosing - GH - Serum Levels
Day 7 - Male & Female
100
90
80
70
60
50
40
30
20
10
0
ng/mL
(-)15 min
0 min
30 min
45 min
60 min
90 min
120 min
Control
3 mg/kg BID
6 mg/kg SID

FIGURE 19



1x/2x Daily Dosing - GH - Serum Levels
(ng/mL)
Day 10 - Male & Female
10
9
8
7
6
5
4
3
2
1
0
0 min
Control
3 mg/kg BID
6 mg/kg SID

FIGURE 20

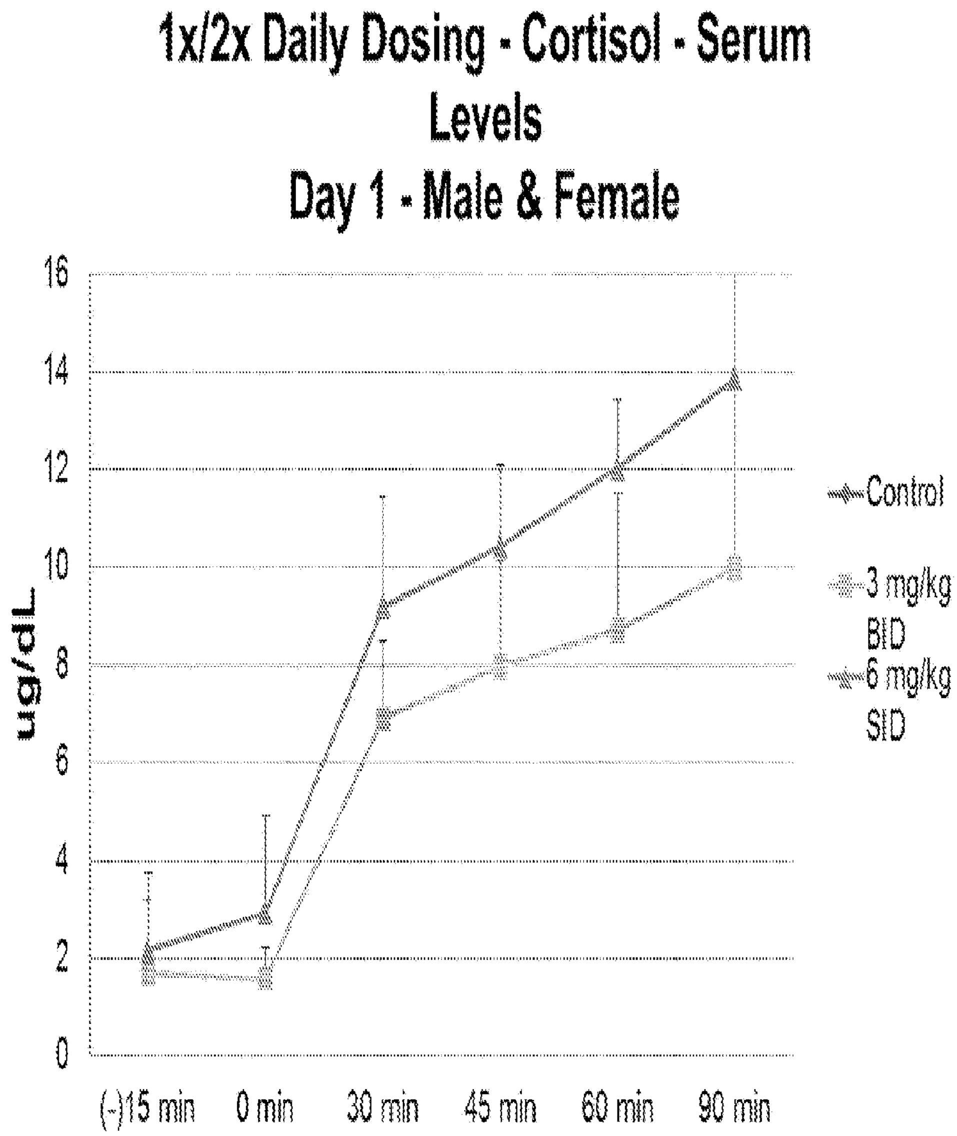

1x/2x Daily Dosing - Cortisol - Serum Levels
Day 1 - Male & Female
ug/dL
16
14
12
10
8
6
4
2
0
(-)15 min
0 min
30 min
45 min
60 min
90 min
Control
3 mg/kg BID
6 mg/kg SID

FIGURE 21

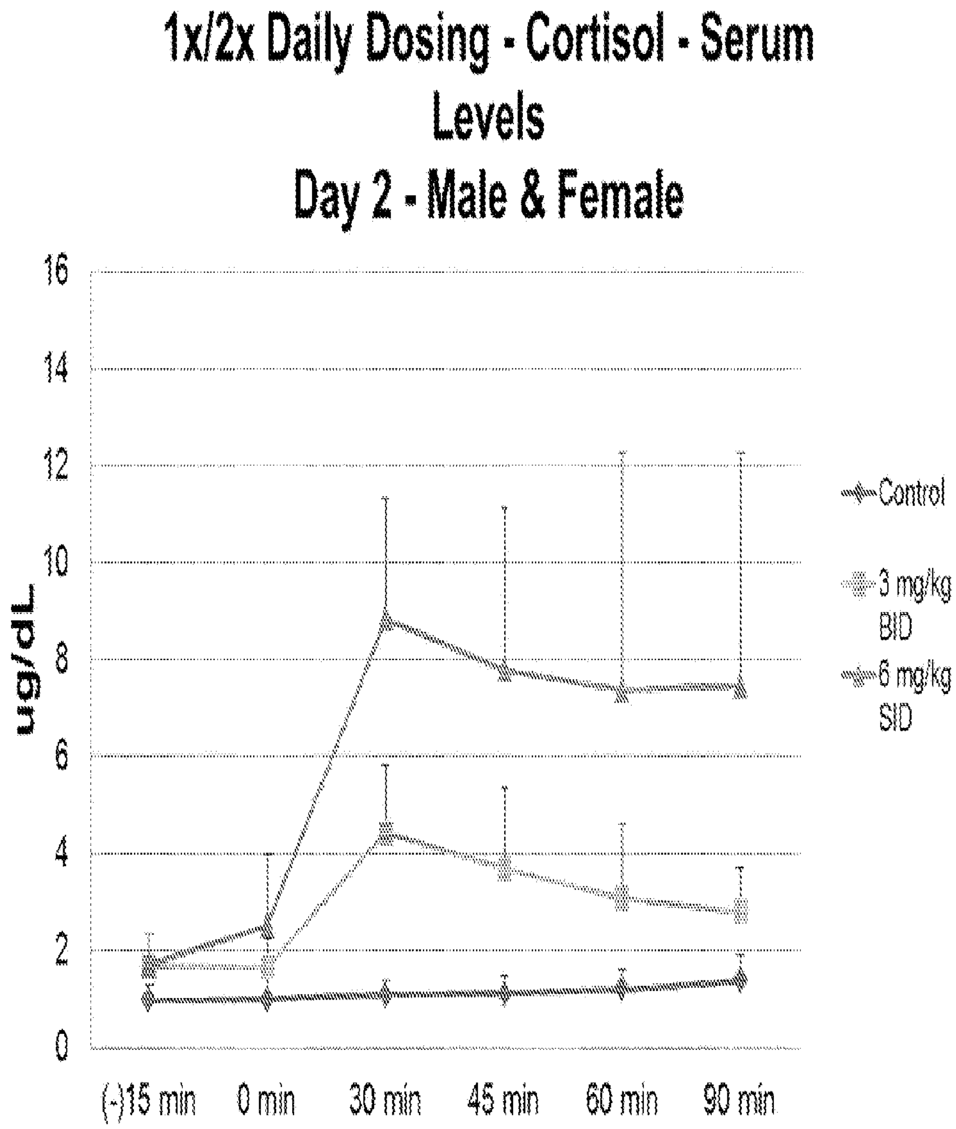

1x/2x Daily Dosing - Cortisol - Serum Levels
Day 2 - Male & Female
ug/dL
16
14
12
10
8
6
4
2
0
(-)15 min
0 min
30 min
45 min
60 min
90 min
Control
3 mg/kg BID
6 mg/kg SID

FIGURE 22

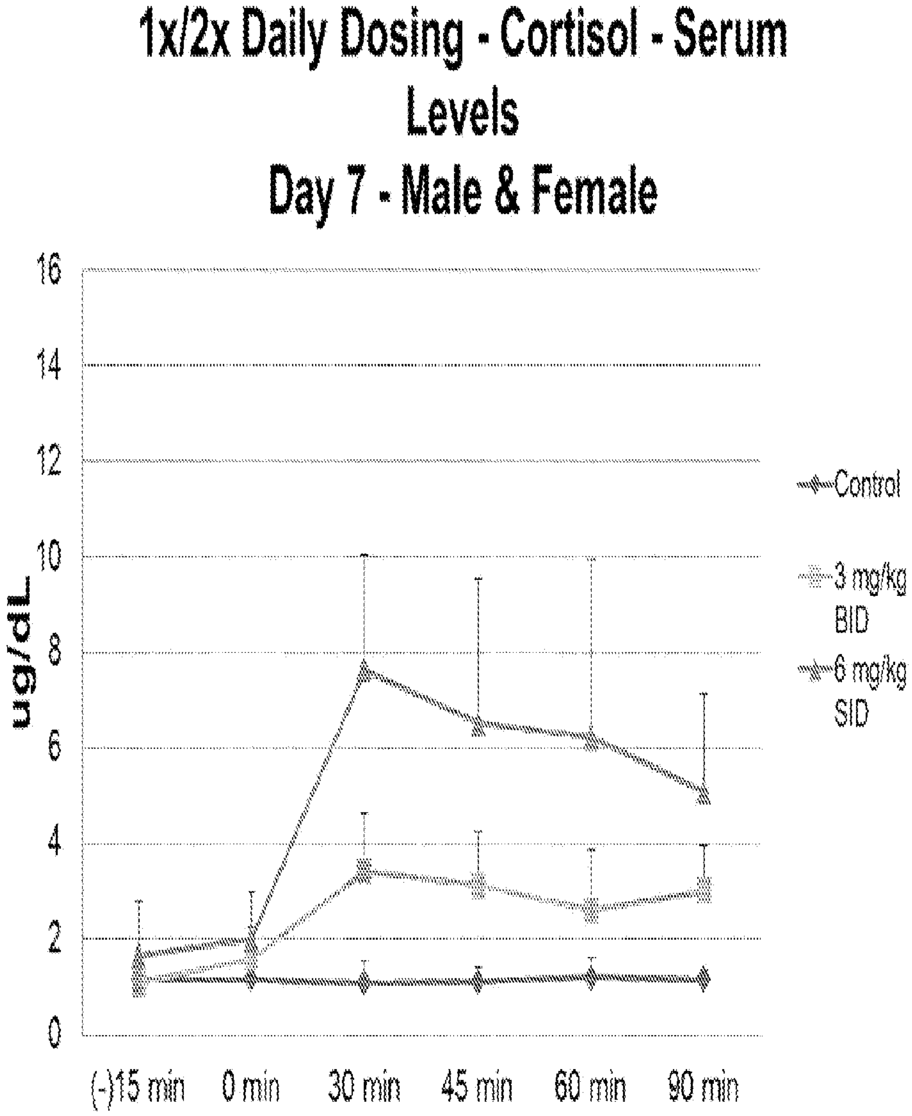

1x/2x Daily Dosing - Cortisol - Serum Levels
Day 7 - Male & Female
ug/dL
16
14
12
10
8
6
4
2
0
(-)15 min
0 min
30 min
45 min
60 min
90 min
Control
3 mg/kg BID
6 mg/kg SID

FIGURE 23

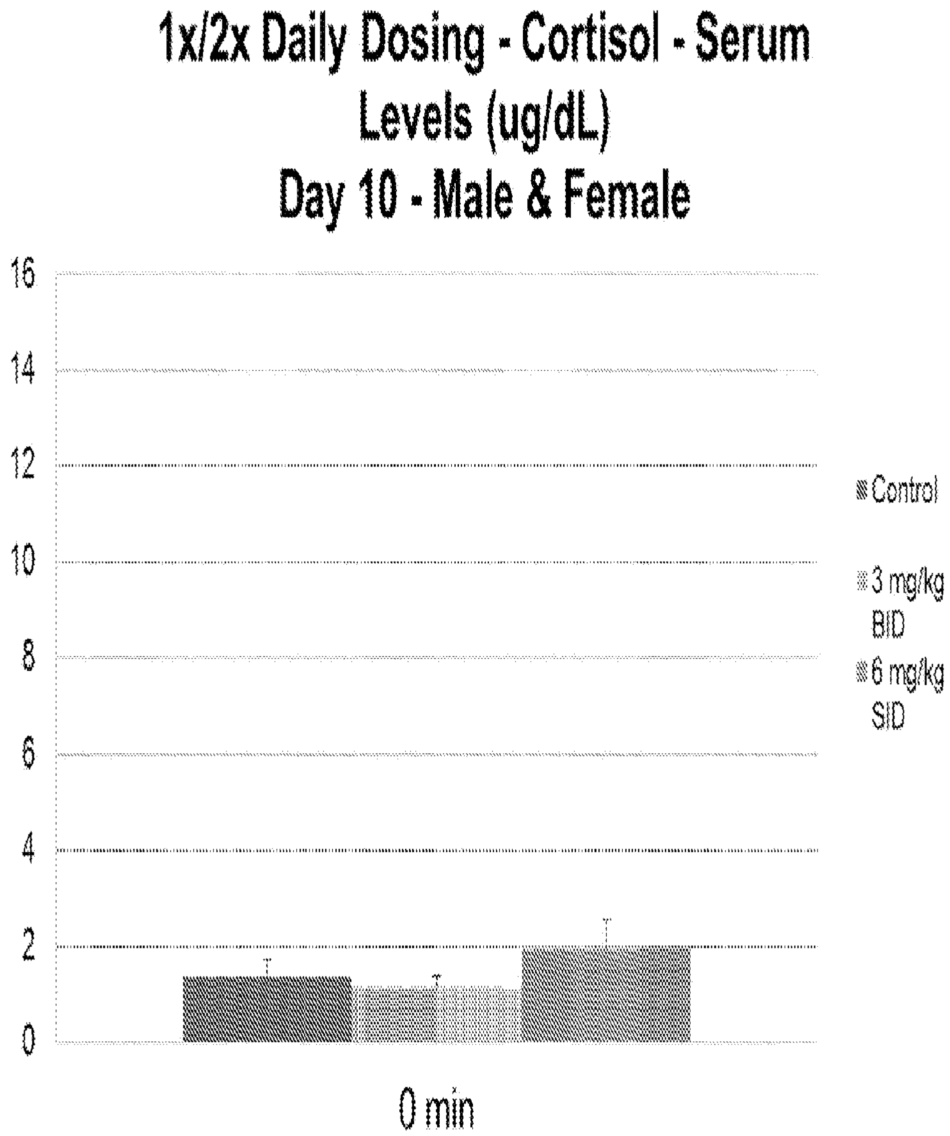

1x/2x Daily Dosing - Cortisol - Serum
Levels (ug/dL)
Day 10 - Male & Female
16
14
12
10
8
6
4
2
0
0 min
Control
3 mg/kg BID
6 mg/kg SID

FIGURE 24

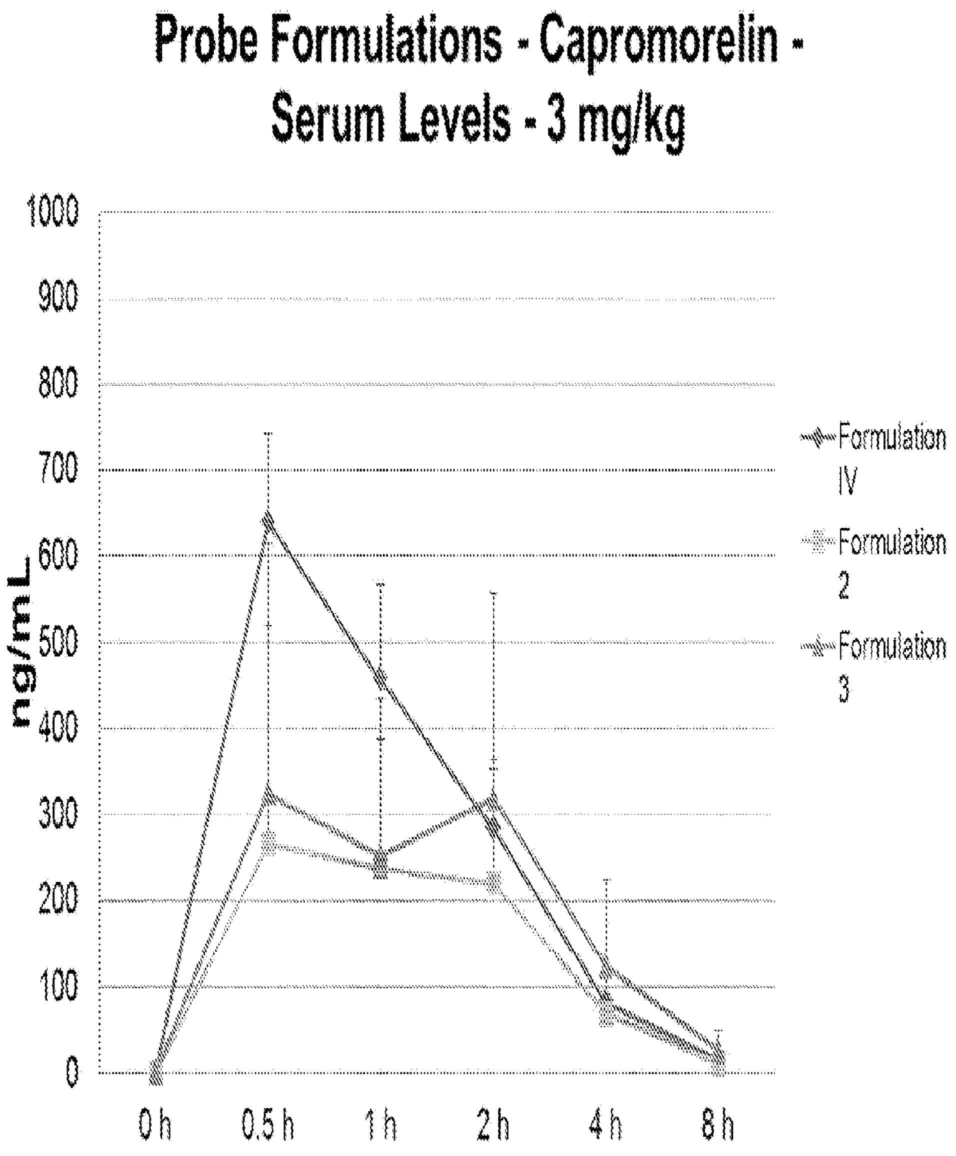

Probe Formulations - Capromorelin -
Serum Levels - 3 mg/kg
ng/mL
1000
900
800
700
600
500
400
300
200
100
0
0 h
0.5 h
1 h
2 h
4 h
8 h
Formulation IV
Formulation 2
Formulation 3

FIGURE 25

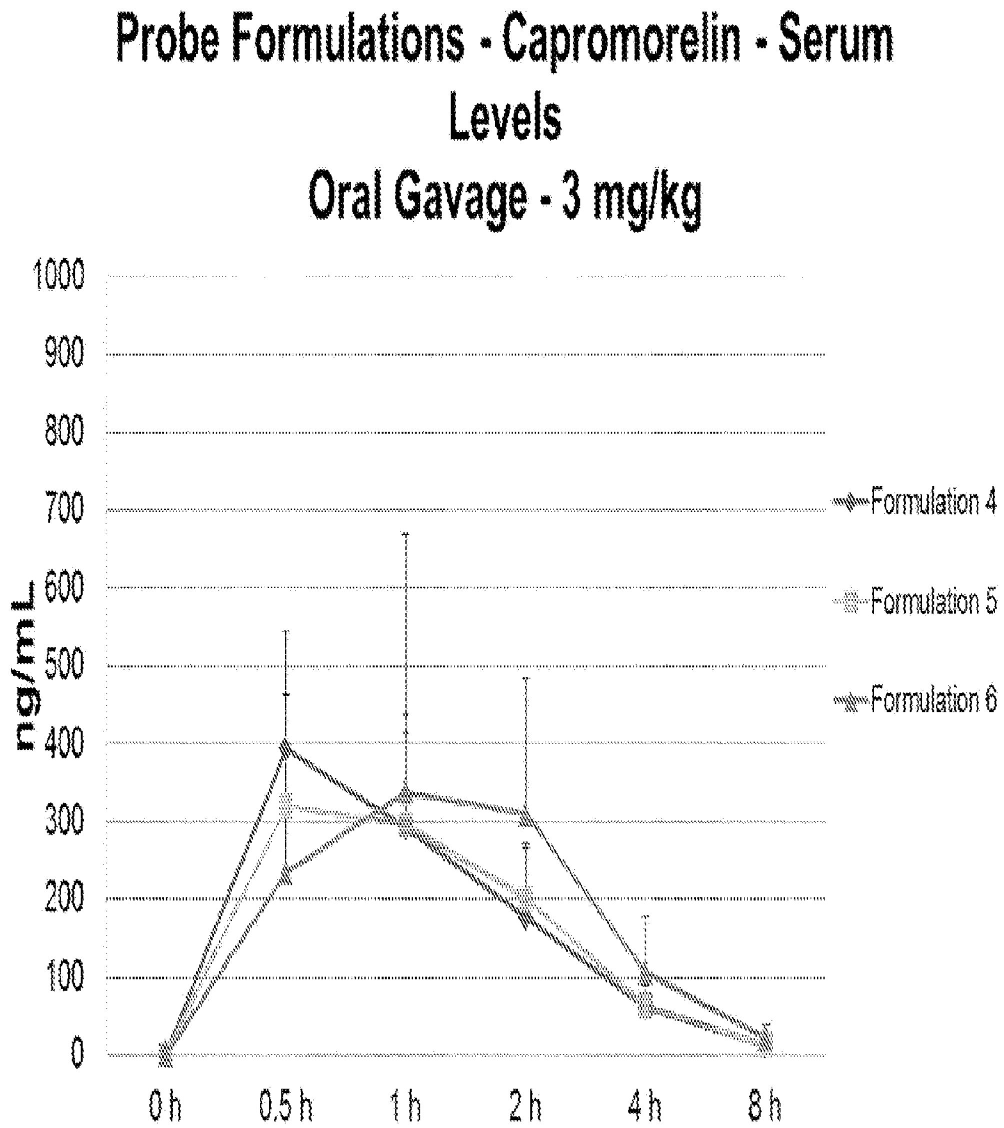

Probe Formulations - Capromorelin - Serum Levels
Oral Gavage - 3 mg/kg
1000
900
800
700
600
500
400
300
200
100
0
ng/mL
0 h
0.5 h
1 h
2 h
4 h
8 h
Formulation 4
Formulation 5
Formulation 6

FIGURE 26

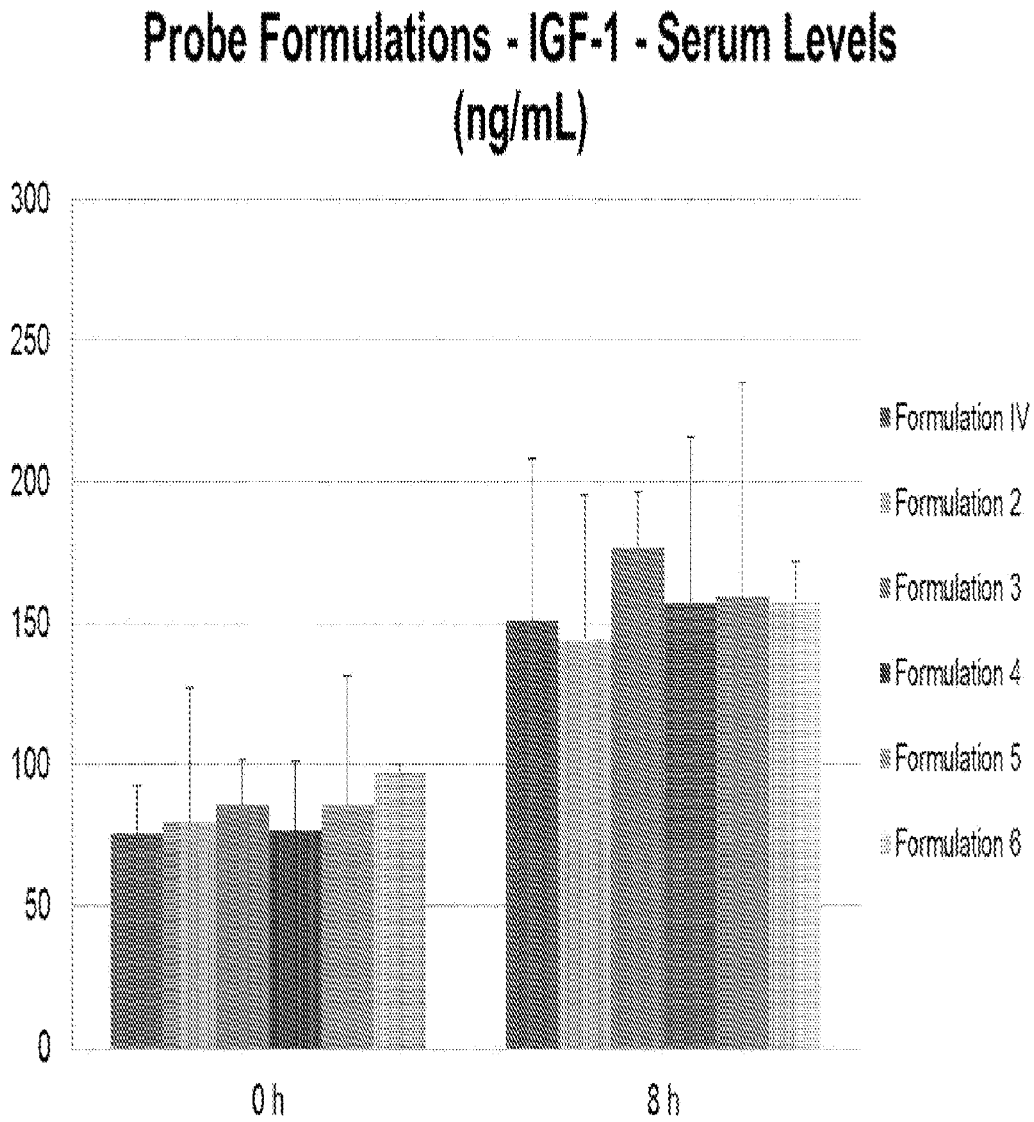

Probe Formulations - IGF-1 - Serum Levels (ng/mL)
300
250
200
150
100
50
0
0 h
8 h
Formulation IV
Formulation 2
Formulation 3
Formulation 4
Formulation 5
Formulation 6

FIGURE 27

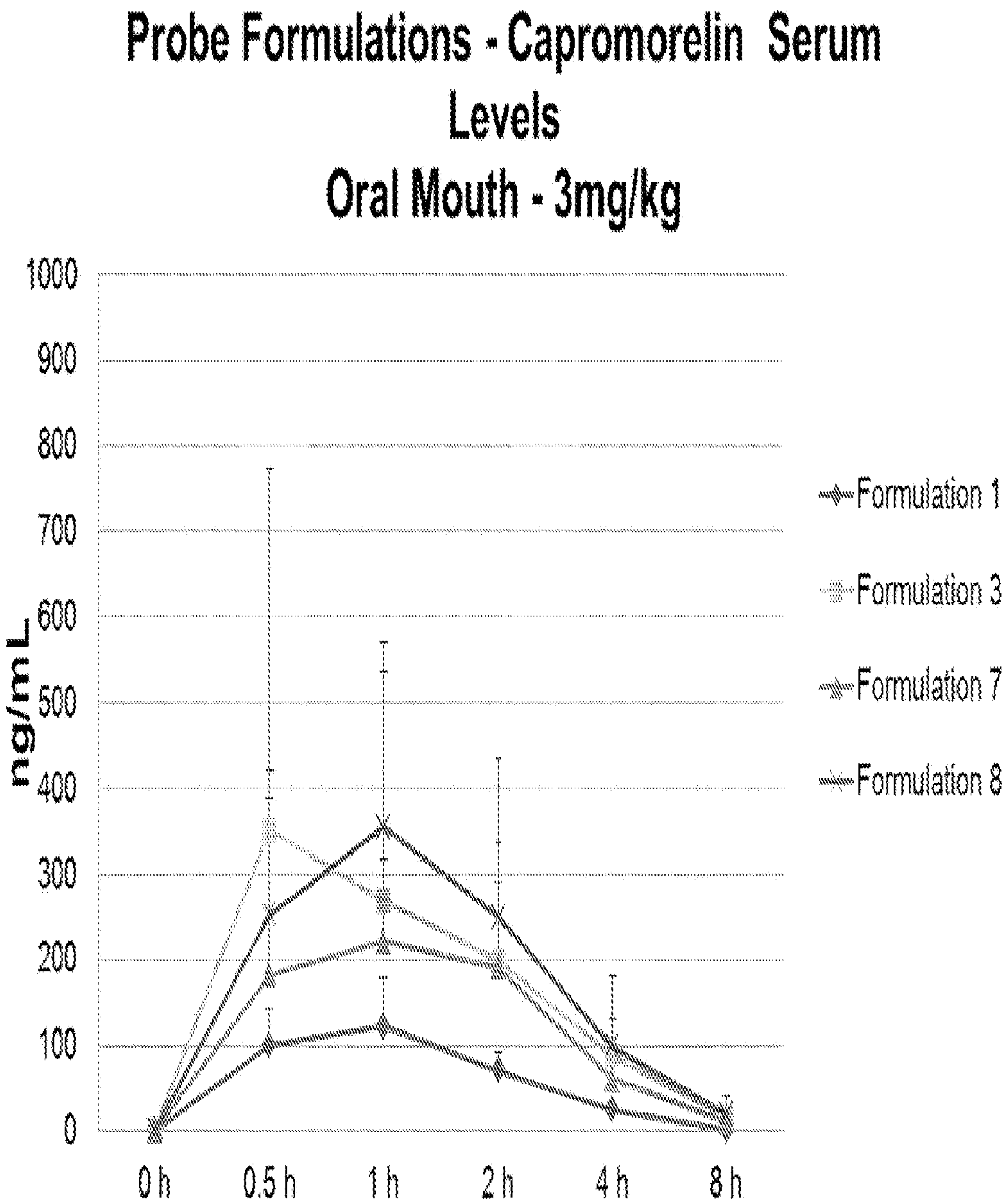

Probe Formulations - Capromorelin Serum Levels
Oral Mouth - 3mg/kg
ng/mL
1000
900
800
700
600
500
400
300
200
100
0
0 h
0.5 h
1 h
2 h
4 h
8 h
Formulation 1
Formulation 3
Formulation 7
Formulation 8

FIGURE 28

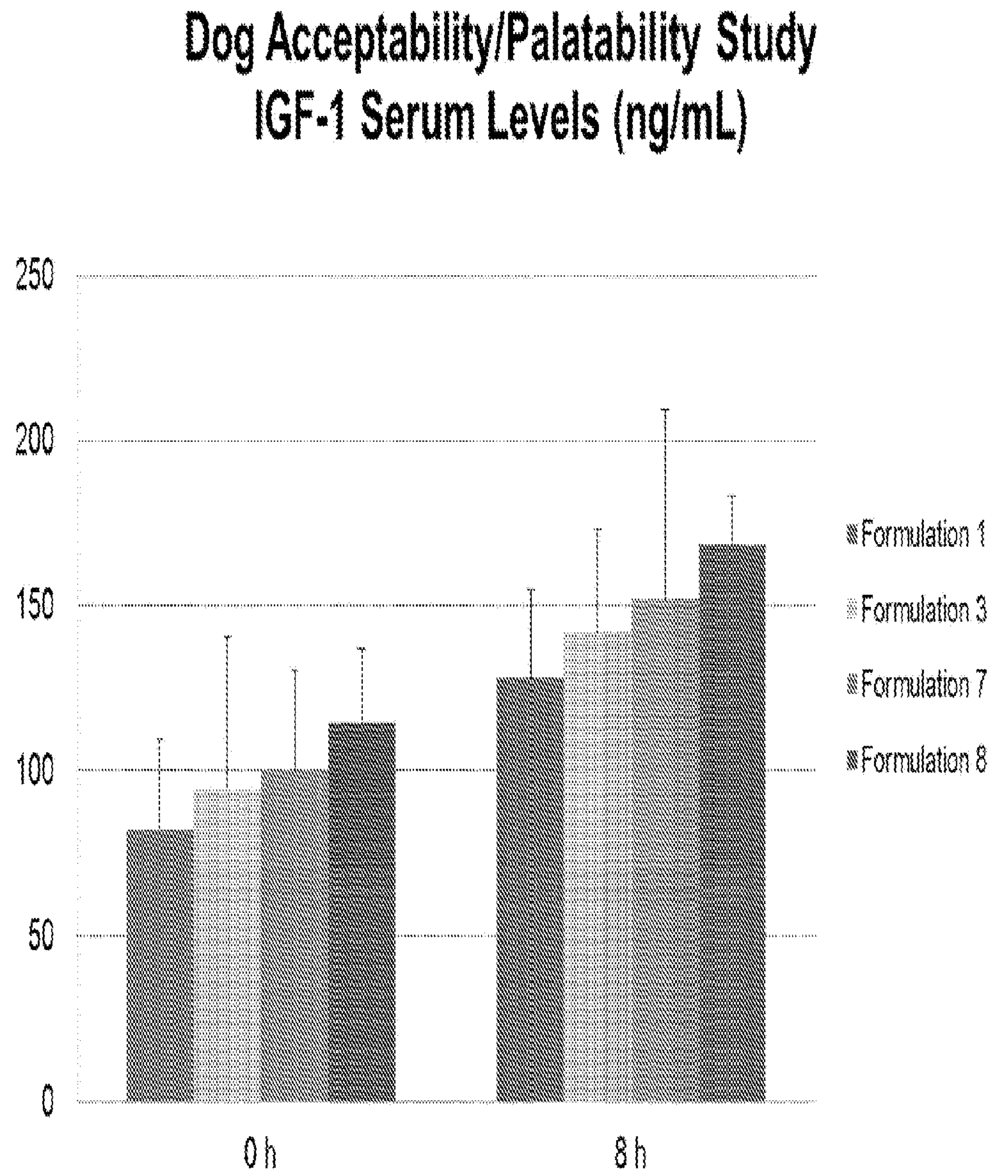

Dog Acceptability/Palatability Study
IGF-1 Serum Levels (ng/mL)
250
200
150
100
50
0
0 h
8 h
Formulation 1
Formulation 3
Formulation 7
Formulation 8

FIGURE 29

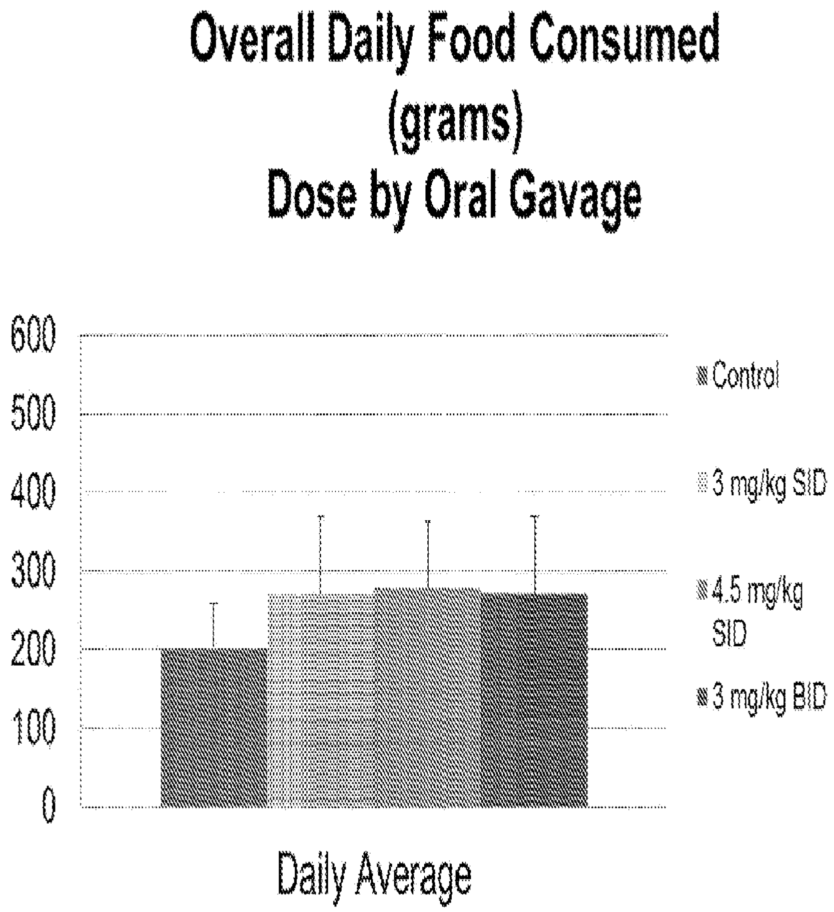

Overall Daily Food Consumed
(grams)
Dose by Oral Gavage
600
500
400
300
200
100
0
Control
3 mg/kg SID
4.5 mg/kg SID
3 mg/kg BID
Daily Average

FIGURE 30

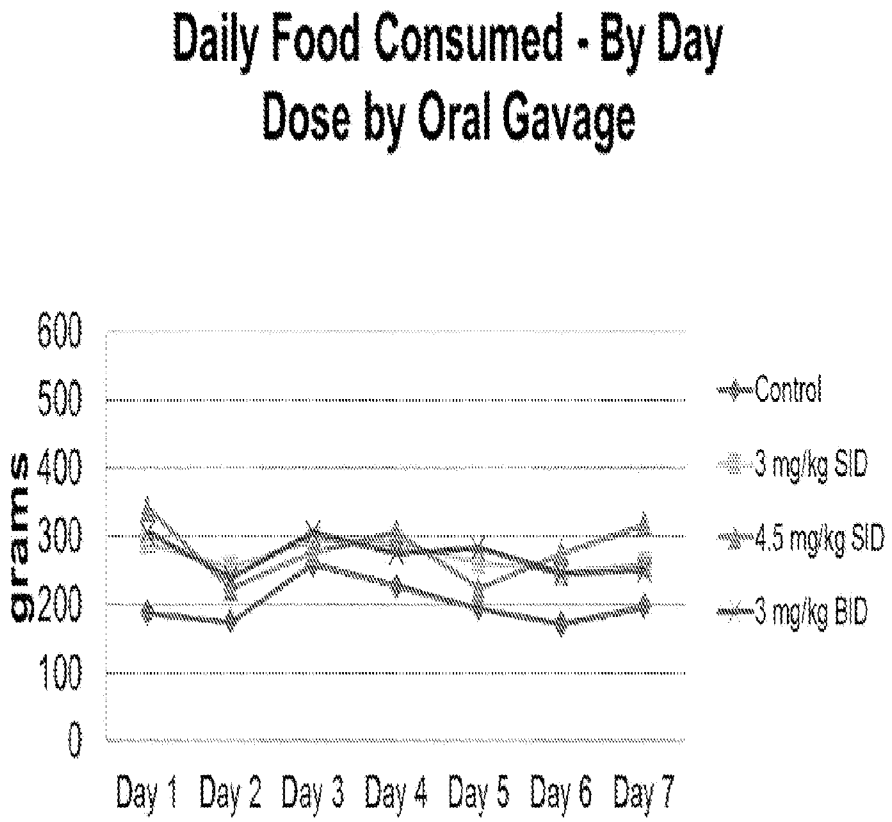

Daily Food Consumed - By Day
Dose by Oral Gavage
600
500
400
300
200
100
0
grams
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Control
3 mg/kg SID
4.5 mg/kg SID
3 mg/kg BID

FIGURE 31

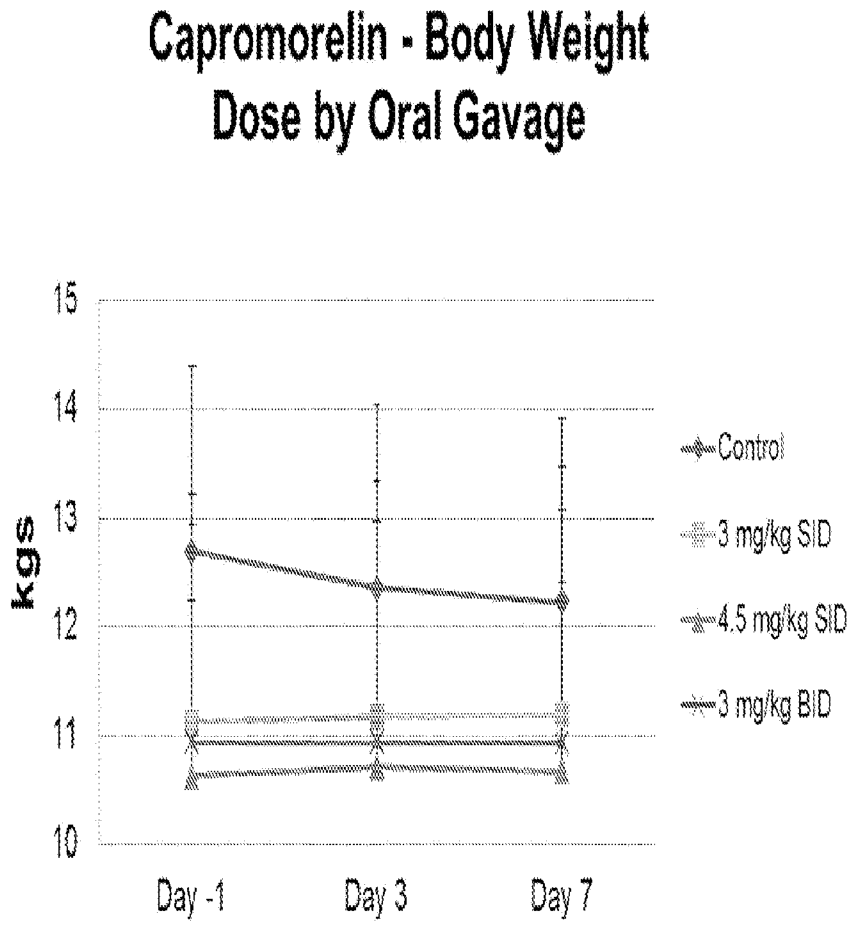

Capromorelin - Body Weight
Dose by Oral Gavage
kgs
15
14
13
12
11
10
Day -1
Day 3
Day 7
Control
3 mg/kg SID
4.5 mg/kg SID
3 mg/kg BID

FIGURE 32

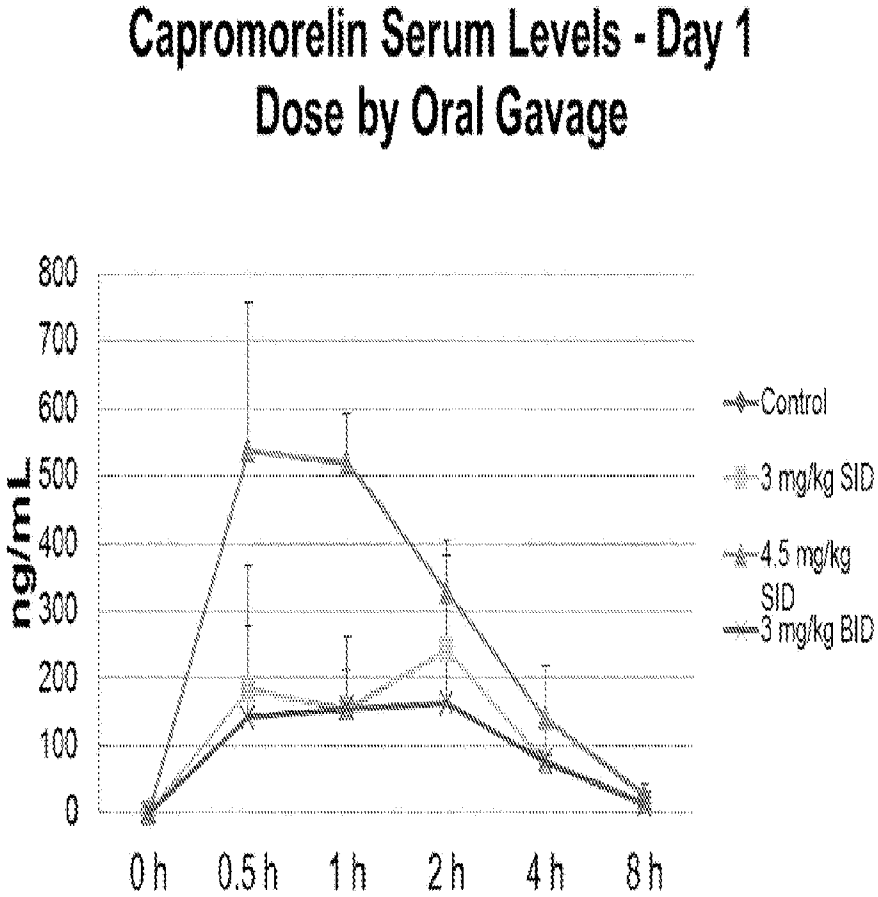

Capromorelin Serum Levels - Day 1
Dose by Oral Gavage
ng/mL
800
700
600
500
400
300
200
100
0
0 h
0.5 h
1 h
2 h
4 h
8 h
Control
3 mg/kg SID
4.5 mg/kg SID
3 mg/kg BID

FIGURE 33

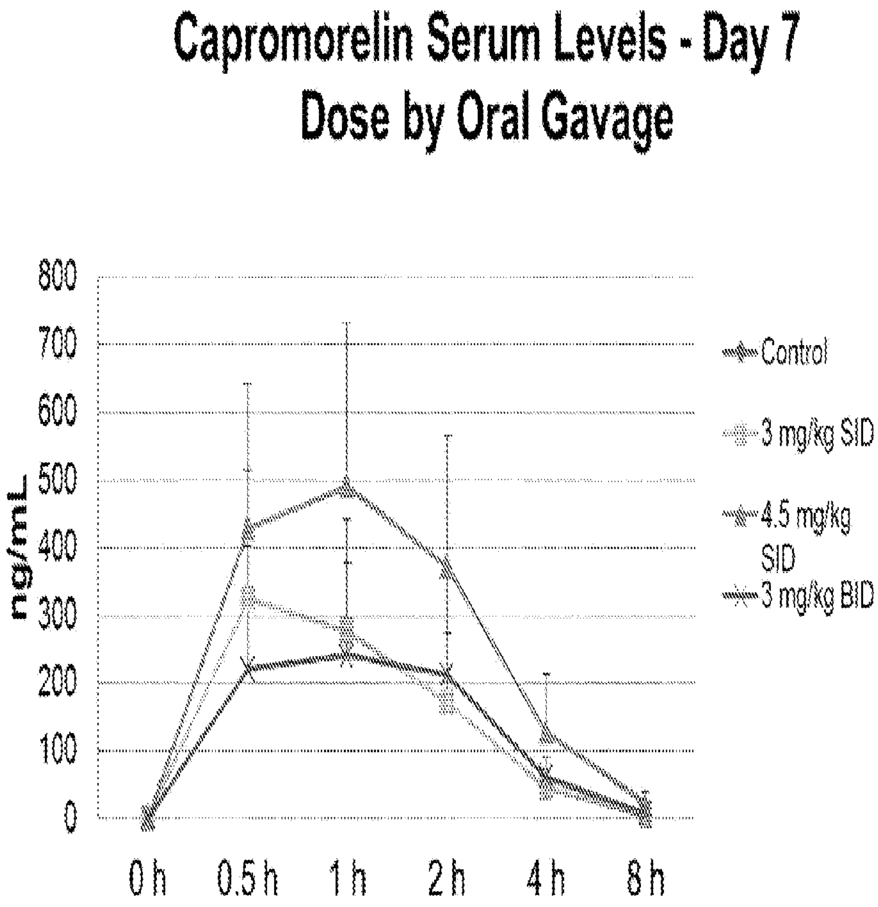

Capromorelin Serum Levels - Day 7
Dose by Oral Gavage
800
700
600
500
400
300
200
100
0
ng/mL
0 h
0.5 h
1 h
2 h
4 h
8 h
Control
3 mg/kg SID
4.5 mg/kg SID
3 mg/kg BID

FIGURE 34

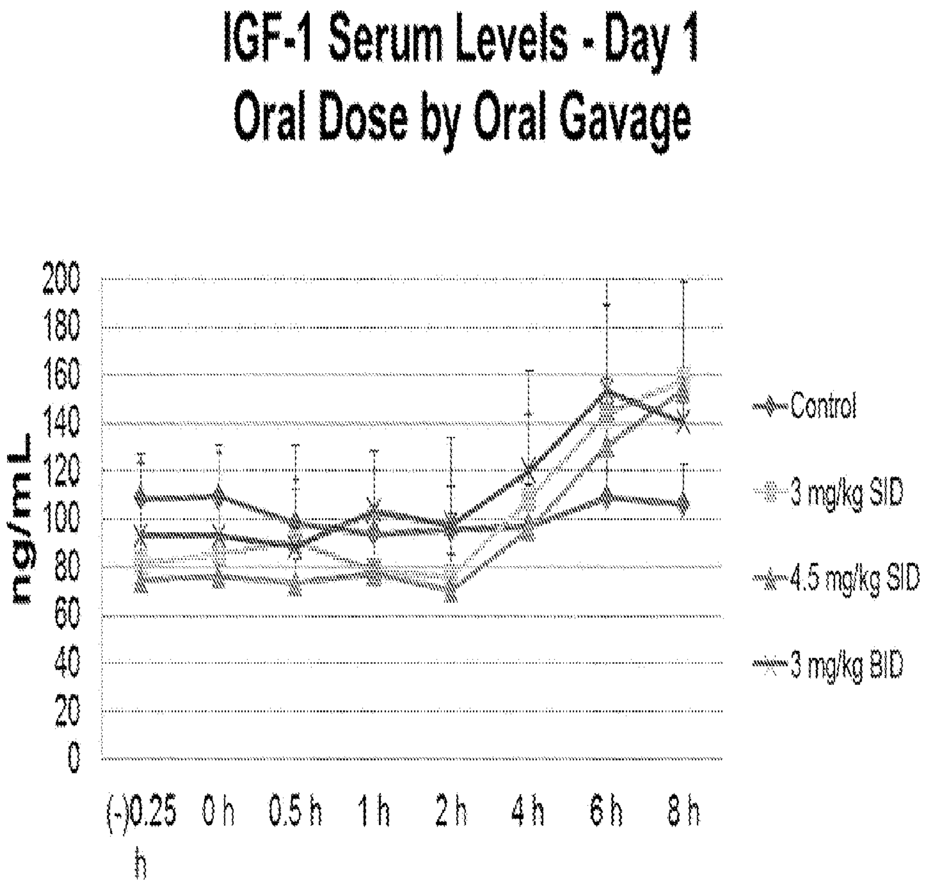

IGF-1 Serum Levels - Day 1
Oral Dose by Oral Gavage
ng/mL
200
180
160
140
120
100
80
60
40
20
0
(-)0.25 h
0 h
0.5 h
1 h
2 h
4 h
6 h
8 h
Control
3 mg/kg SID
4.5 mg/kg SID
3 mg/kg BID

FIGURE 35

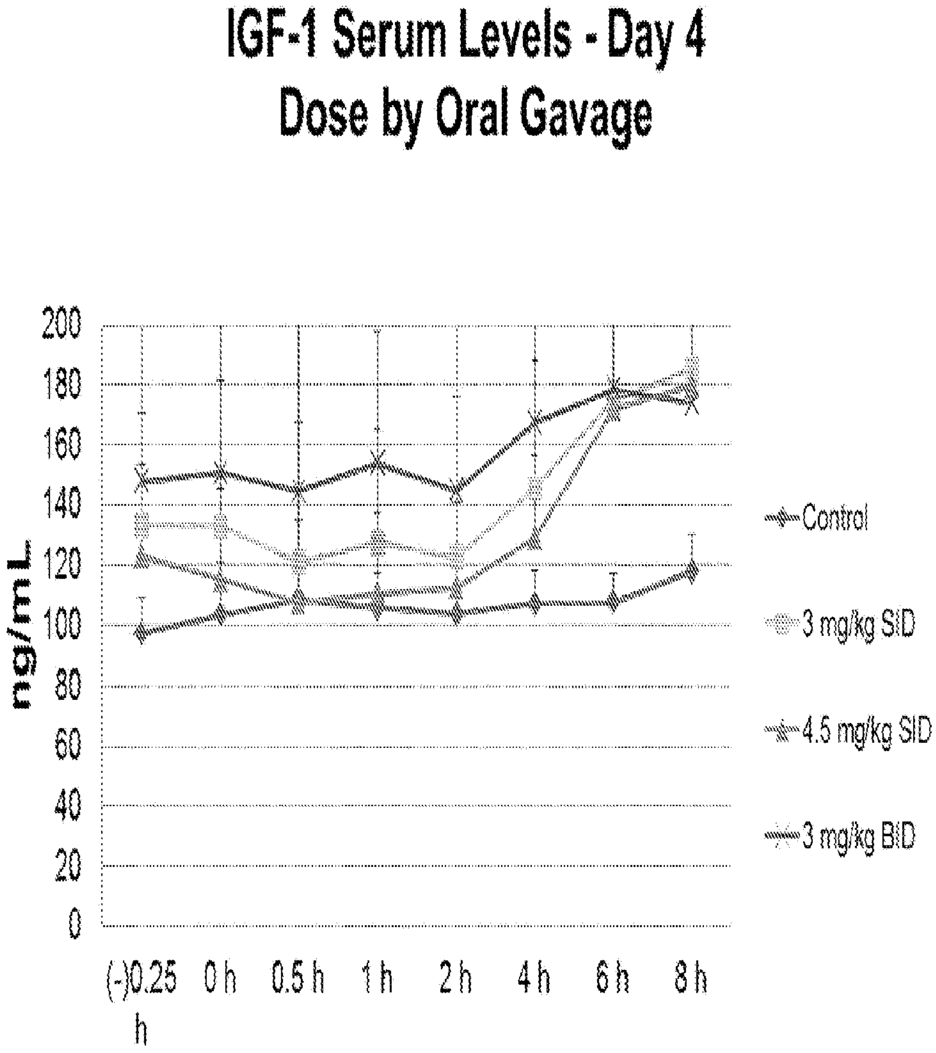
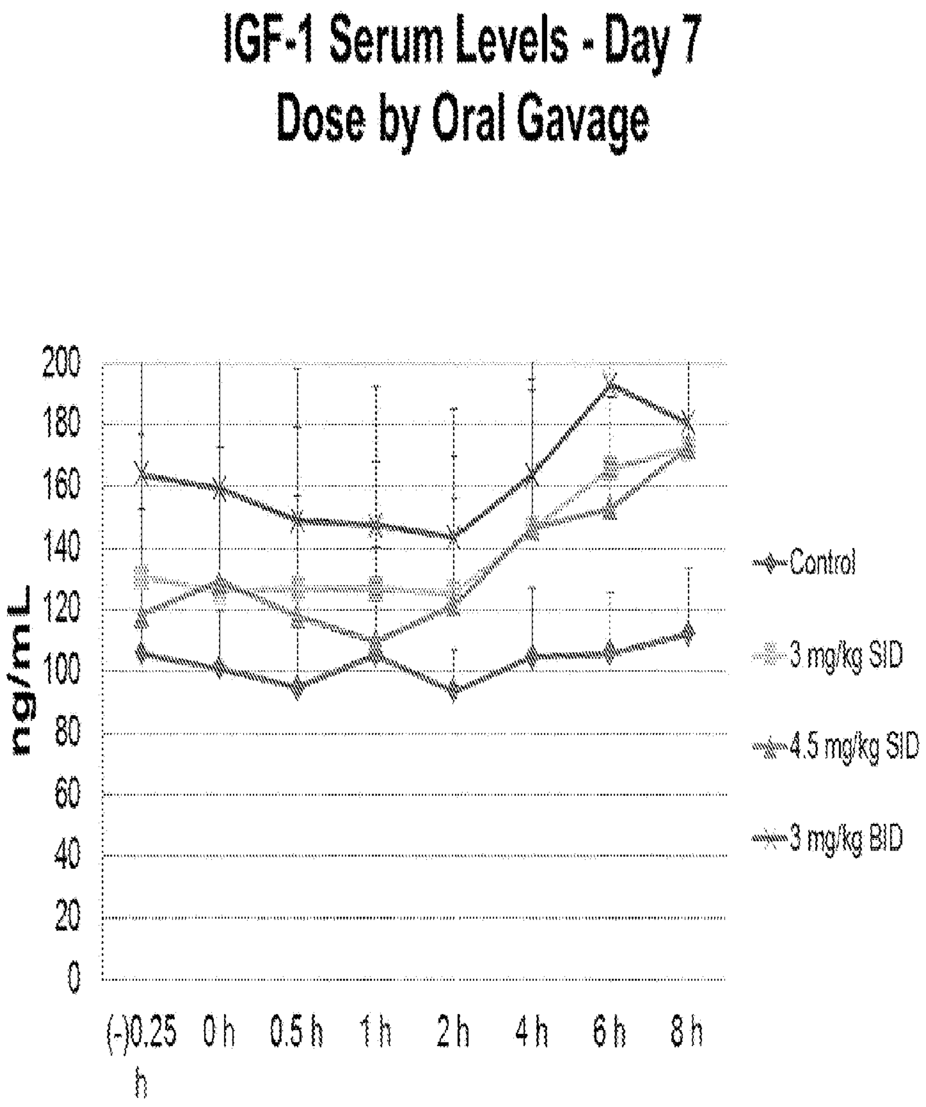

IGF-1 Serum Levels - Day 4
Dose by Oral Gavage
ng/mL
200
180
160
140
120
100
80
60
40
20
0
(-)0.25 h
0 h
0.5 h
1 h
2 h
4 h
6 h
8 h
Control
3 mg/kg SID
4.5 mg/kg SID
3 mg/kg BID

FIGURE 36



IGF-1 Serum Levels - Day 7
Dose by Oral Gavage
ng/mL
200
180
160
140
120
100
80
60
40
20
0
(-)0.25 h
0 h
0.5 h
1 h
2 h
4 h
6 h
8 h
Control
3 mg/kg SID
4.5 mg/kg SID
3 mg/kg BID

FIGURE 37

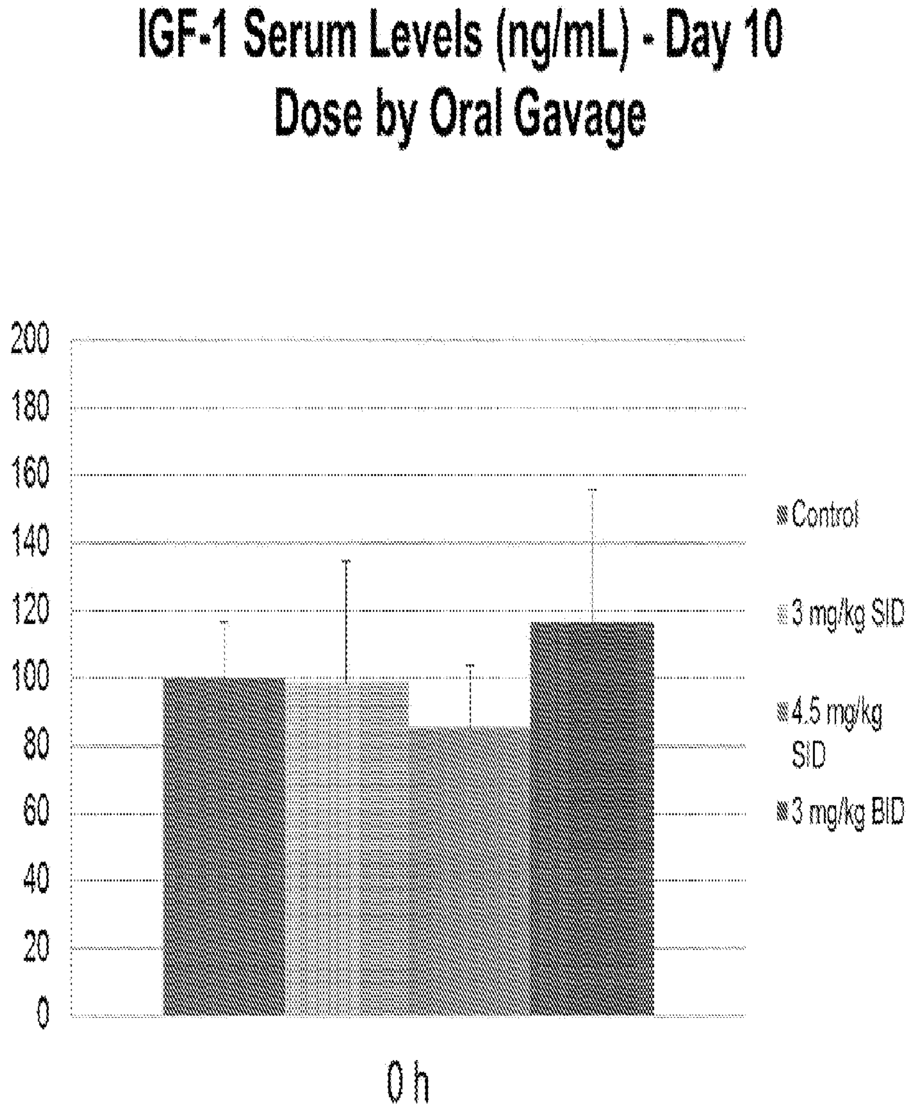

IGF-1 Serum Levels (ng/mL) - Day 10
Dose by Oral Gavage
200
180
160
140
120
100
80
60
40
20
0
0 h
Control
3 mg/kg SID
4.5 mg/kg SID
3 mg/kg BID

FIGURE 38

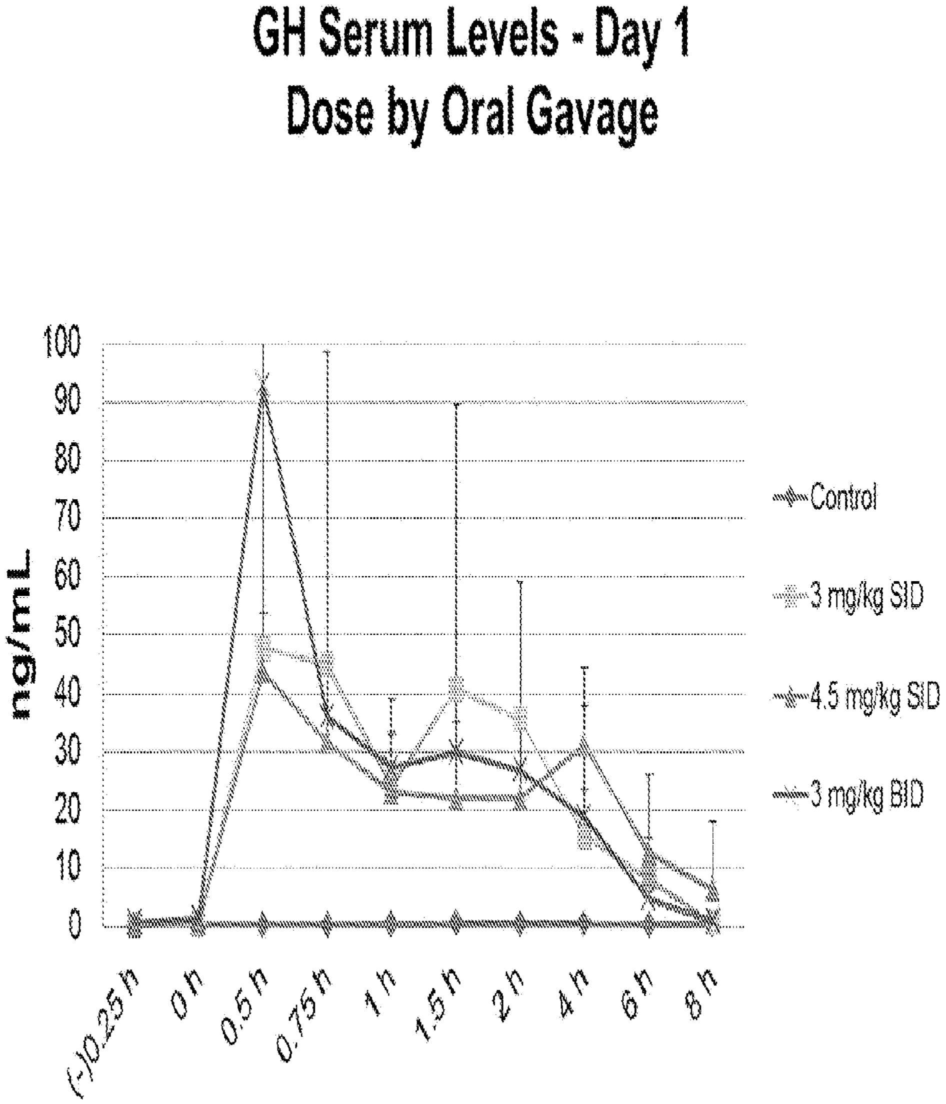

GH Serum Levels - Day 1
Dose by Oral Gavage
ng/mL
100
90
80
70
60
50
40
30
20
10
0
(-)0.25 h
0 h
0.5 h
0.75 h
1 h
1.5 h
2 h
4 h
6 h
8 h
Control
3 mg/kg SID
4.5 mg/kg SID
3 mg/kg BID

FIGURE 39

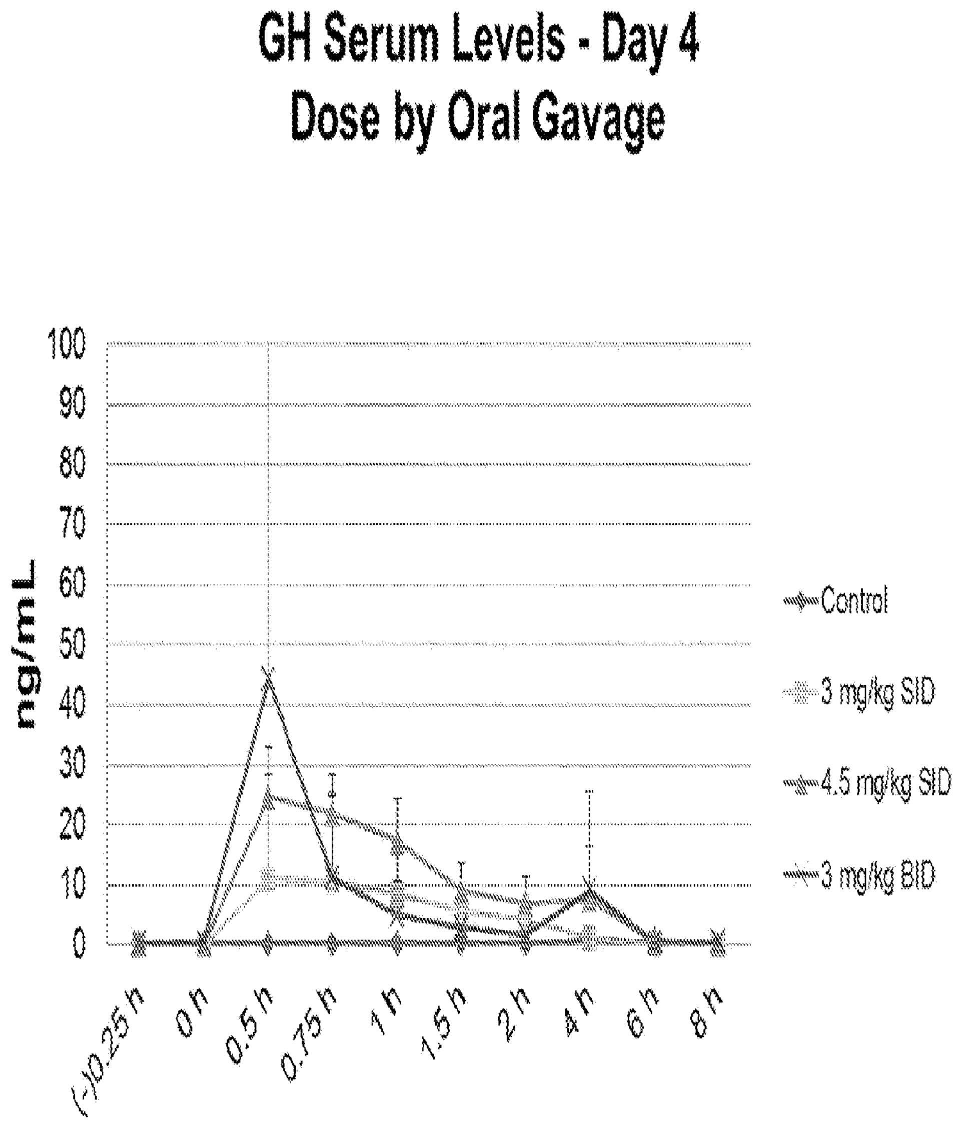

GH Serum Levels - Day 4
Dose by Oral Gavage
100
90
80
70
60
50
40
30
20
10
0
ng/mL
Control
3 mg/kg SID
4.5 mg/kg SID
3 mg/kg BID
(-)0.25 h
0 h
0.5 h
0.75 h
1 h
1.5 h
2 h
4 h
6 h
8 h

FIGURE 40

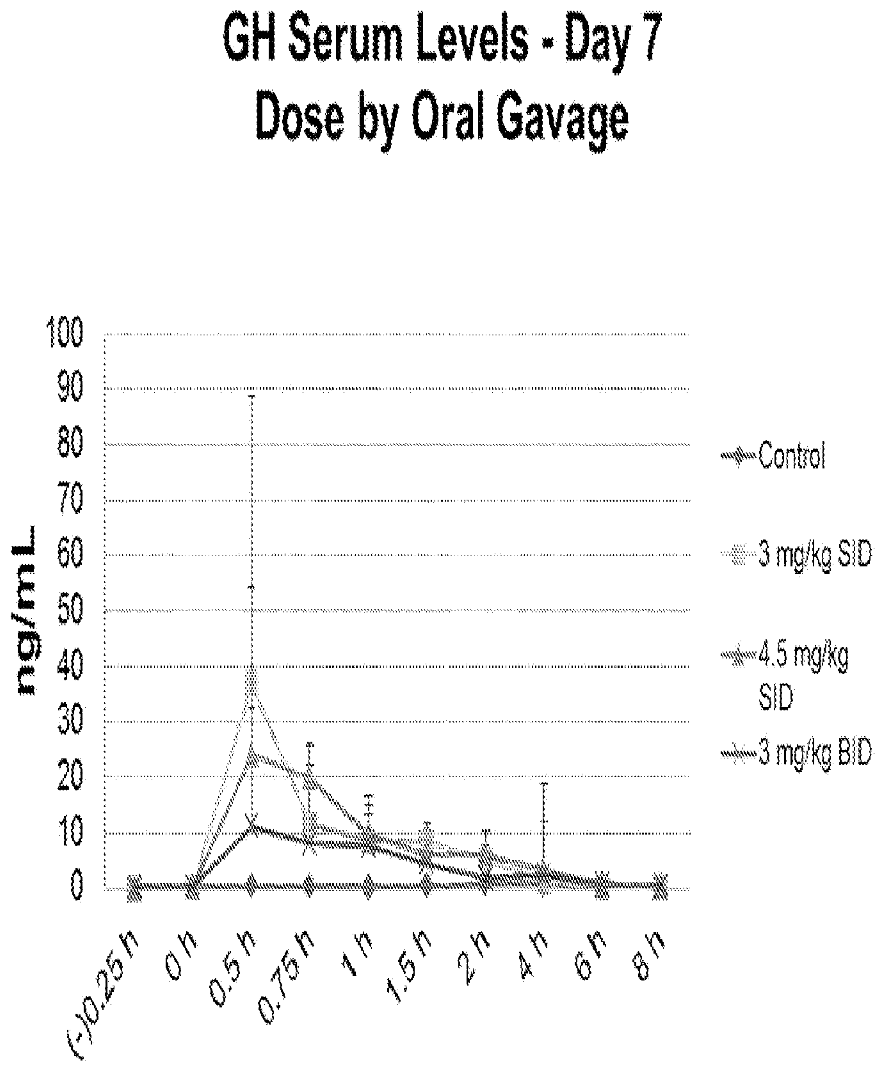

GH Serum Levels - Day 7
Dose by Oral Gavage
ng/mL
100
90
80
70
60
50
40
30
20
10
0
(-)0.25 h
0 h
0.5 h
0.75 h
1 h
1.5 h
2 h
4 h
6 h
8 h
Control
3 mg/kg SID
4.5 mg/kg SID
3 mg/kg BID

FIGURE 41

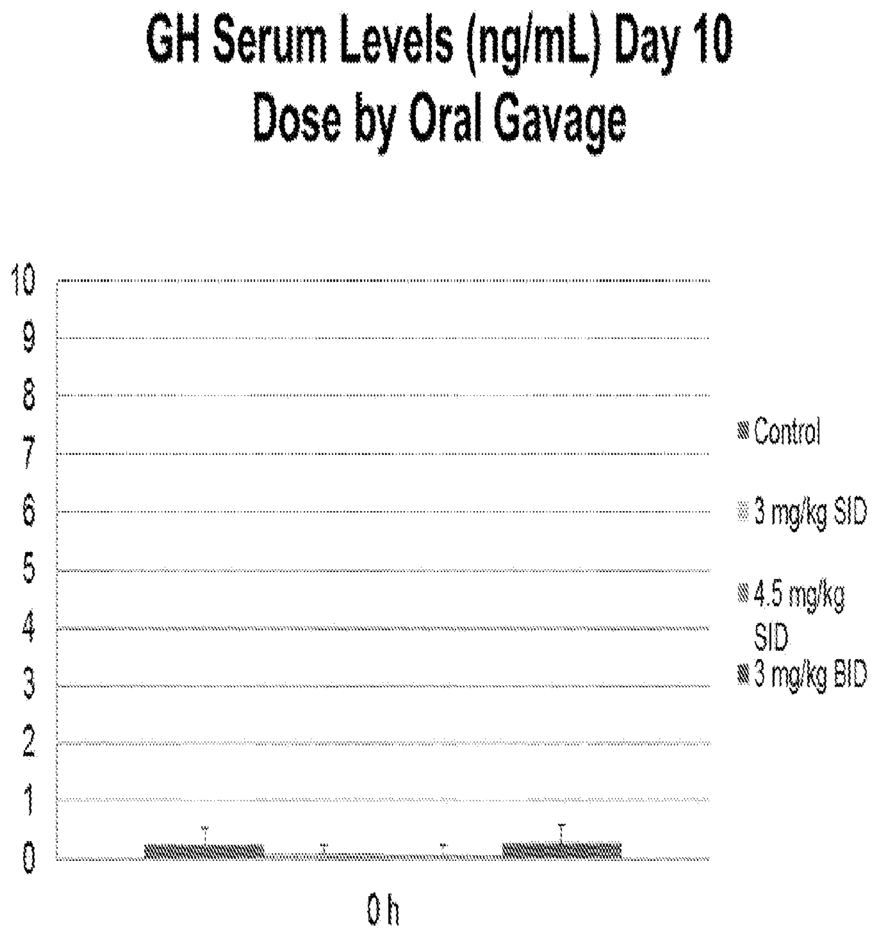
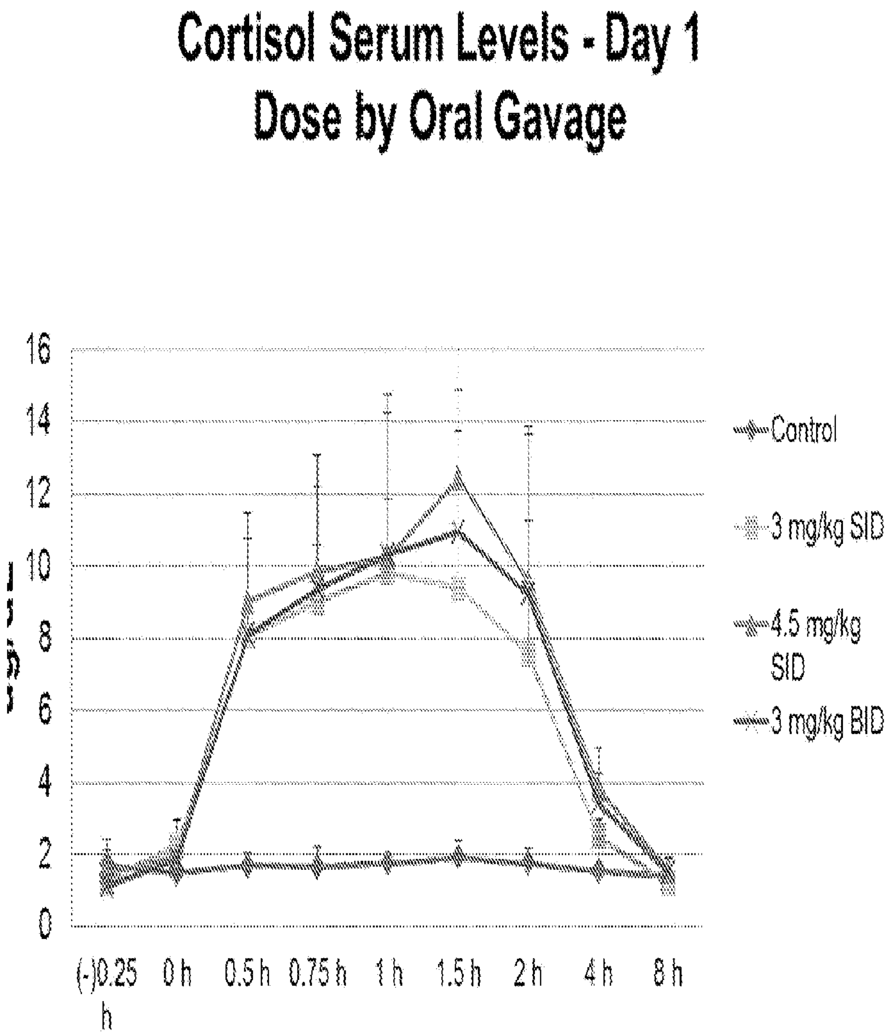

GH Serum Levels (ng/mL) Day 10
Dose by Oral Gavage
10
9
8
7
6
5
4
3
2
1
0
0 h
Control
3 mg/kg SID
4.5 mg/kg SID
3 mg/kg BID

FIGURE 42



Cortisol Serum Levels - Day 1
Dose by Oral Gavage
16
14
12
10
8
6
4
2
0
(-)0.25 h
0 h
0.5 h
0.75 h
1 h
1.5 h
2 h
4 h
8 h
Control
3 mg/kg SID
4.5 mg/kg SID
3 mg/kg BID

FIGURE 43

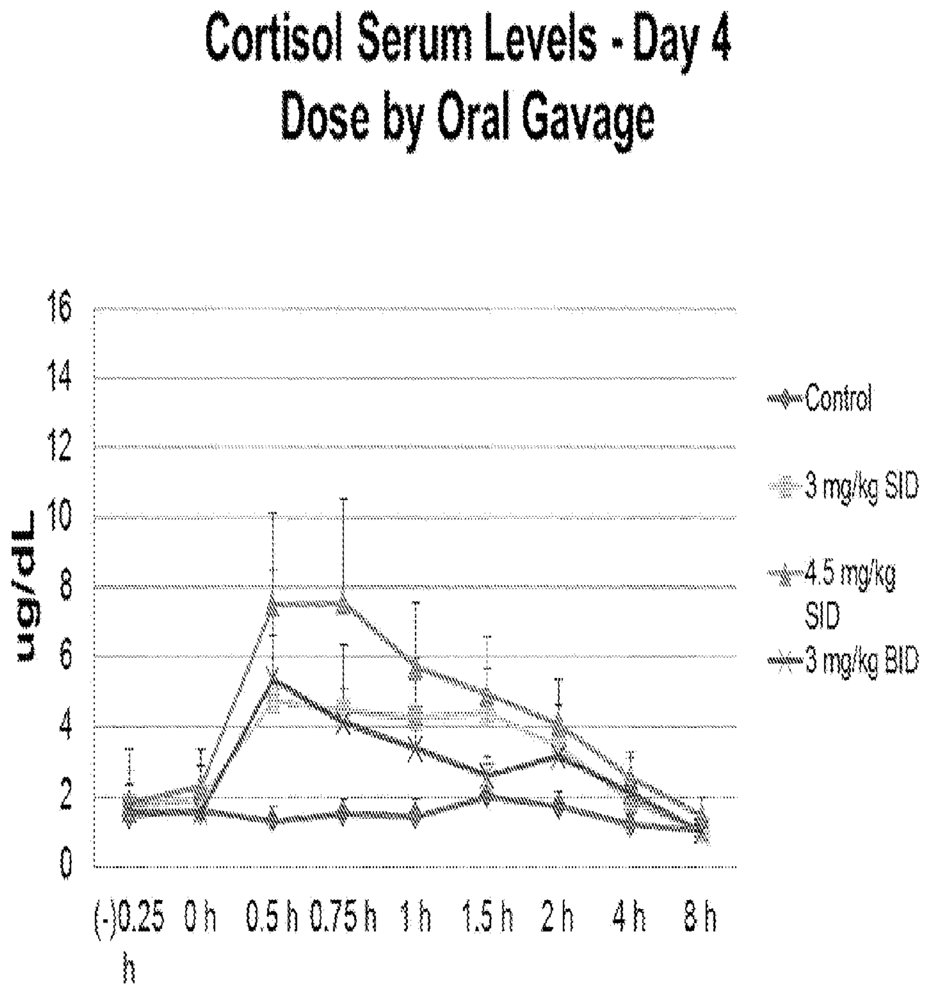

Cortisol Serum Levels - Day 4
Dose by Oral Gavage
ug/dL
16
14
12
10
8
6
4
2
0
(-)0.25 h
0 h
0.5 h
0.75 h
1 h
1.5 h
2 h
4 h
8 h
Control
3 mg/kg SID
4.5 mg/kg SID
3 mg/kg BID

FIGURE 44

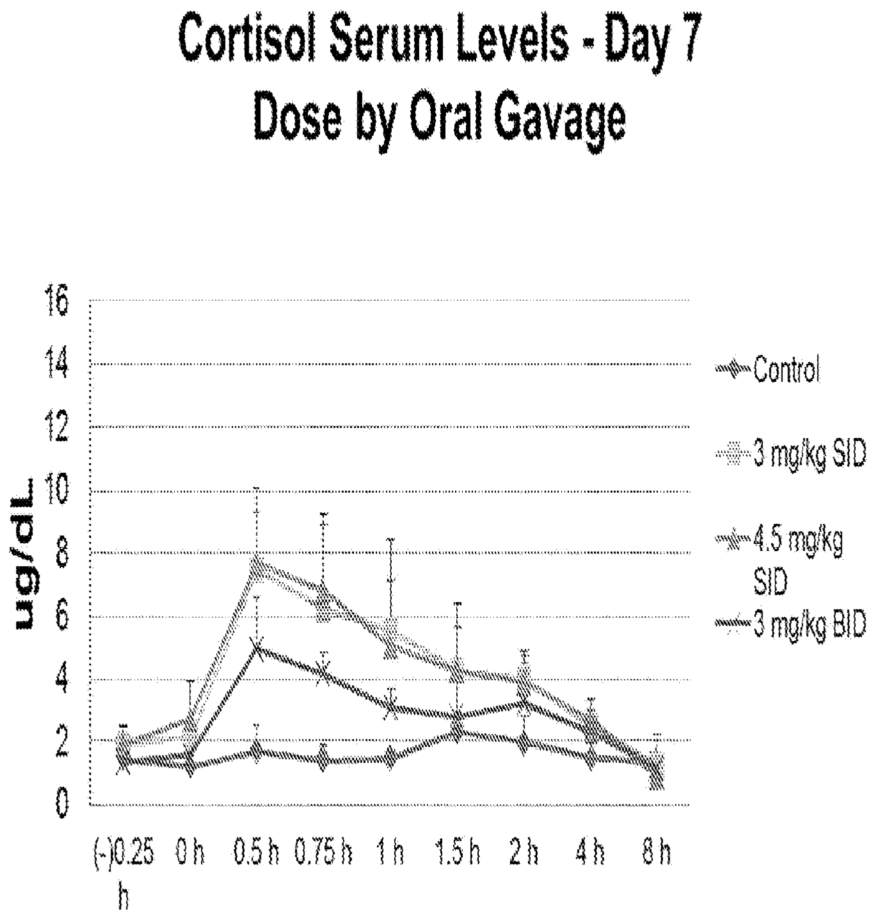

Cortisol Serum Levels - Day 7
Dose by Oral Gavage
ug/dL
16
14
12
10
8
6
4
2
0
(-)0.25 h
0 h
0.5 h
0.75 h
1 h
1.5 h
2 h
4 h
8 h
Control
3 mg/kg SID
4.5 mg/kg SID
3 mg/kg BID

FIGURE 45

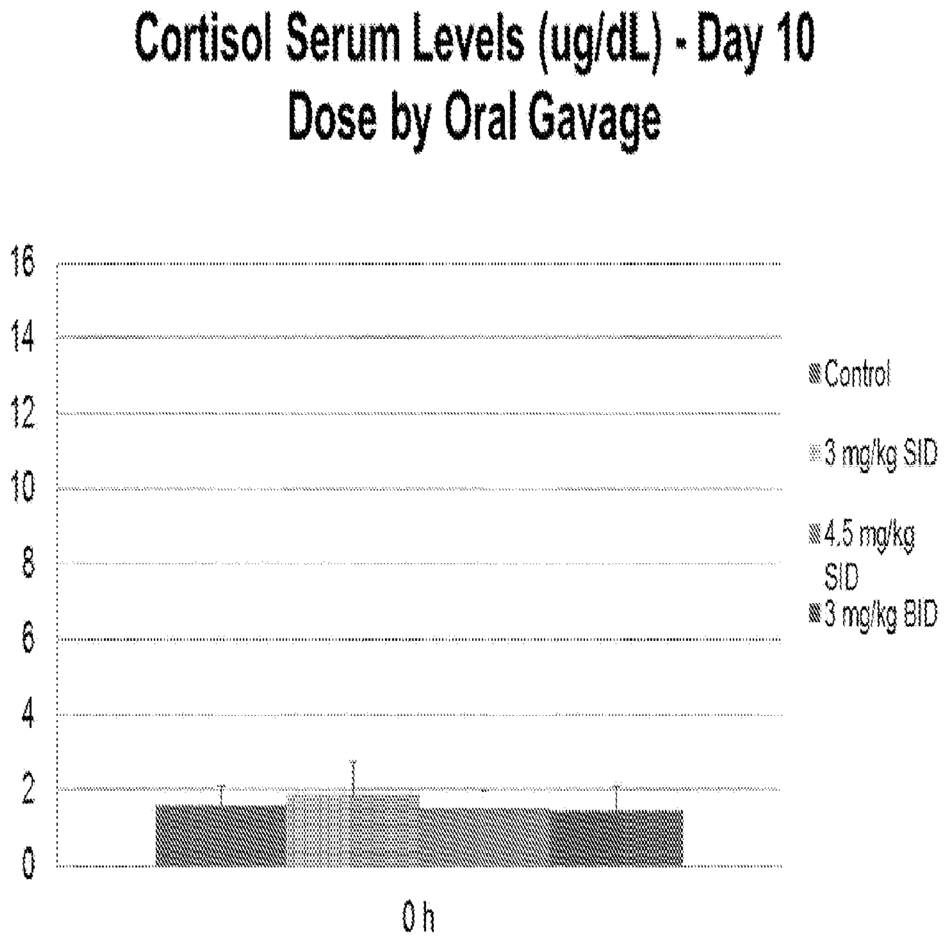

Cortisol Serum Levels (ug/dL) - Day 10
Dose by Oral Gavage
16
14
12
10
8
6
4
2
0
0 h
Control
3 mg/kg SID
4.5 mg/kg SID
3 mg/kg BID

FIGURE 46

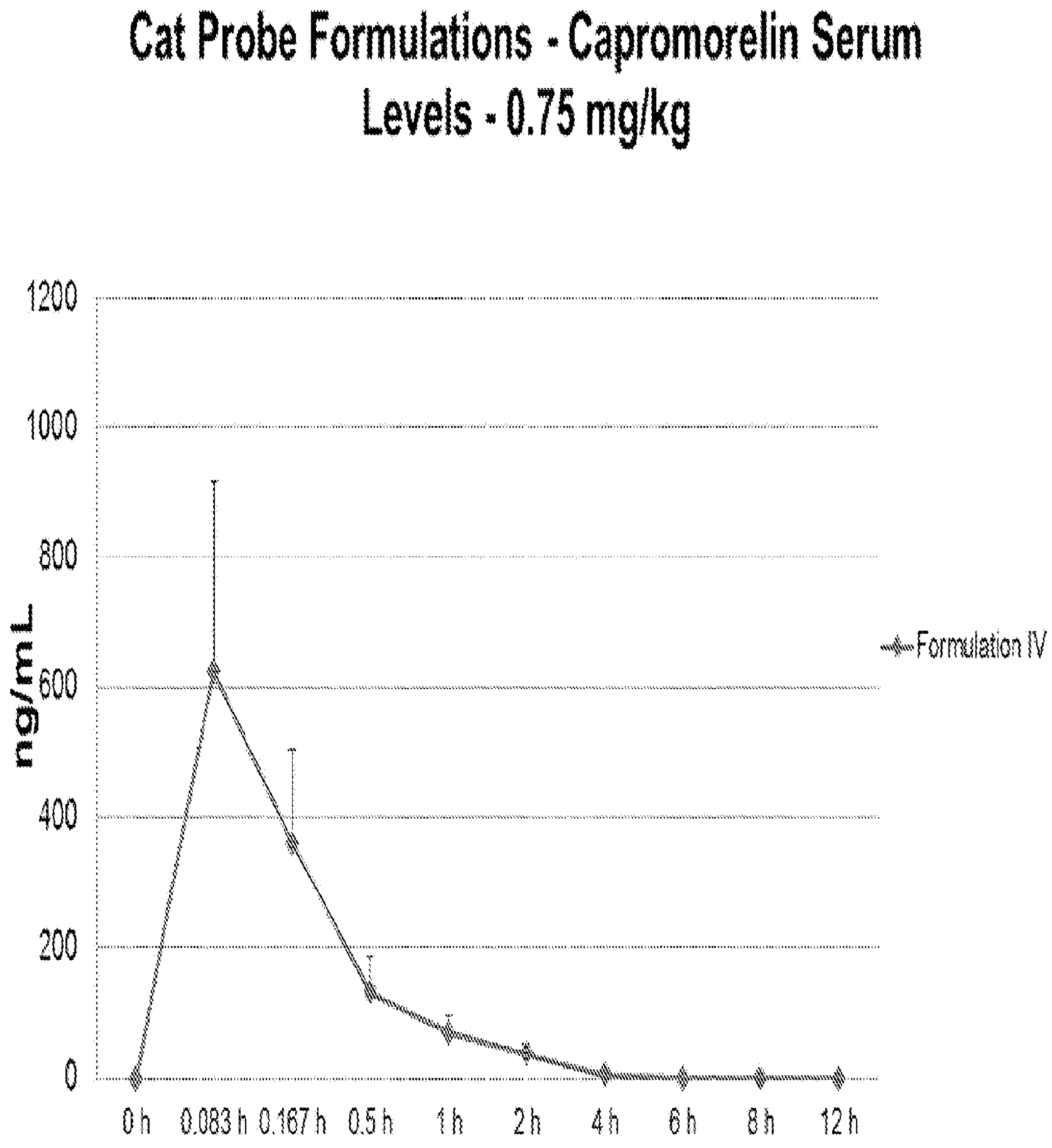

Cat Probe Formulations - Capromorelin Serum Levels - 0.75 mg/kg
ng/mL
1200
1000
800
600
400
200
0
0 h
0.083 h
0.167 h
0.5 h
1 h
2 h
4 h
6 h
8 h
12 h
Formulation IV

FIGURE 47

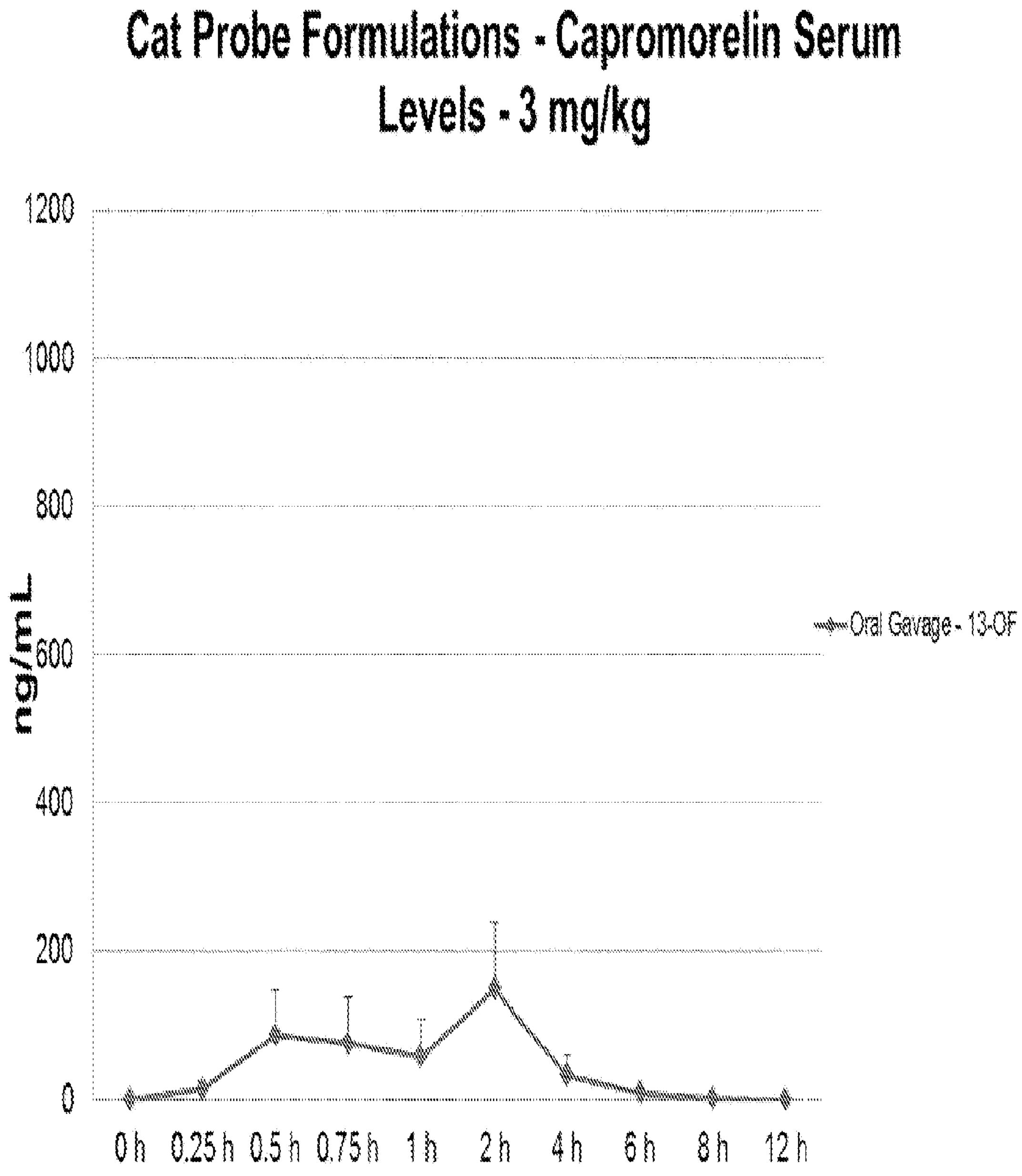

Cat Probe Formulations - Capromorelin Serum Levels - 3 mg/kg
1200
1000
800
600
400
200
0
ng/mL
Oral Gavage - 13-OF
0 h
0.25 h
0.5 h
0.75 h
1 h
2 h
4 h
6 h
8 h
12 h

FIGURE 48

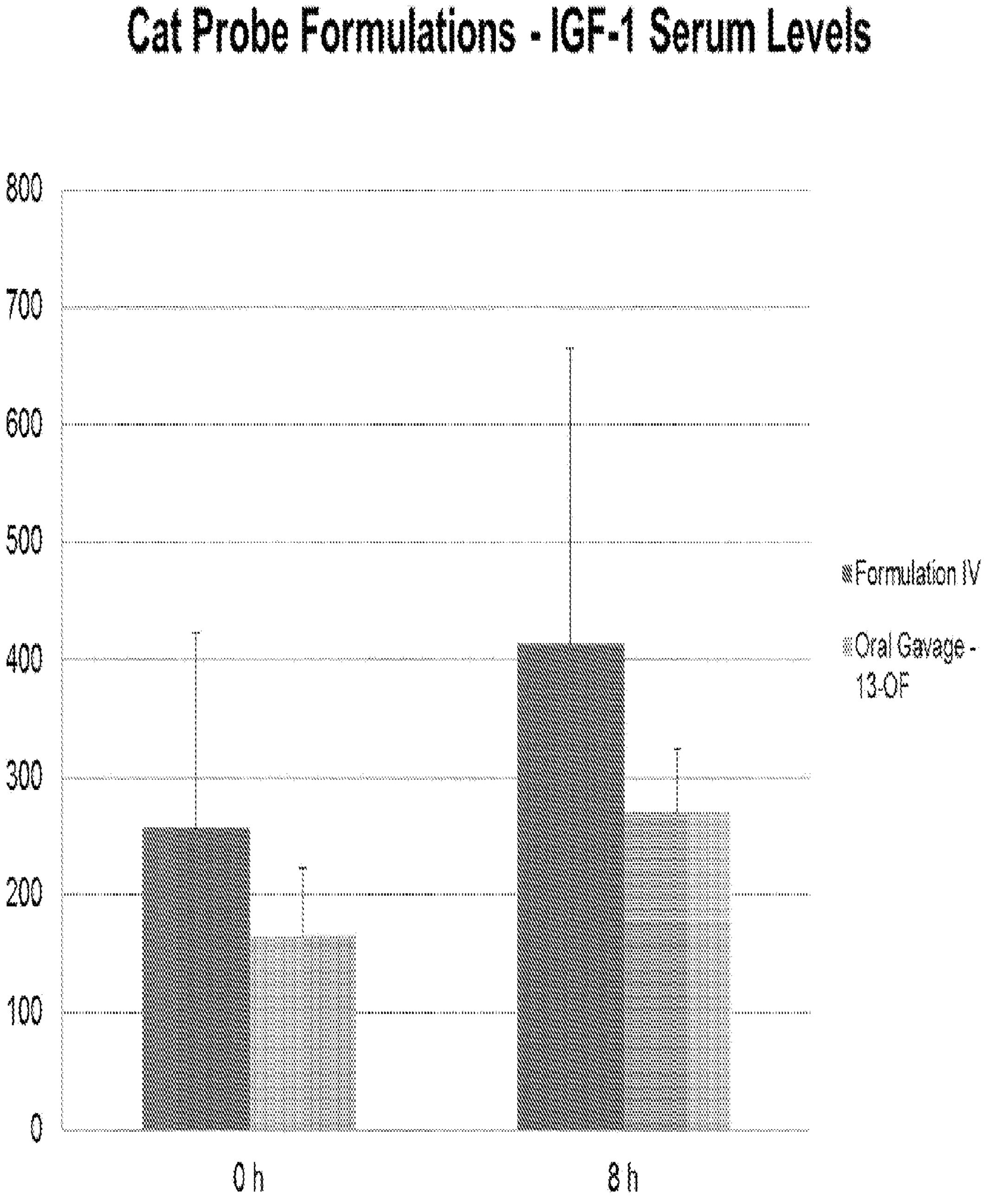

Cat Probe Formulations - IGF-1 Serum Levels
800
700
600
500
400
300
200
100
0
0 h
8 h
Formulation IV
Oral Gavage - 13-OF

FIGURE 49

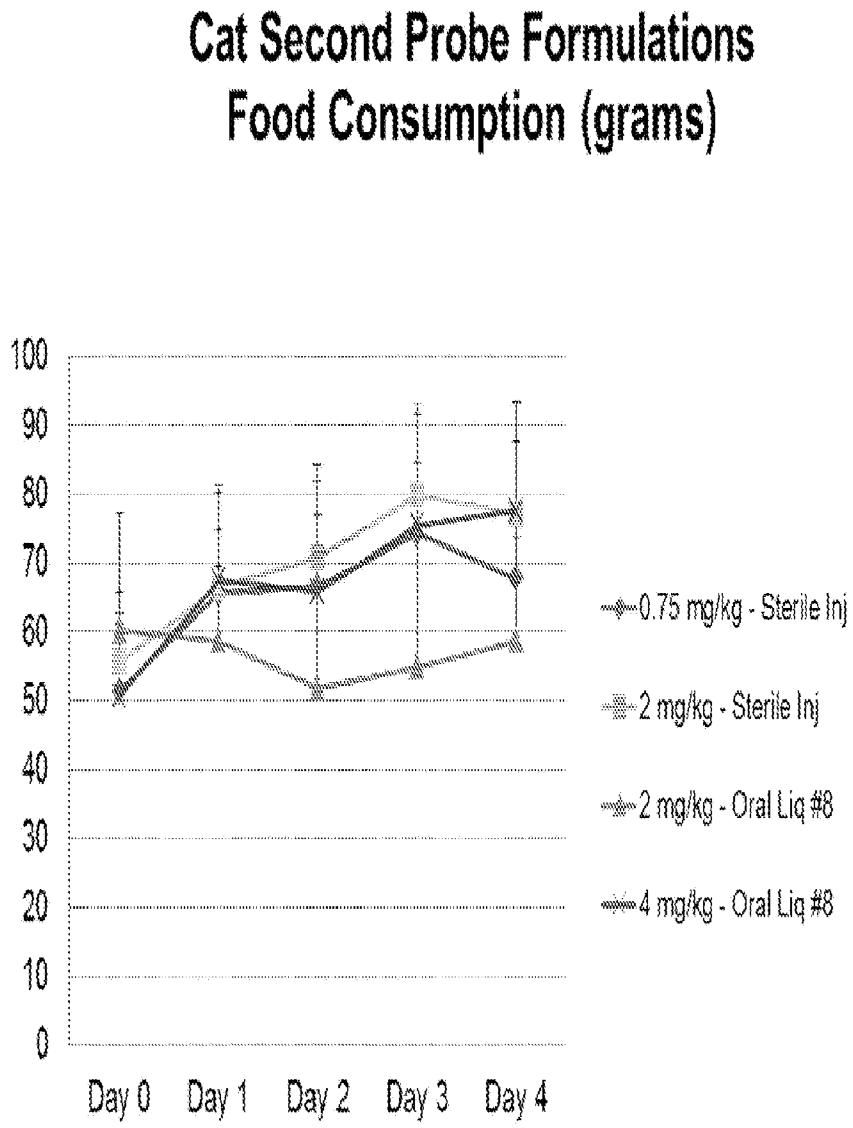

Cat Second Probe Formulations
Food Consumption (grams)
100
90
80
70
60
50
40
30
20
10
0
Day 0
Day 1
Day 2
Day 3
Day 4
0.75 mg/kg - Sterile Inj
2 mg/kg - Sterile Inj
2 mg/kg - Oral Liq #8
4 mg/kg - Oral Liq #8

FIGURE 50

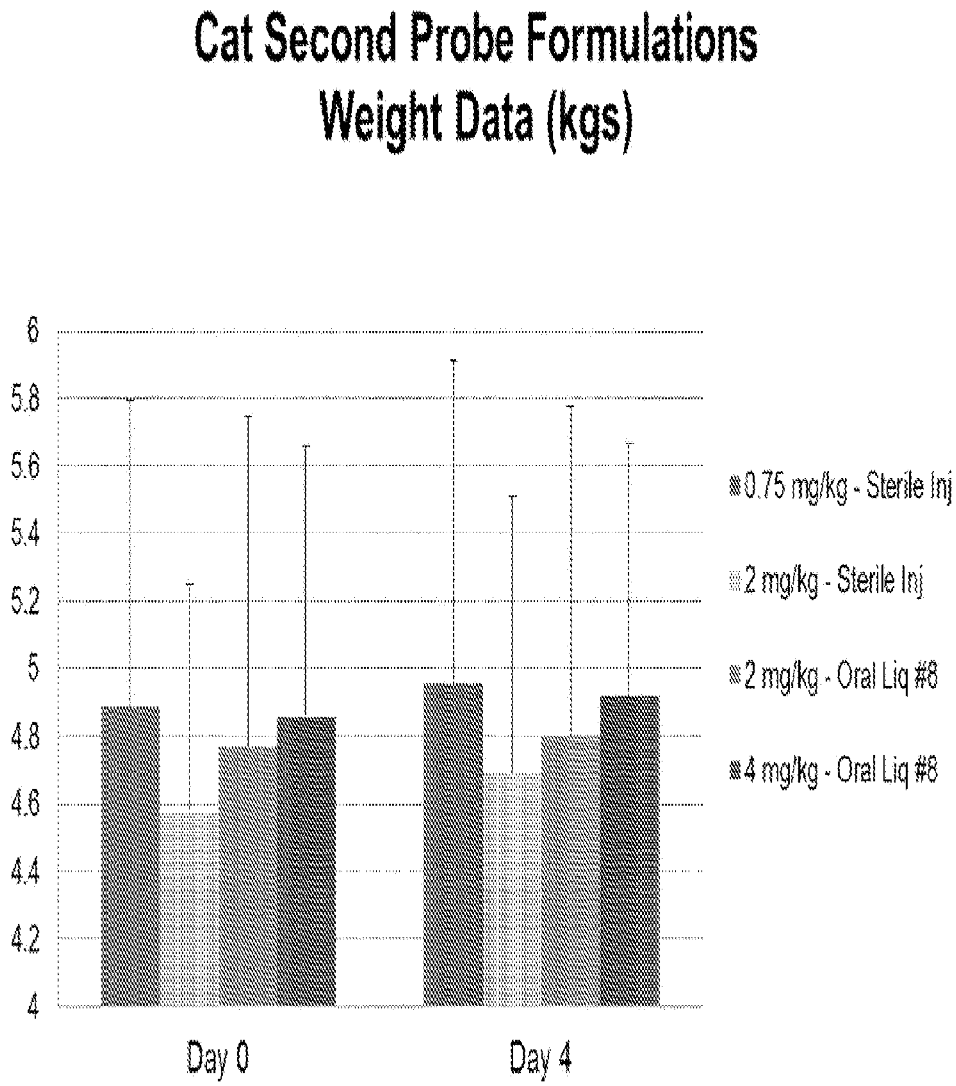

Cat Second Probe Formulations
Weight Data (kgs)
6
5.8
5.6
5.4
5.2
5
4.8
4.6
4.4
4.2
4
Day 0
Day 4
0.75 mg/kg - Sterile Inj
2 mg/kg - Sterile Inj
2 mg/kg - Oral Liq #8
4 mg/kg - Oral Liq #8

FIGURE 51

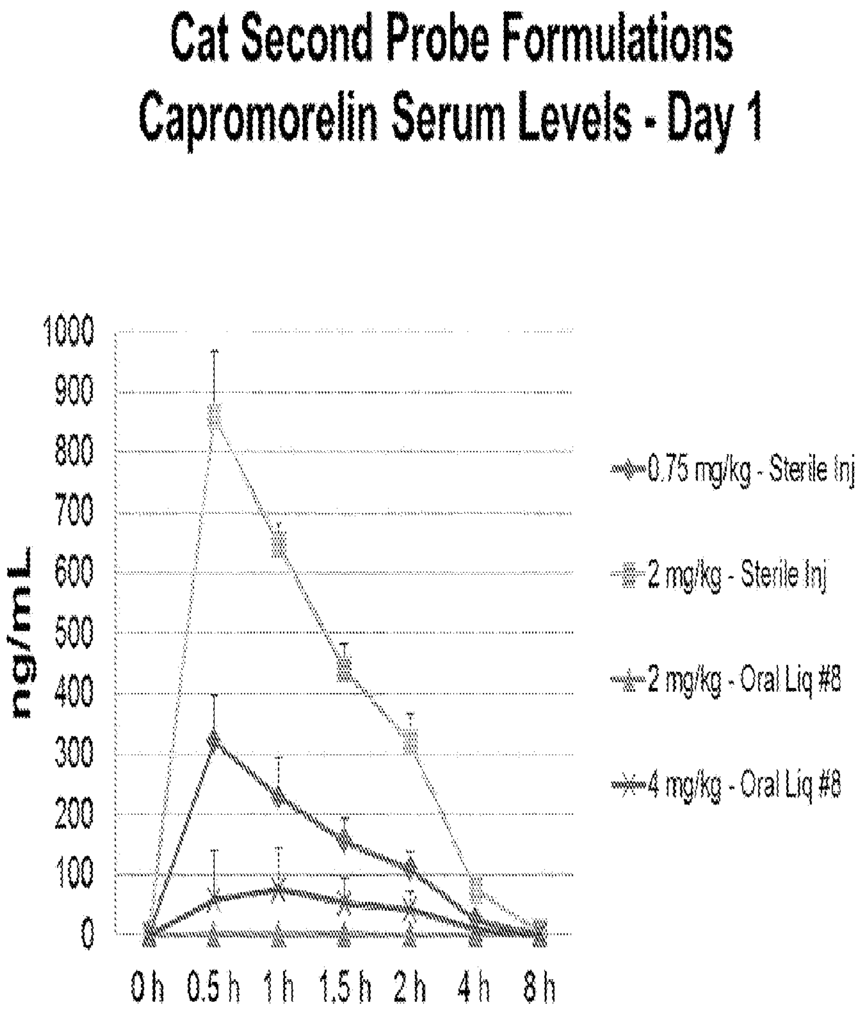

Cat Second Probe Formulations
Capromorelin Serum Levels - Day 1
ng/mL
1000
900
800
700
600
500
400
300
200
100
0
0 h
0.5 h
1 h
1.5 h
2 h
4 h
8 h
0.75 mg/kg - Sterile Inj
2 mg/kg - Sterile Inj
2 mg/kg - Oral Liq #8
4 mg/kg - Oral Liq #8

FIGURE 52

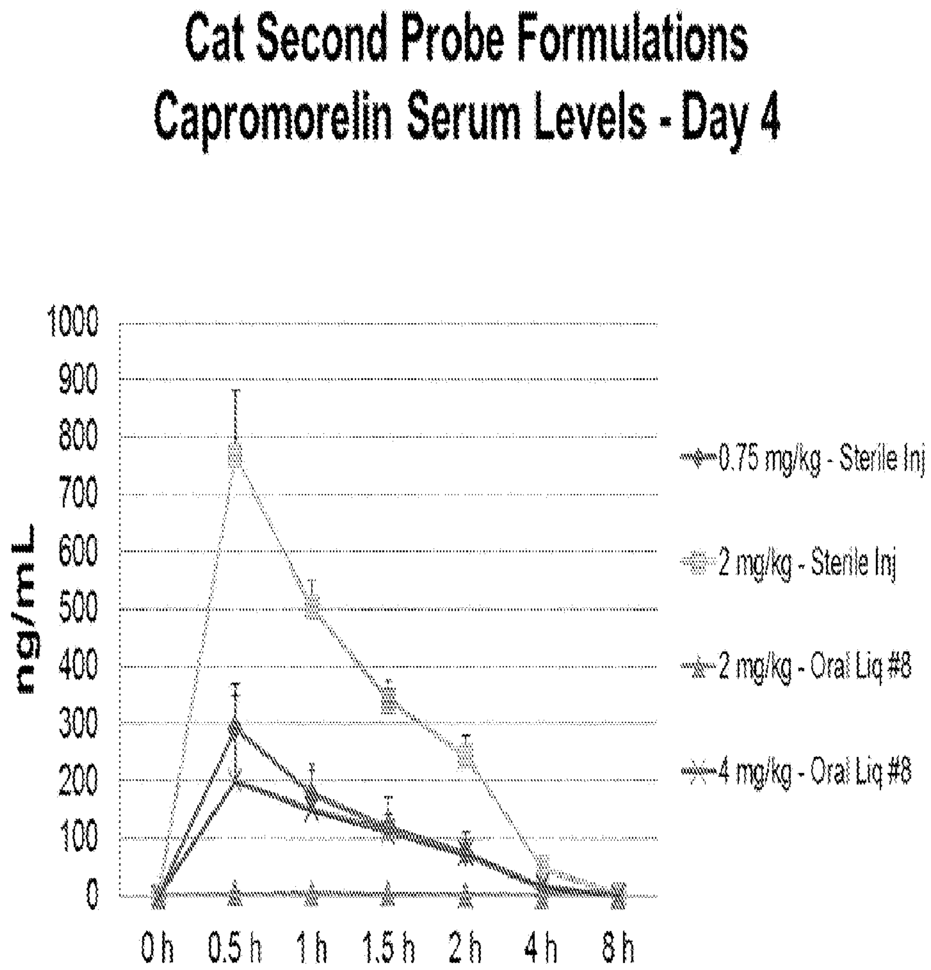

Cat Second Probe Formulations
Capromorelin Serum Levels - Day 4
ng/mL
1000
900
800
700
600
500
400
300
200
100
0
0 h
0.5 h
1 h
1.5 h
2 h
4 h
8 h
0.75 mg/kg - Sterile Inj
2 mg/kg - Sterile Inj
2 mg/kg - Oral Liq #8
4 mg/kg - Oral Liq #8

FIGURE 53

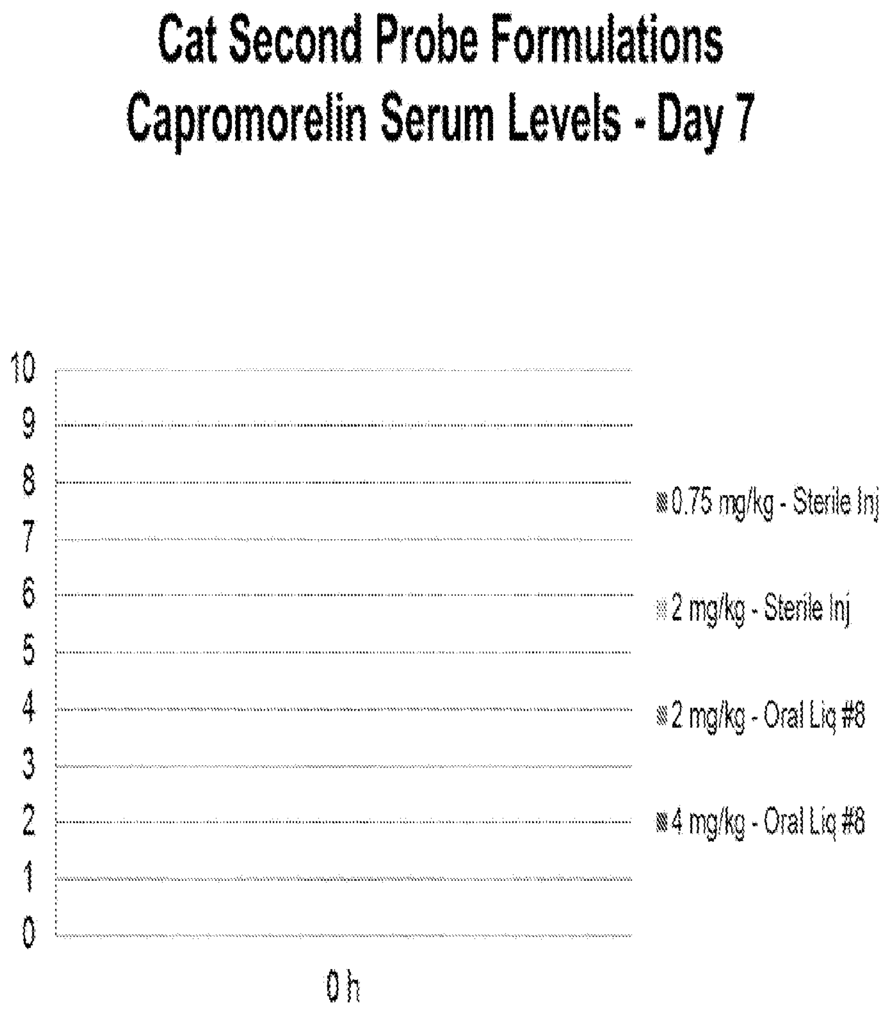

Cat Second Probe Formulations
Capromorelin Serum Levels - Day 7
10
9
8
7
6
5
4
3
2
1
0
0 h
0.75 mg/kg - Sterile Inj
2 mg/kg - Sterile Inj
2 mg/kg - Oral Liq #8
4 mg/kg - Oral Liq #8

FIGURE 54

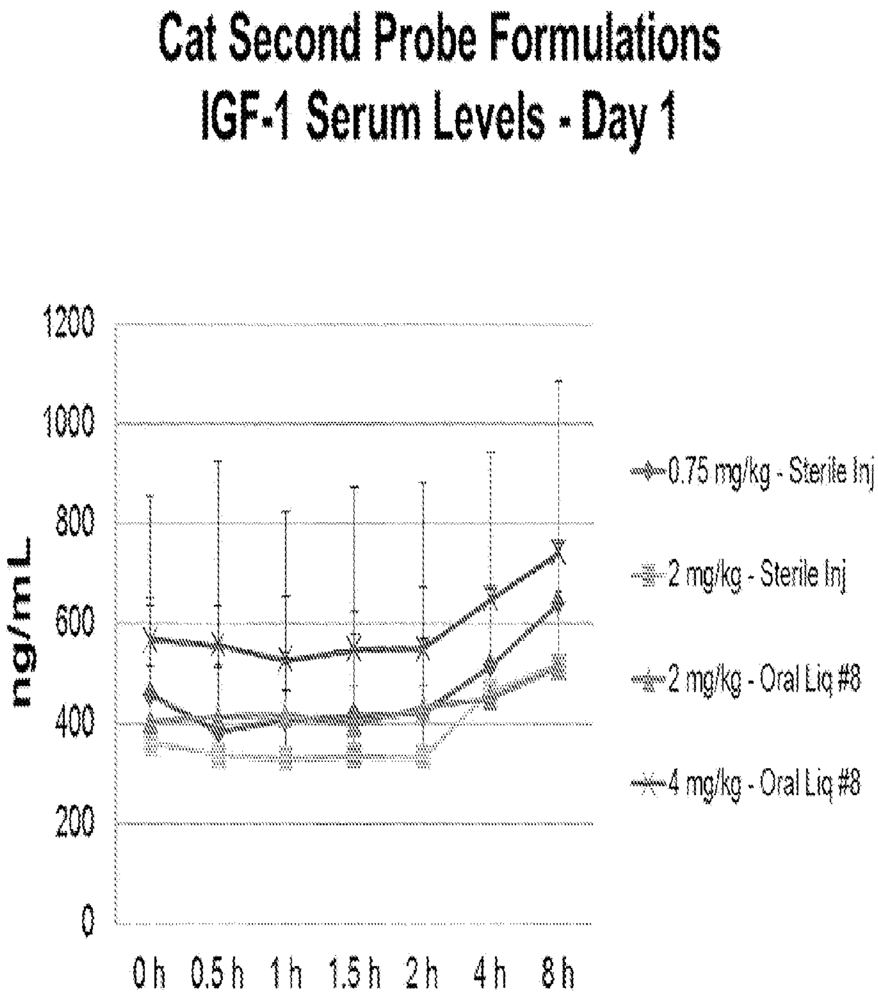

Cat Second Probe Formulations
IGF-1 Serum Levels - Day 1
1200
1000
800
600
400
200
0
ng/mL
0 h
0.5 h
1 h
1.5 h
2 h
4 h
8 h
0.75 mg/kg - Sterile Inj
2 mg/kg - Sterile Inj
2 mg/kg - Oral Liq #8
4 mg/kg - Oral Liq #8

FIGURE 55

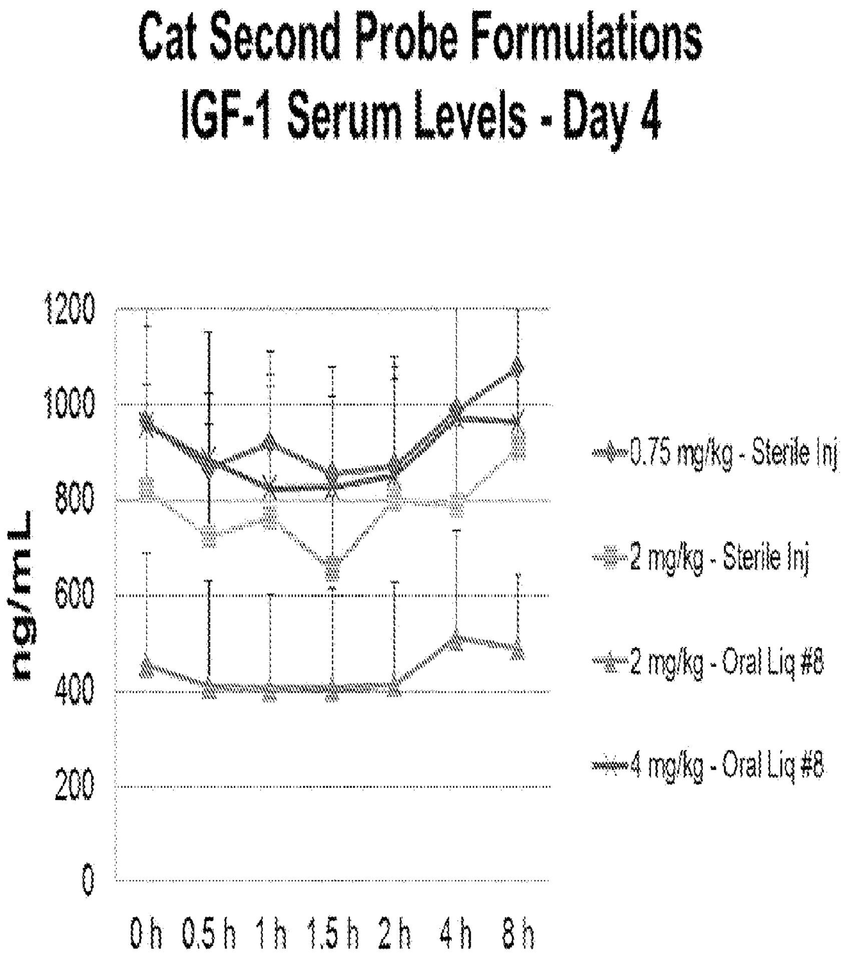

Cat Second Probe Formulations
IGF-1 Serum Levels - Day 4
ng/mL
1200
1000
800
600
400
200
0
0 h
0.5 h
1 h
1.5 h
2 h
4 h
8 h
0.75 mg/kg - Sterile Inj
2 mg/kg - Sterile Inj
2 mg/kg - Oral Liq #8
4 mg/kg - Oral Liq #8

FIGURE 56

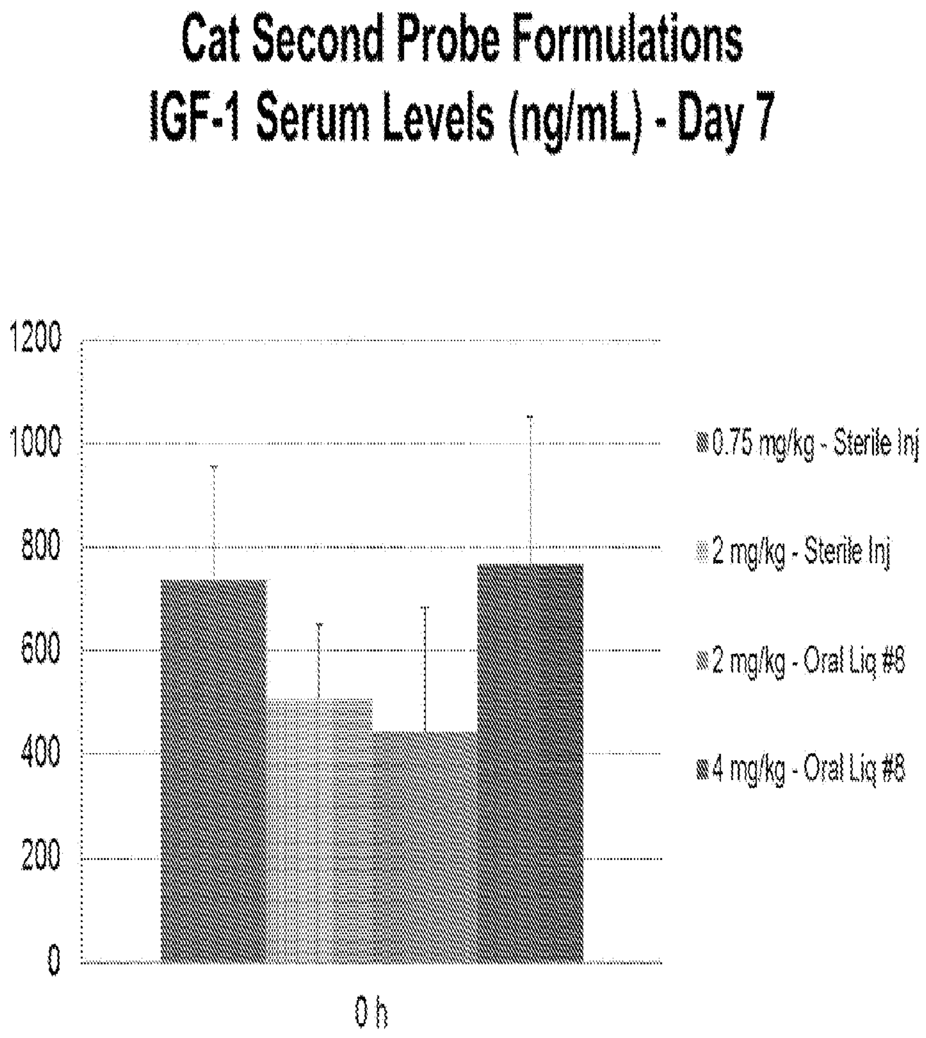

Cat Second Probe Formulations
IGF-1 Serum Levels (ng/mL) - Day 7
1200
1000
800
600
400
200
0
0 h
0.75 mg/kg - Sterile Inj
2 mg/kg - Sterile Inj
2 mg/kg - Oral Liq #8
4 mg/kg - Oral Liq #8

FIGURE 57

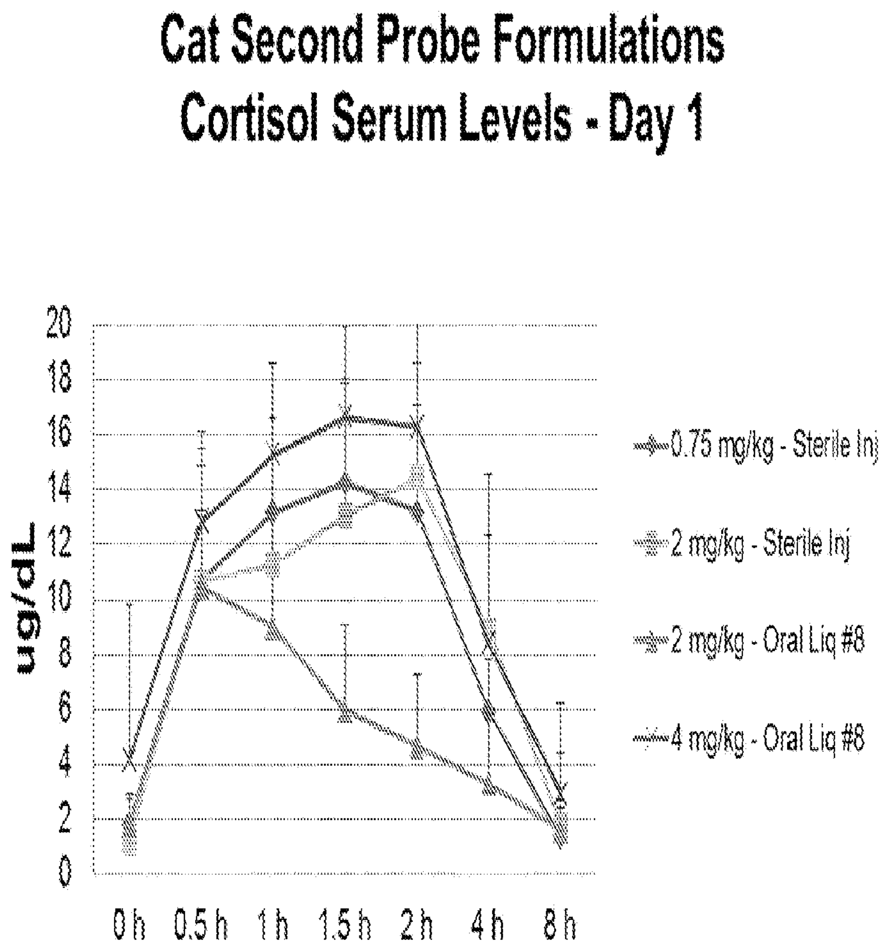

Cat Second Probe Formulations
Cortisol Serum Levels - Day 1
ug/dL
20
18
16
14
12
10
8
6
4
2
0
0 h
0.5 h
1 h
1.5 h
2 h
4 h
8 h
0.75 mg/kg - Sterile Inj
2 mg/kg - Sterile Inj
2 mg/kg - Oral Liq #8
4 mg/kg - Oral Liq #8

FIGURE 58

Cat Second Probe Formulations
Cortisol Serum Levels - Day 4

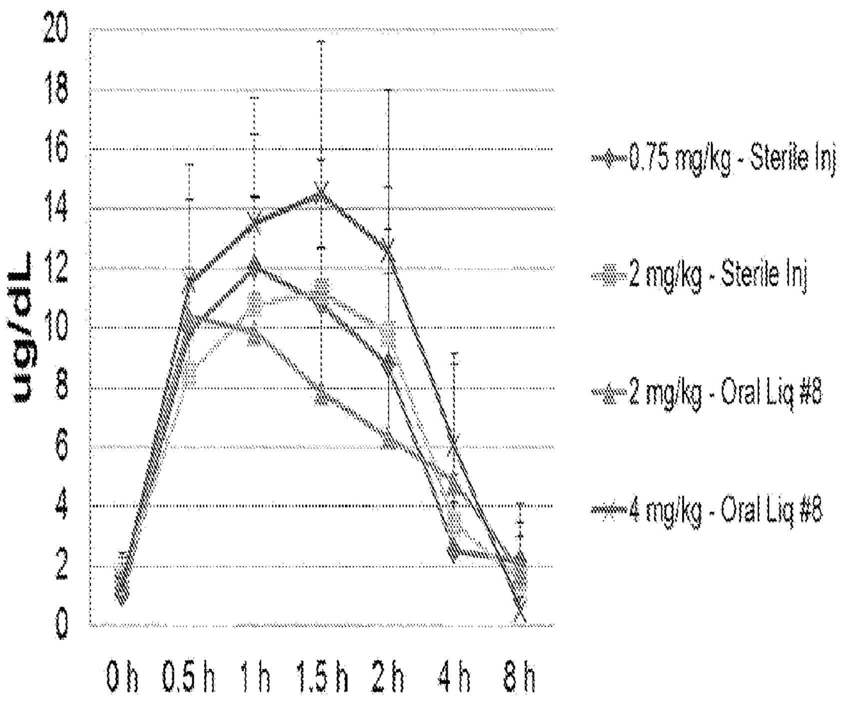


FIGURE 59

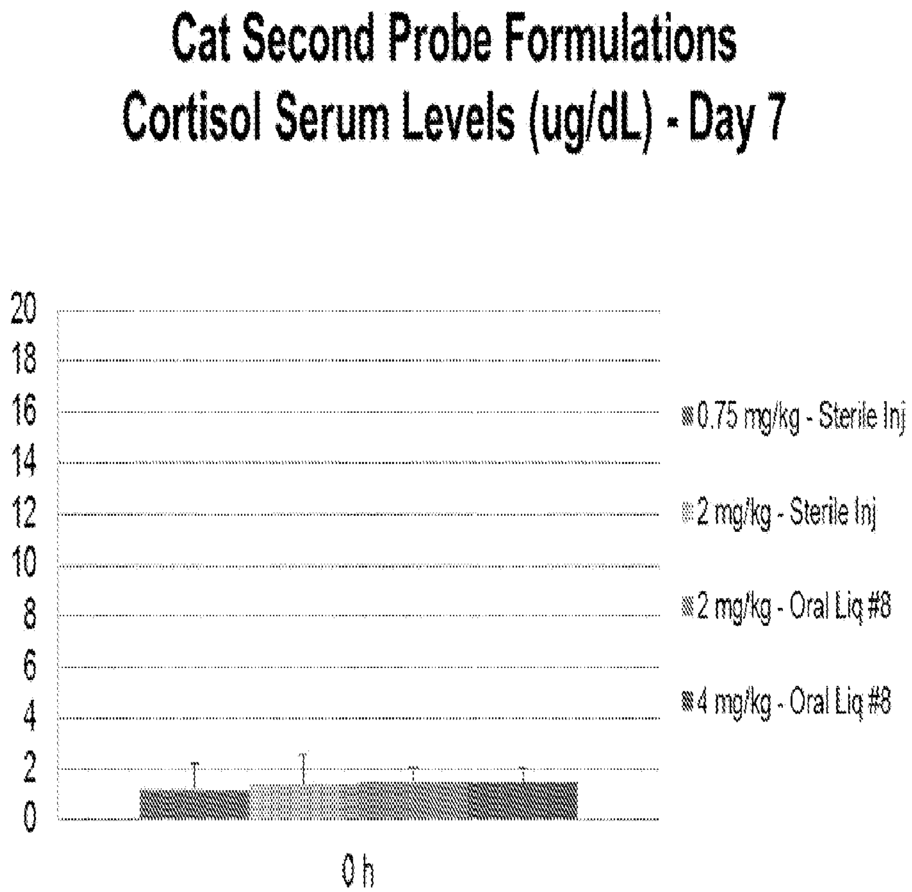
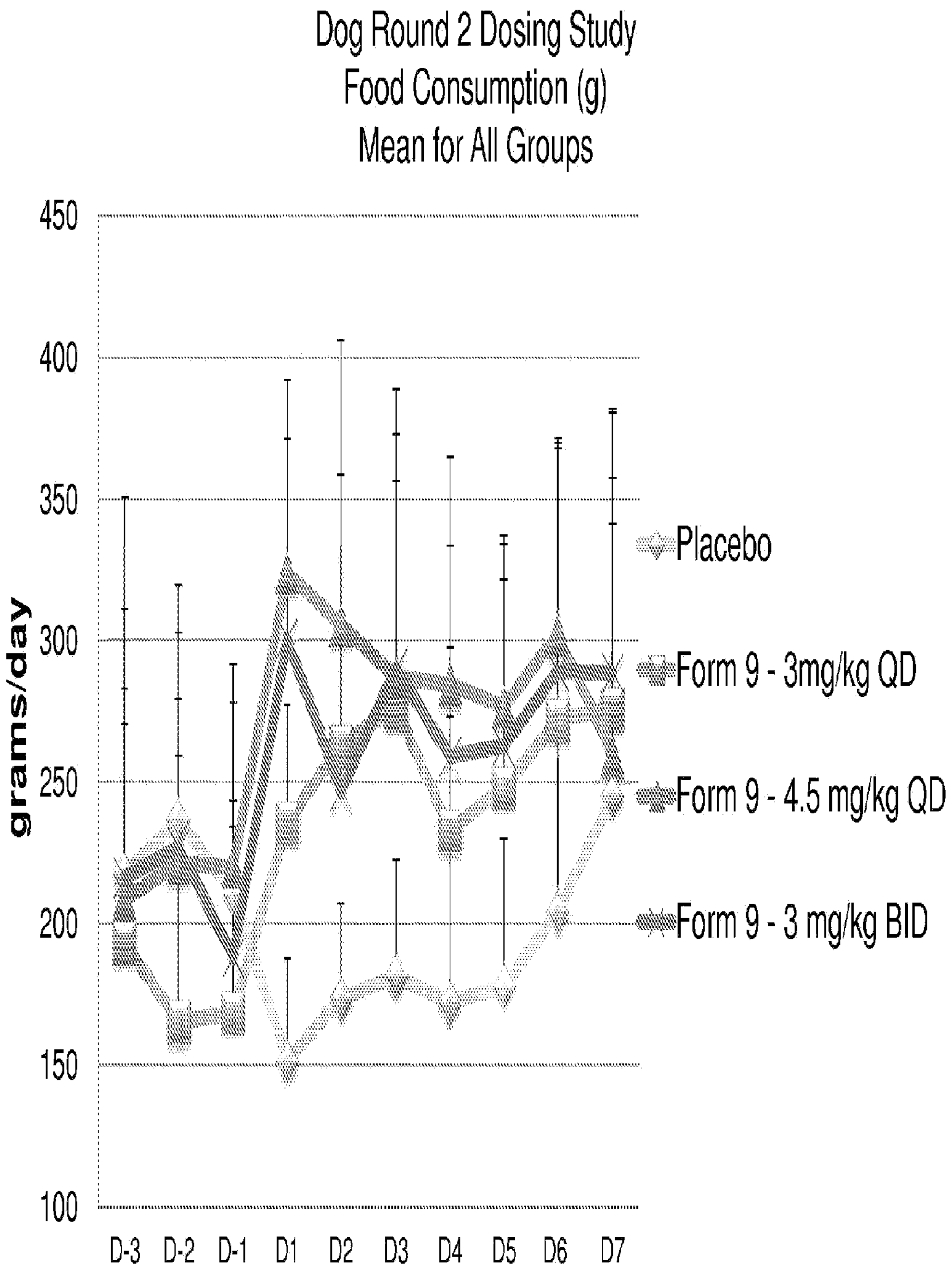

Cat Second Probe Formulations
Cortisol Serum Levels (ug/dL) - Day 7
20
18
16
14
12
10
8
6
4
2
0
0 h
0.75 mg/kg - Sterile Inj
2 mg/kg - Sterile Inj
2 mg/kg - Oral Liq #8
4 mg/kg - Oral Liq #8

FIGURE 60



Dog Round 2 Dosing Study
Food Consumption (g)
Mean for All Groups
grams/day
450
400
350
300
250
200
150
100
D-3
D-2
D-1
D1
D2
D3
D4
D5
D6
D7
Placebo
Form 9 - 3mg/kg QD
Form 9 - 4.5 mg/kg QD
Form 9 - 3 mg/kg BID

FIGURE 61

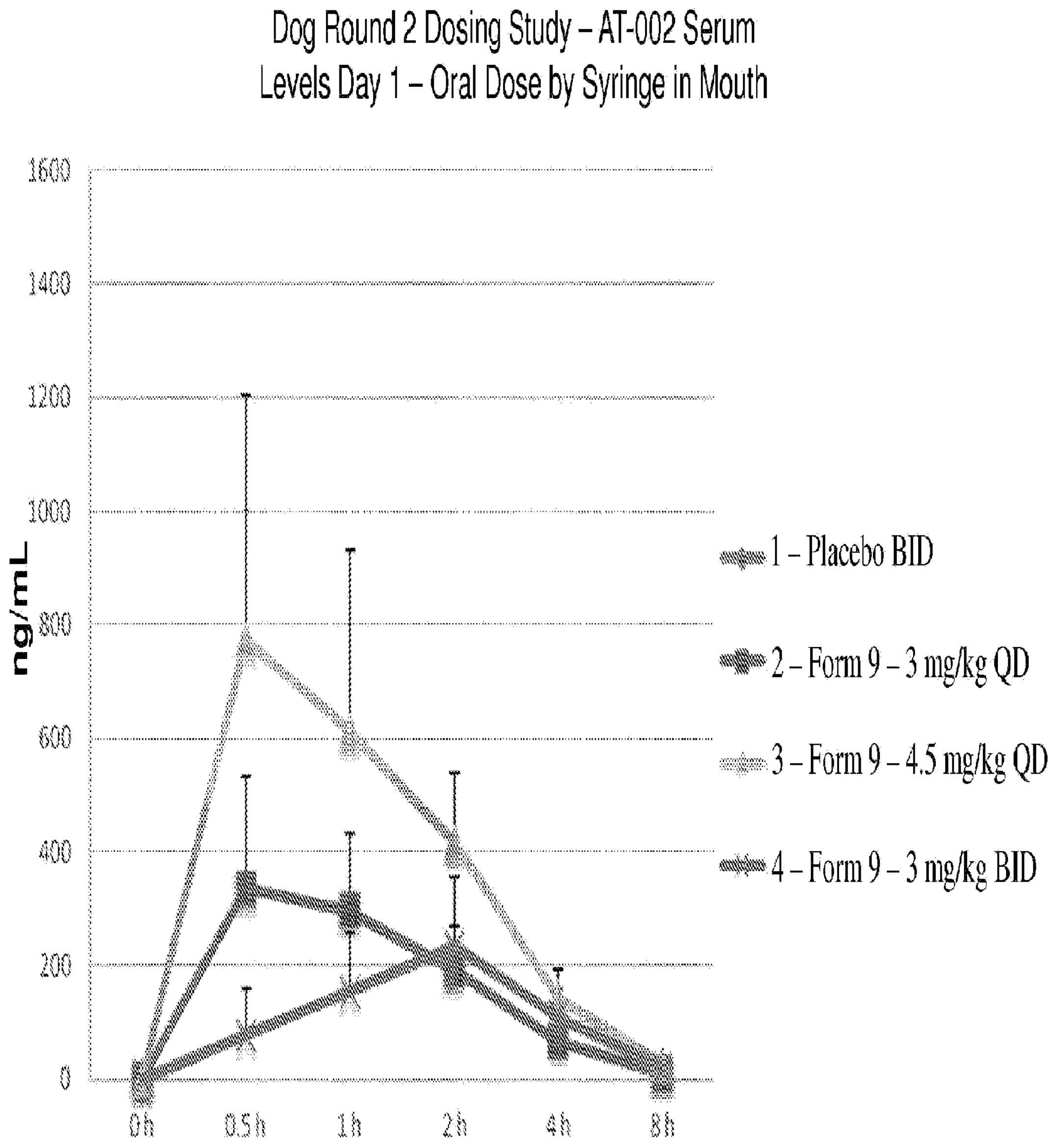

Dog Round 2 Dosing Study – AT-002 Serum Levels Day 1 – Oral Dose by Syringe in Mouth
1600
1400
1200
1000
800
600
400
200
0
ng/mL
0 h
0.5 h
1 h
2 h
4 h
8 h
1 – Placebo BID
2 – Form 9 – 3 mg/kg QD
3 – Form 9 – 4.5 mg/kg QD
4 – Form 9 – 3 mg/kg BID

FIGURE 62

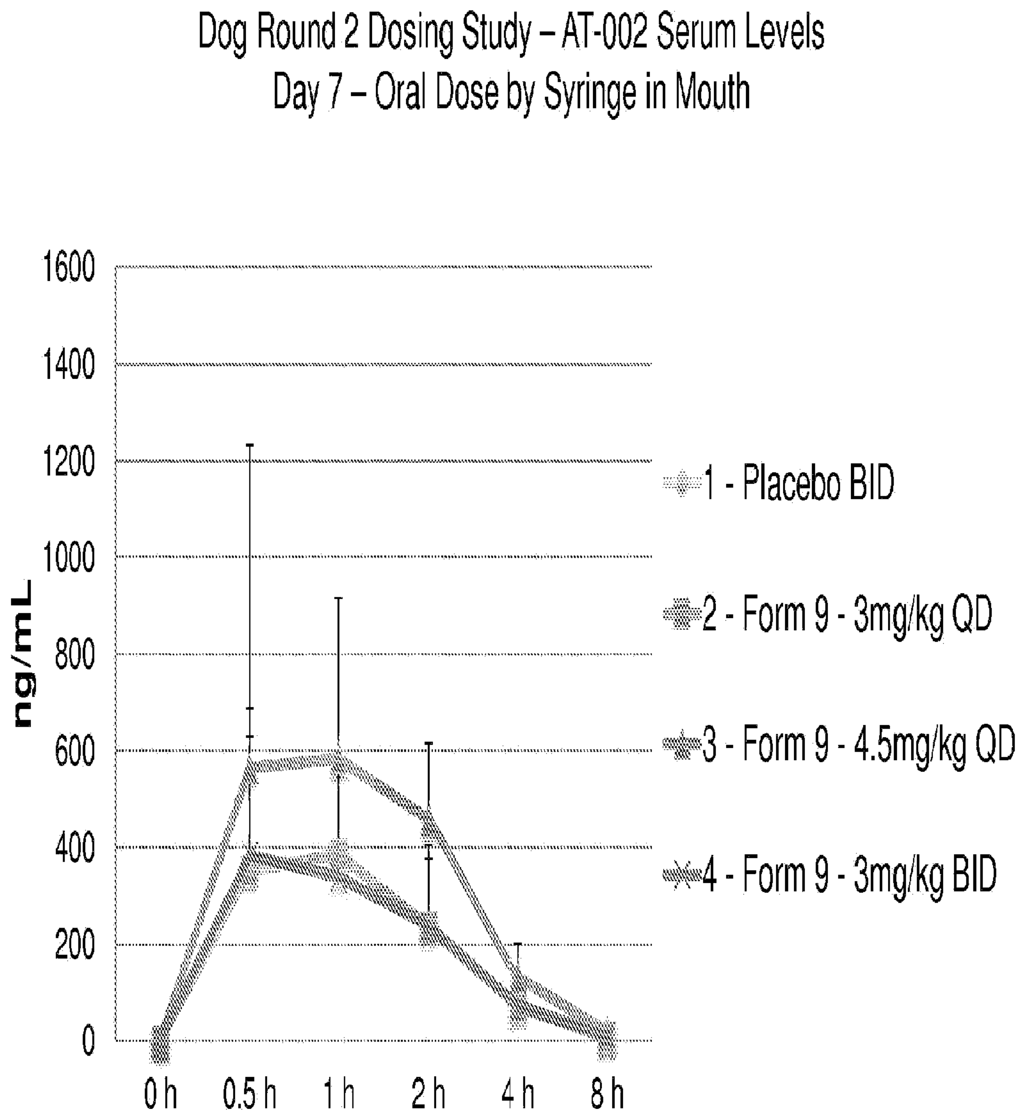

Dog Round 2 Dosing Study – AT-002 Serum Levels
Day 7 – Oral Dose by Syringe in Mouth
ng/mL
1600
1400
1200
1000
800
600
400
200
0
0 h
0.5 h
1 h
2 h
4 h
8 h
1 - Placebo BID
2 - Form 9 - 3mg/kg QD
3 - Form 9 - 4.5mg/kg QD
4 - Form 9 - 3mg/kg BID

FIGURE 63

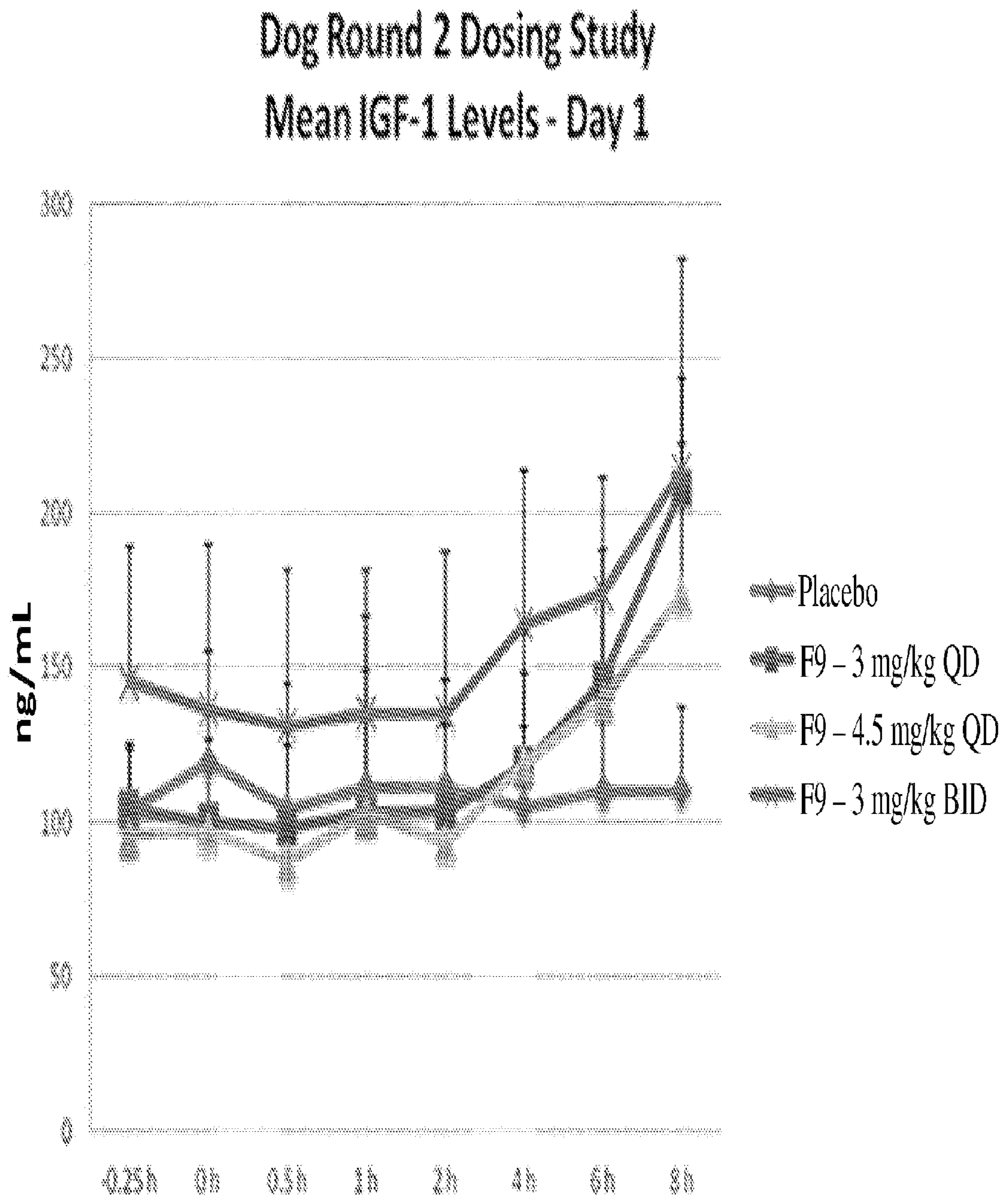

Dog Round 2 Dosing Study
Mean IGF-1 Levels - Day 1
ng/mL
300
250
200
150
100
50
0
-0.25h
0h
0.5h
1h
2h
4h
6h
8h
Placebo
F9 – 3 mg/kg QD
F9 – 4.5 mg/kg QD
F9 – 3 mg/kg BID

FIGURE 64A

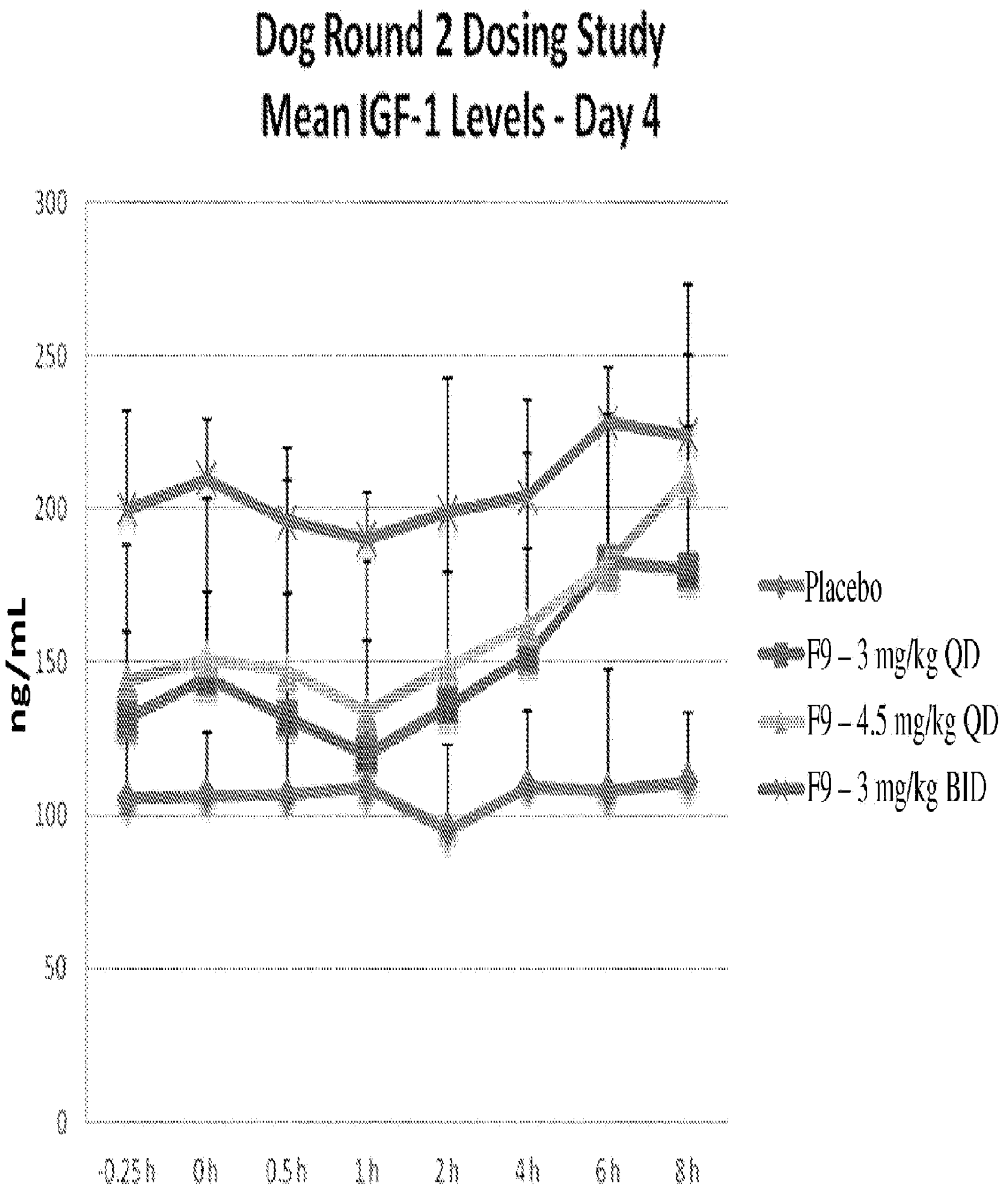

Dog Round 2 Dosing Study
Mean IGF-1 Levels - Day 4
ng/mL
300
250
200
150
100
50
0
-0.25 h
0 h
0.5 h
1 h
2 h
4 h
6 h
8 h
Placebo
F9 – 3 mg/kg QD
F9 – 4.5 mg/kg QD
F9 – 3 mg/kg BID

FIGURE 64B

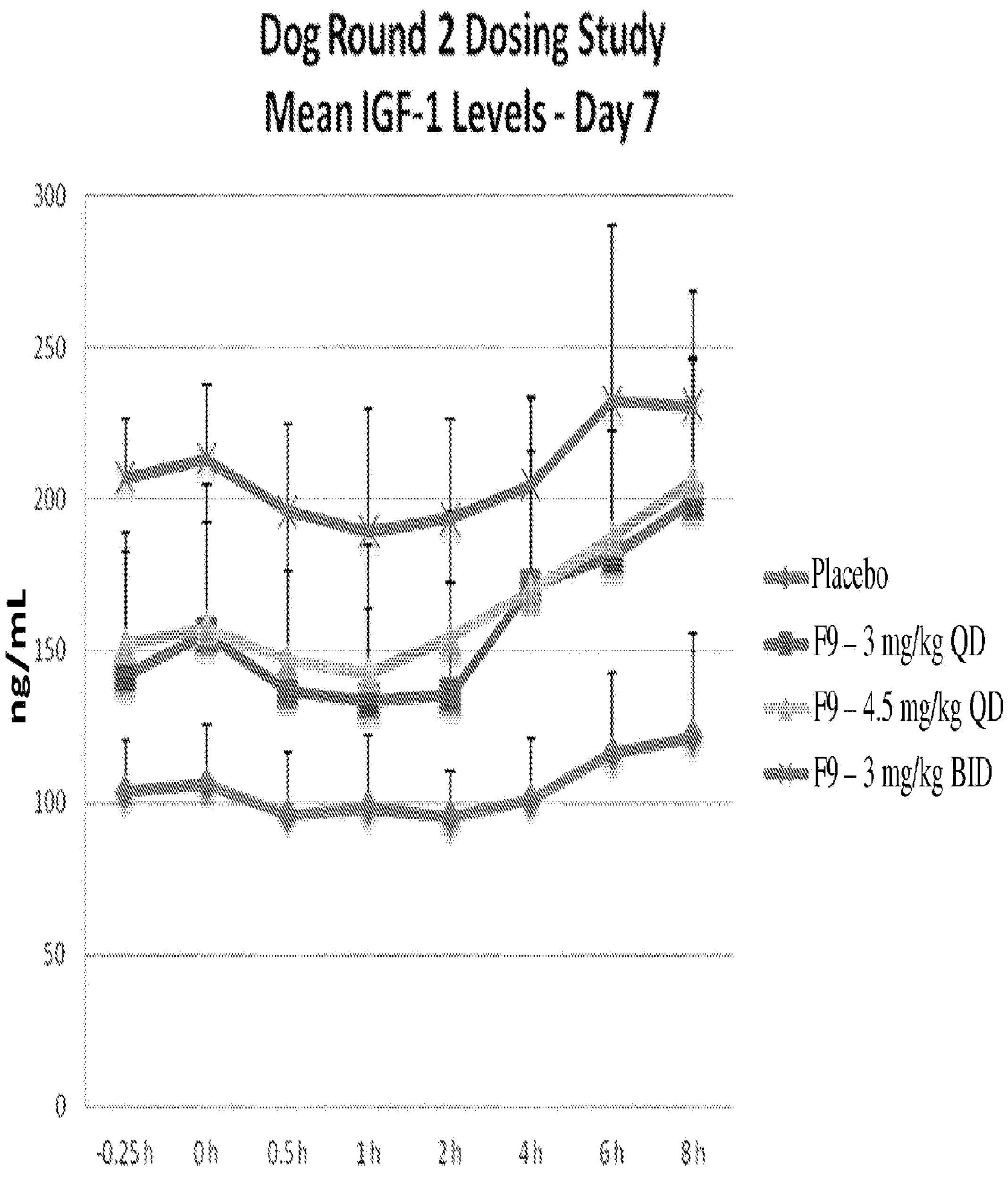
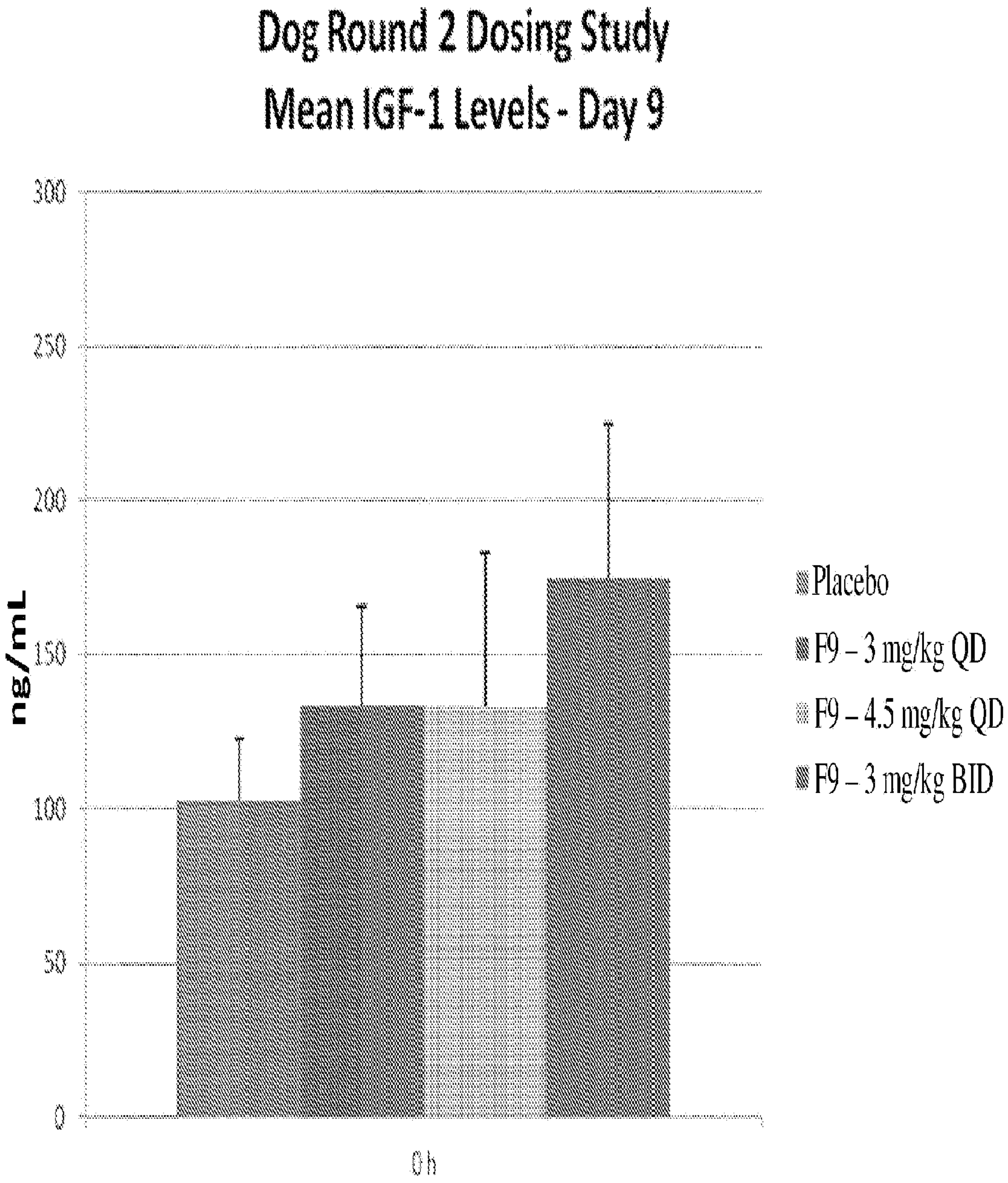

Dog Round 2 Dosing Study
Mean IGF-1 Levels - Day 7
ng/mL
300
250
200
150
100
50
0
-0.25h
0h
0.5h
1h
2h
4h
6h
8h
Placebo
F9 – 3 mg/kg QD
F9 – 4.5 mg/kg QD
F9 – 3 mg/kg BID

FIGURE 65



Dog Round 2 Dosing Study
Mean IGF-1 Levels - Day 9
ng/mL
300
250
200
150
100
50
0
0 h
Placebo
F9 – 3 mg/kg QD
F9 – 4.5 mg/kg QD
F9 – 3 mg/kg BID

FIGURE 66

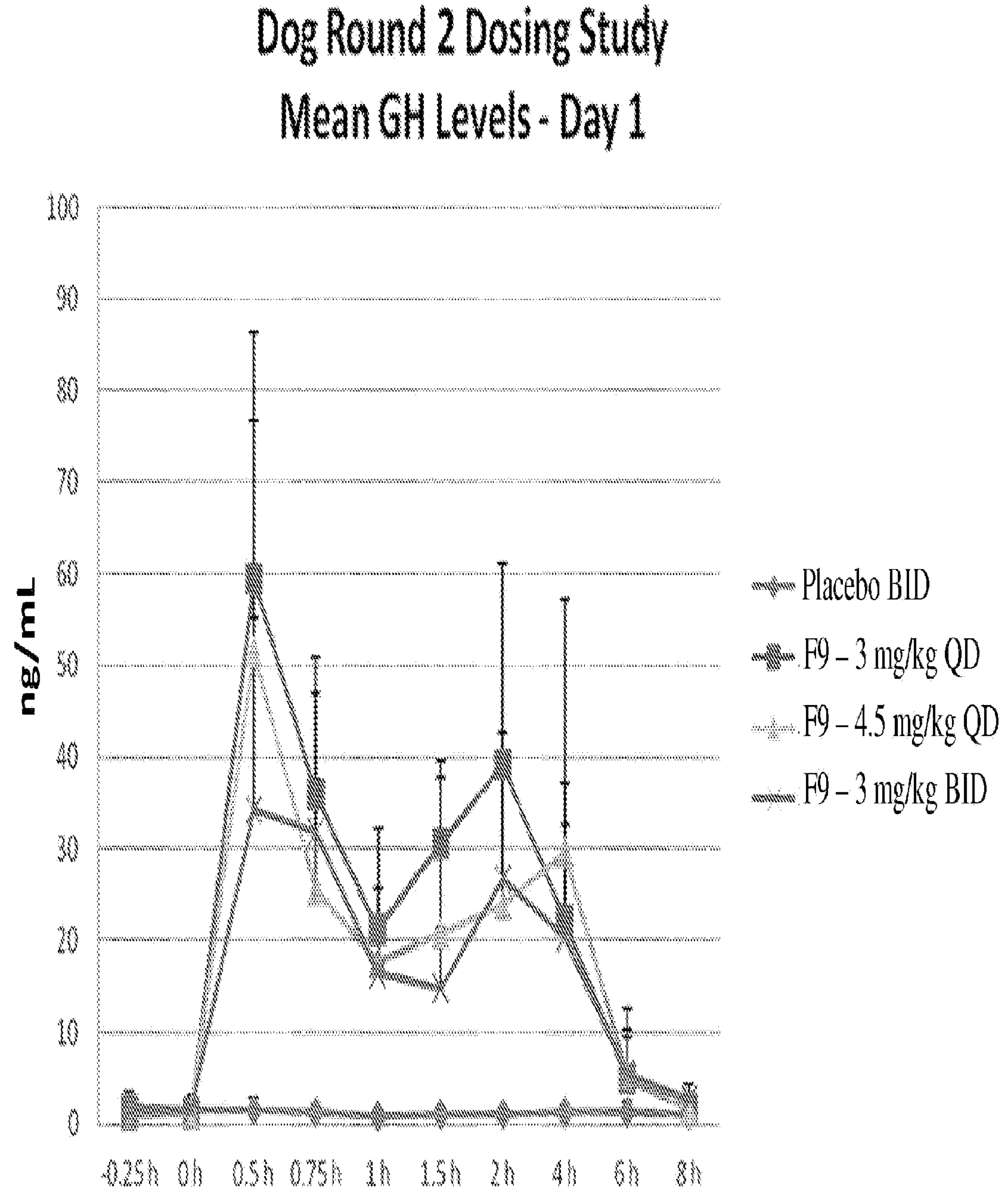

Dog Round 2 Dosing Study
Mean GH Levels - Day 1
ng/mL
100
90
80
70
60
50
40
30
20
10
0
-0.25h
0h
0.5h
0.75h
1h
1.5h
2h
4h
6h
8h
Placebo BID
F9 – 3 mg/kg QD
F9 – 4.5 mg/kg QD
F9 – 3 mg/kg BID

FIGURE 67

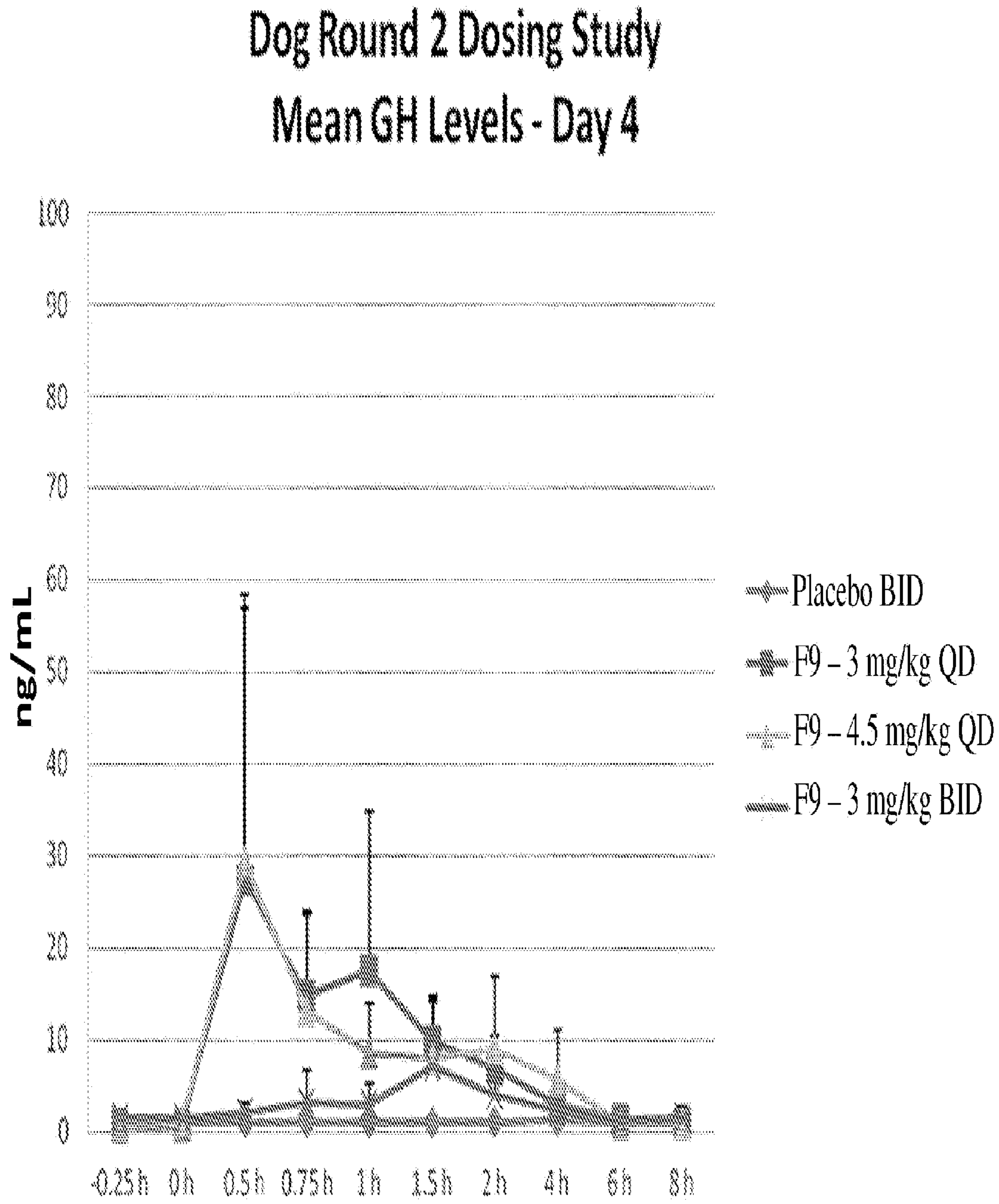

Dog Round 2 Dosing Study
Mean GH Levels - Day 4
ng/mL
100
90
80
70
60
50
40
30
20
10
0
-0.25h
0h
0.5h
0.75h
1h
1.5h
2h
4h
6h
8h
Placebo BID
F9 – 3 mg/kg QD
F9 – 4.5 mg/kg QD
F9 – 3 mg/kg BID

FIGURE 68

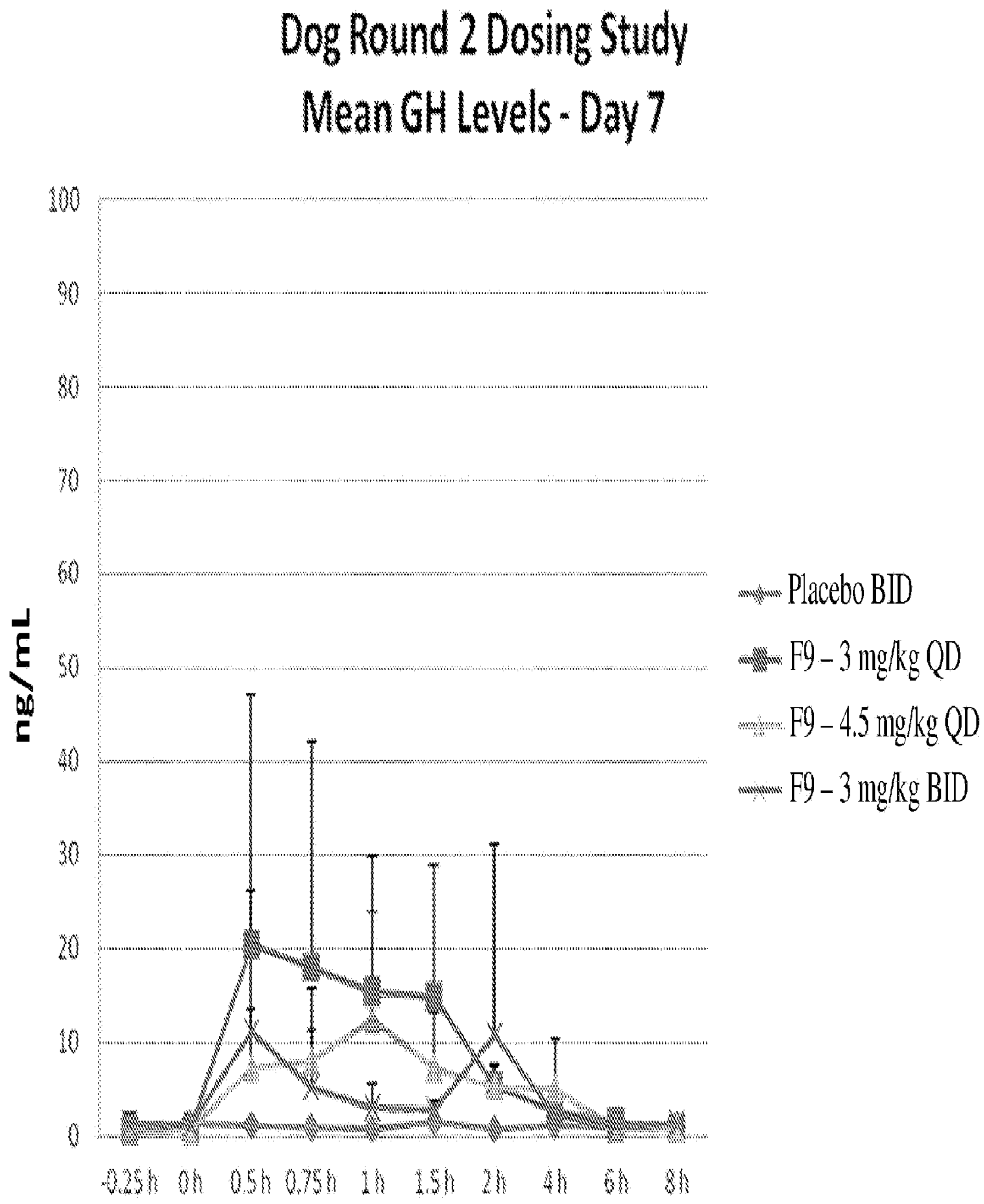

Dog Round 2 Dosing Study
Mean GH Levels - Day 7
ng/mL
100
90
80
70
60
50
40
30
20
10
0
-0.25 h
0 h
0.5 h
0.75 h
1 h
1.5 h
2 h
4 h
6 h
8 h
Placebo BID
F9 – 3 mg/kg QD
F9 – 4.5 mg/kg QD
F9 – 3 mg/kg BID

FIGURE 69

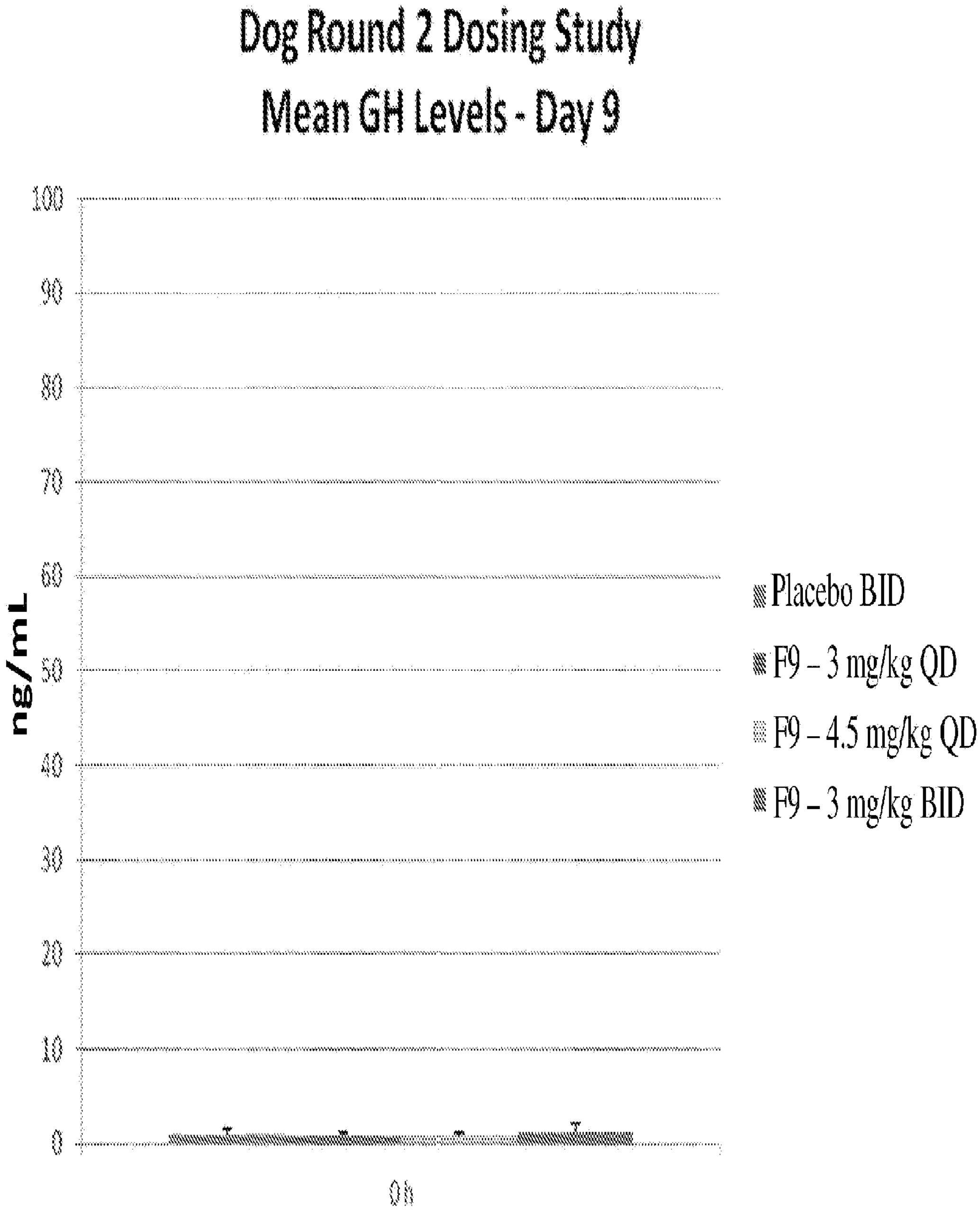

Dog Round 2 Dosing Study
Mean GH Levels - Day 9
ng/mL
100
90
80
70
60
50
40
30
20
10
0
0 h
Placebo BID
F9 – 3 mg/kg QD
F9 – 4.5 mg/kg QD
F9 – 3 mg/kg BID

FIGURE 70

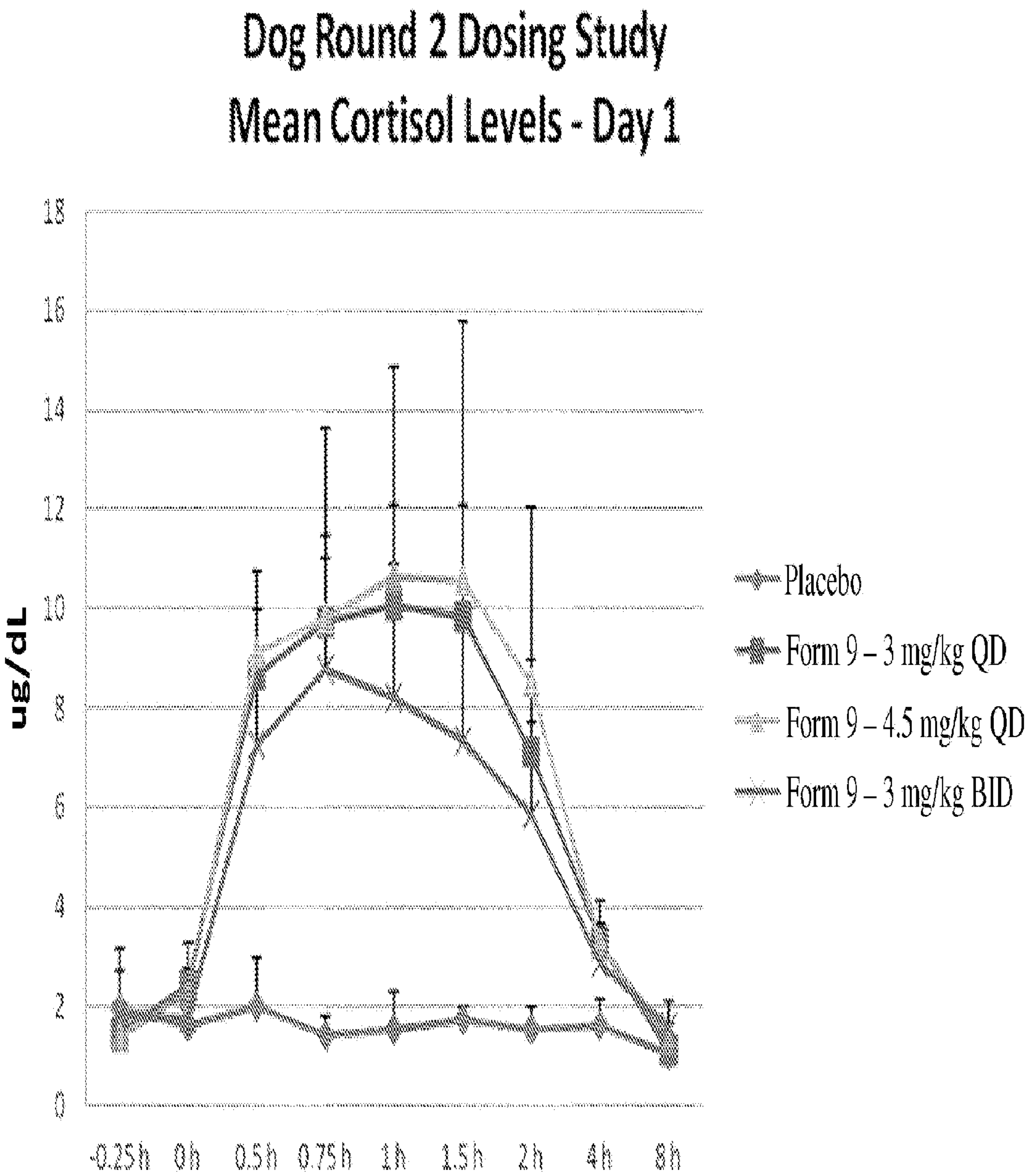

Dog Round 2 Dosing Study
Mean Cortisol Levels - Day 1
ug/dL
18
16
14
12
10
8
6
4
2
0
-0.25h
0h
0.5h
0.75h
1h
1.5h
2h
4h
8h
Placebo
Form 9 – 3 mg/kg QD
Form 9 – 4.5 mg/kg QD
Form 9 – 3 mg/kg BID

FIGURE 71

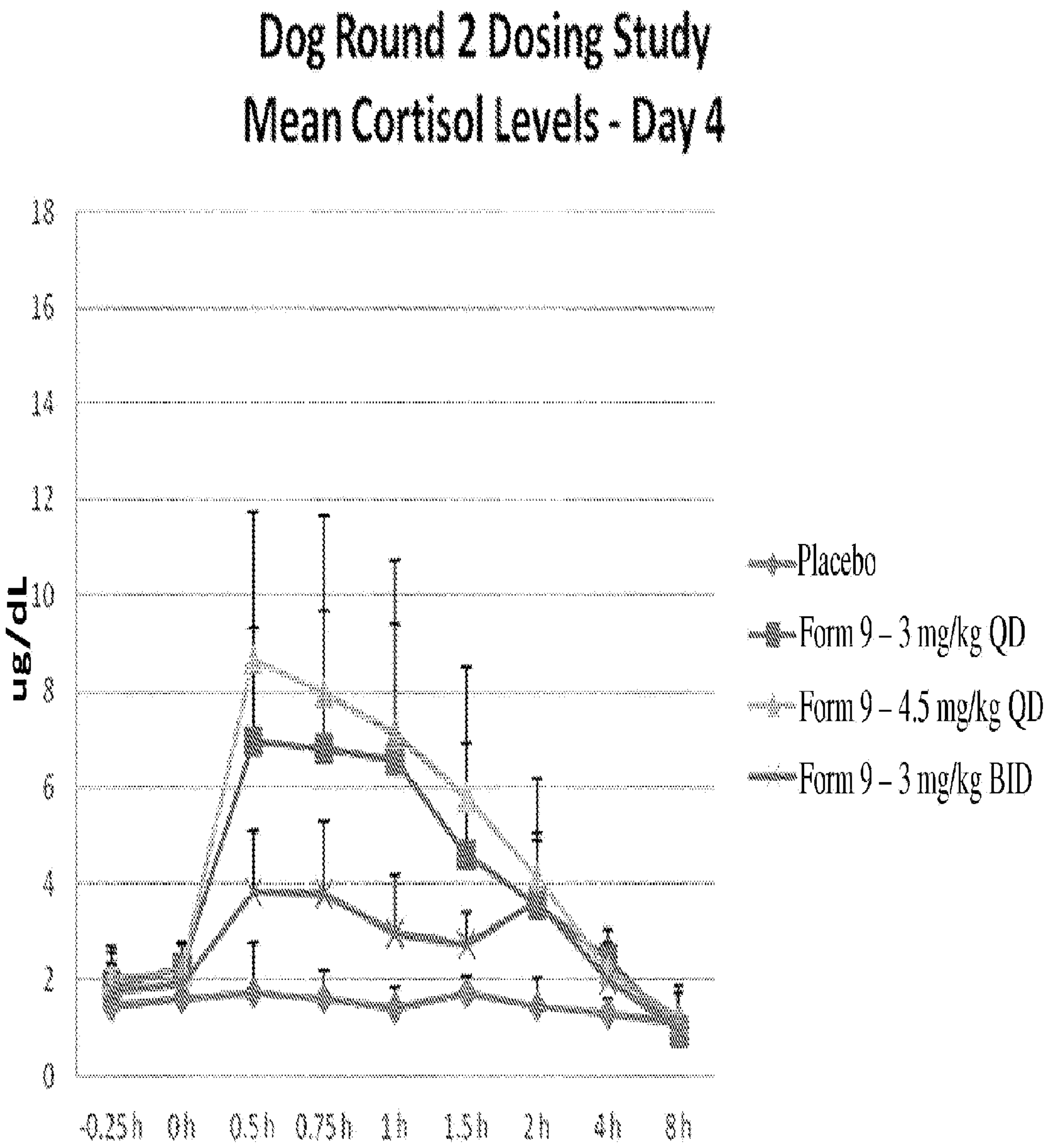

Dog Round 2 Dosing Study
Mean Cortisol Levels - Day 4
ug/dL
0
2
4
6
8
10
12
14
16
18
-0.25 h
0 h
0.5 h
0.75 h
1 h
1.5 h
2 h
4 h
8 h
Placebo
Form 9 – 3 mg/kg QD
Form 9 – 4.5 mg/kg QD
Form 9 – 3 mg/kg BID

FIGURE 72

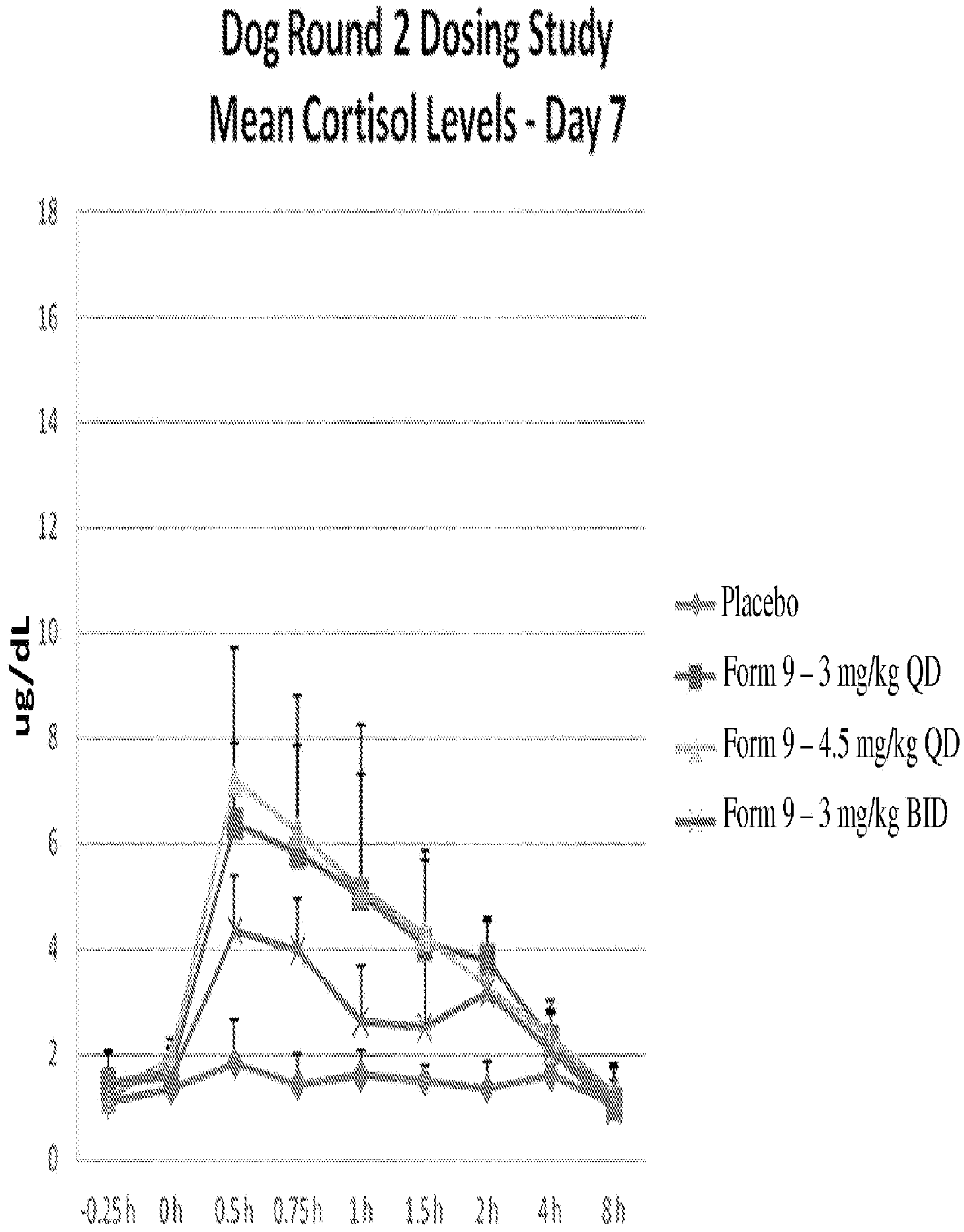

Dog Round 2 Dosing Study
Mean Cortisol Levels - Day 7
ug/dL
18
16
14
12
10
8
6
4
2
0
-0.25 h
0 h
0.5 h
0.75 h
1 h
1.5 h
2 h
4 h
8 h
Placebo
Form 9 – 3 mg/kg QD
Form 9 – 4.5 mg/kg QD
Form 9 – 3 mg/kg BID

FIGURE 73

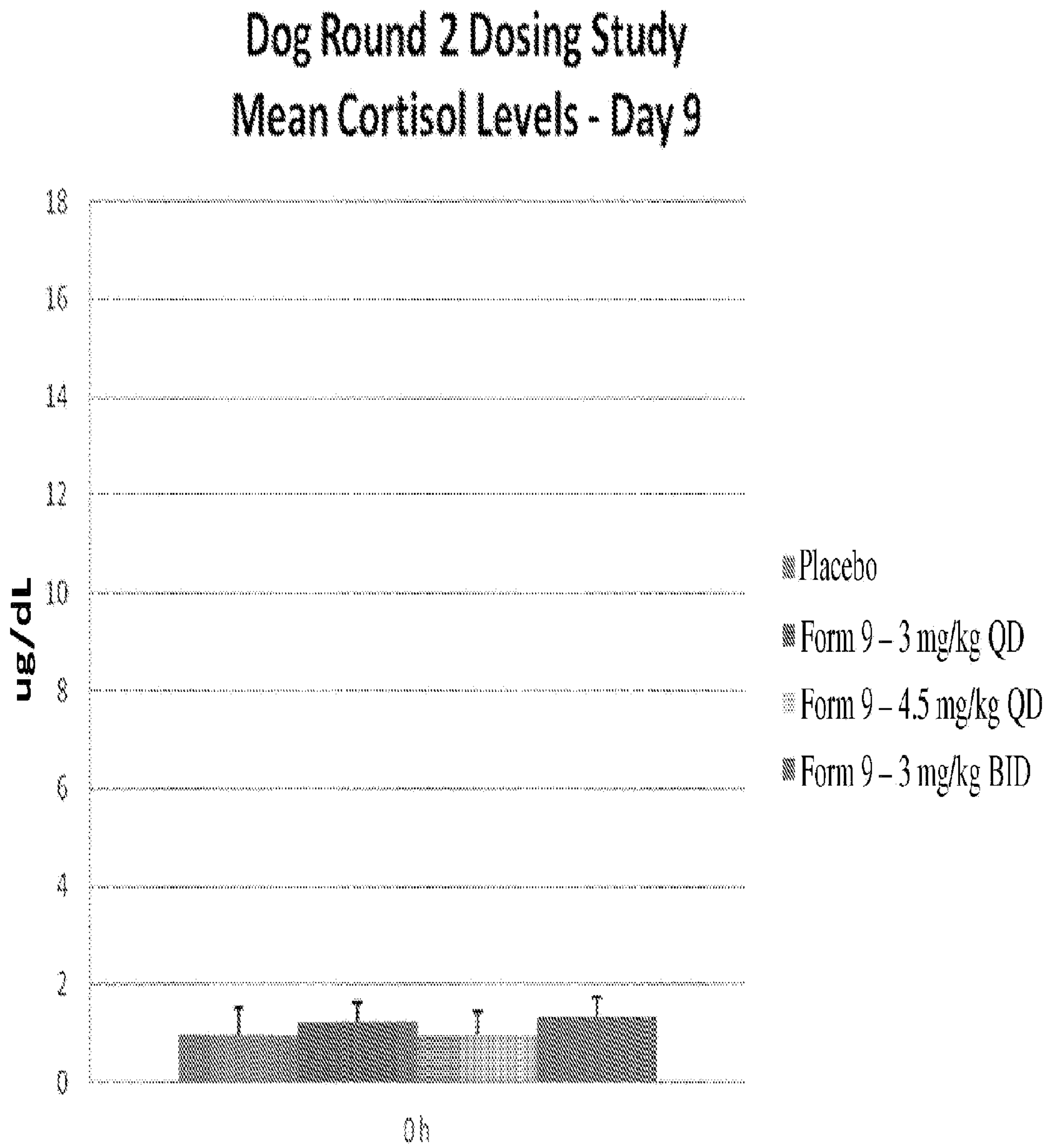

Dog Round 2 Dosing Study
Mean Cortisol Levels - Day 9
ug/dL
18
16
14
12
10
8
6
4
2
0
0 h
Placebo
Form 9 – 3 mg/kg QD
Form 9 – 4.5 mg/kg QD
Form 9 – 3 mg/kg BID

FIGURE 74

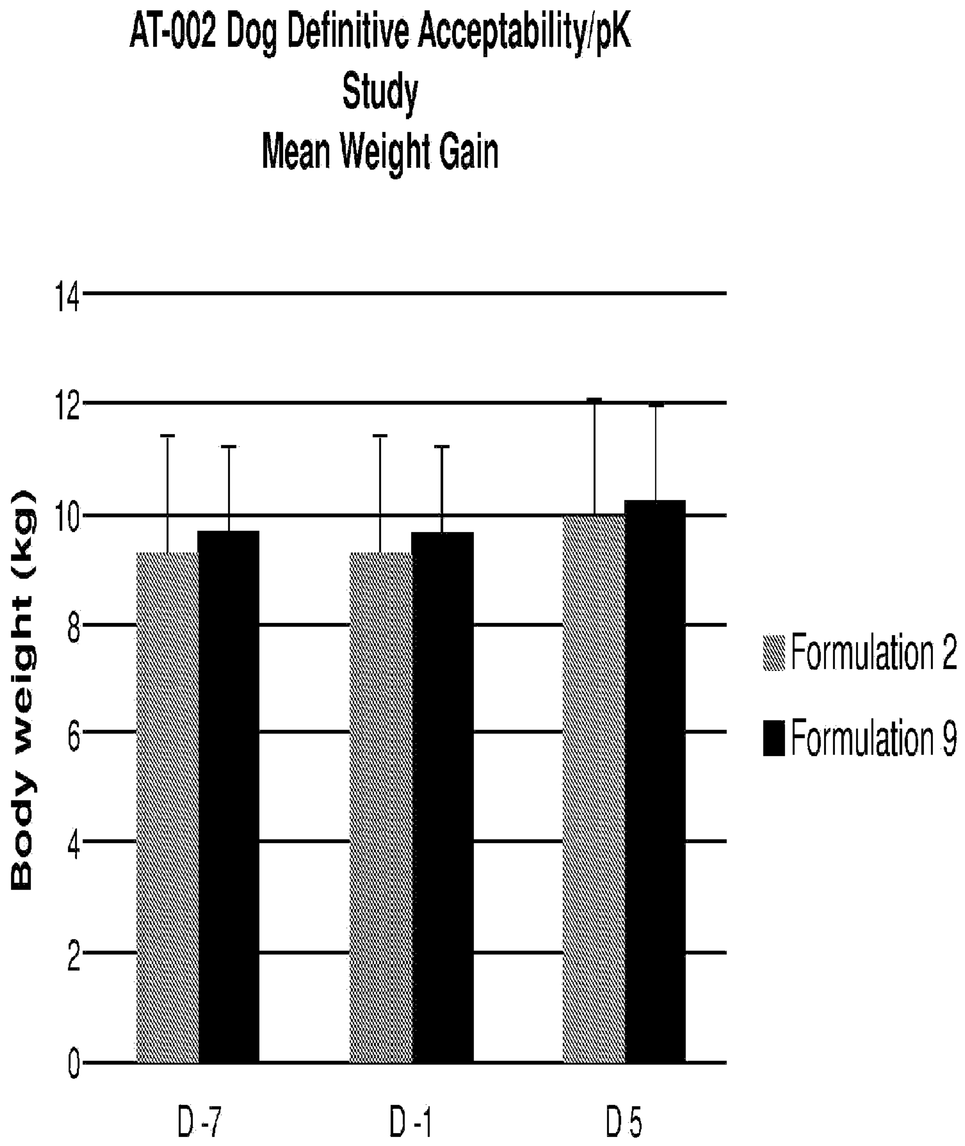

AT-002 Dog Definitive Acceptability/pK
Study
Mean Weight Gain
Body weight (kg)
14
12
10
8
6
4
2
0
D -7
D -1
D 5
Formulation 2
Formulation 9

FIGURE 75

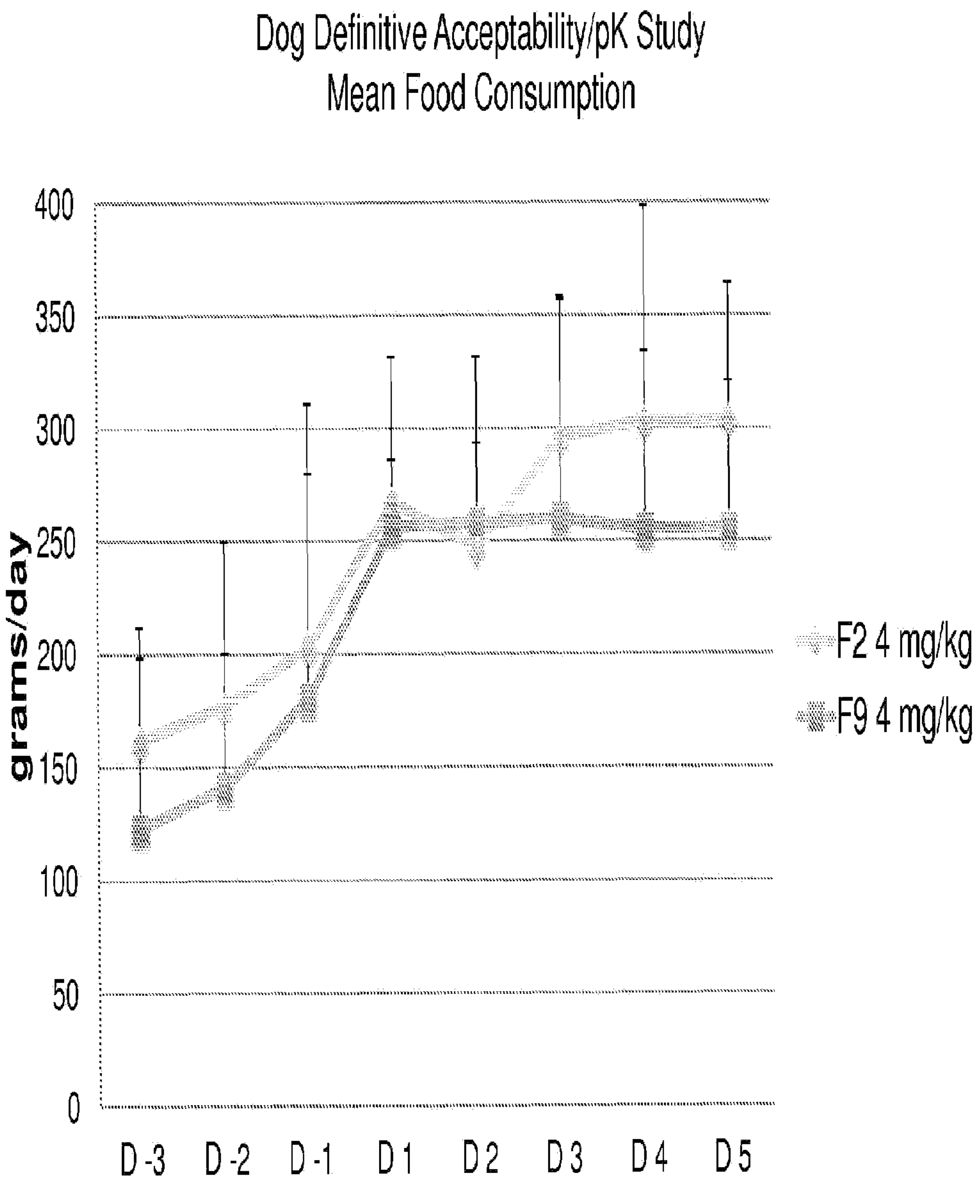

Dog Definitive Acceptability/pK Study
Mean Food Consumption
grams/day
400
350
300
250
200
150
100
50
0
D -3
D -2
D -1
D 1
D 2
D 3
D 4
D 5
F2 4 mg/kg
F9 4 mg/kg

FIGURE 76

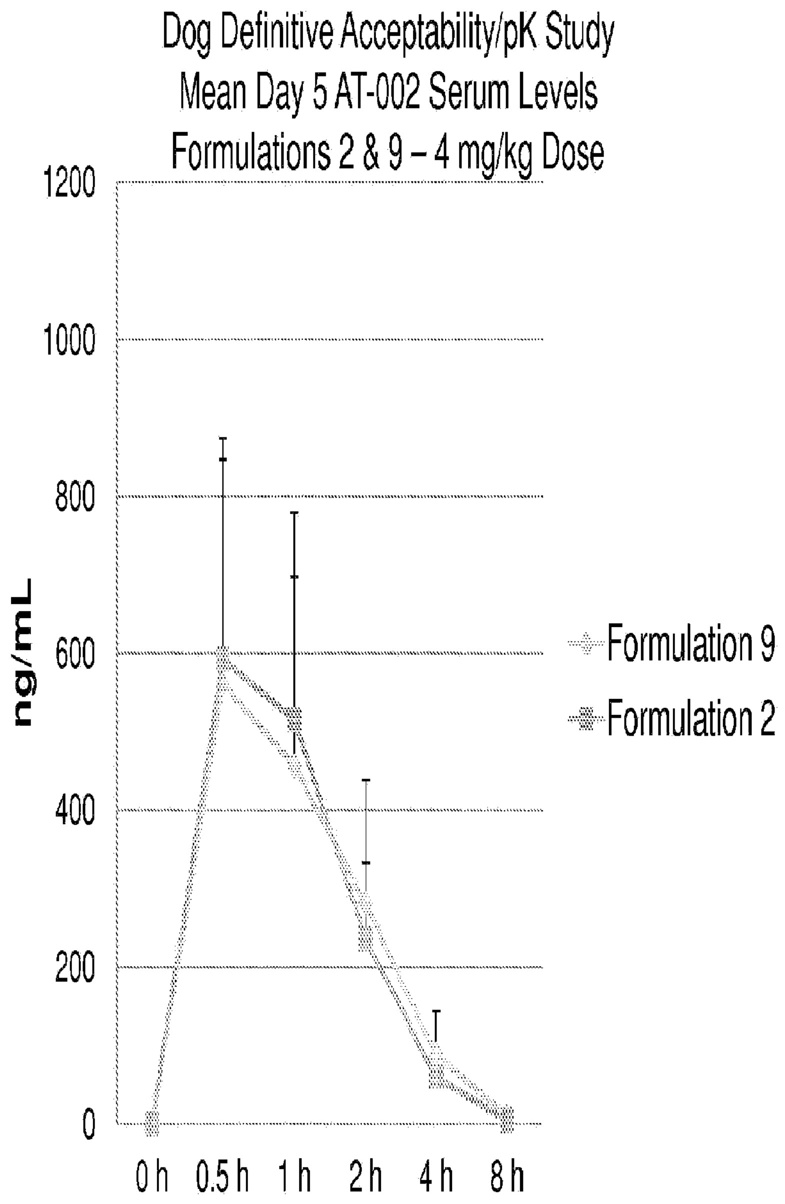

Dog Definitive Acceptability/pK Study
Mean Day 5 AT-002 Serum Levels
Formulations 2 & 9 – 4 mg/kg Dose
1200
1000
800
600
400
200
0
ng/mL
0 h
0.5 h
1 h
2 h
4 h
8 h
Formulation 9
Formulation 2

FIGURE 77

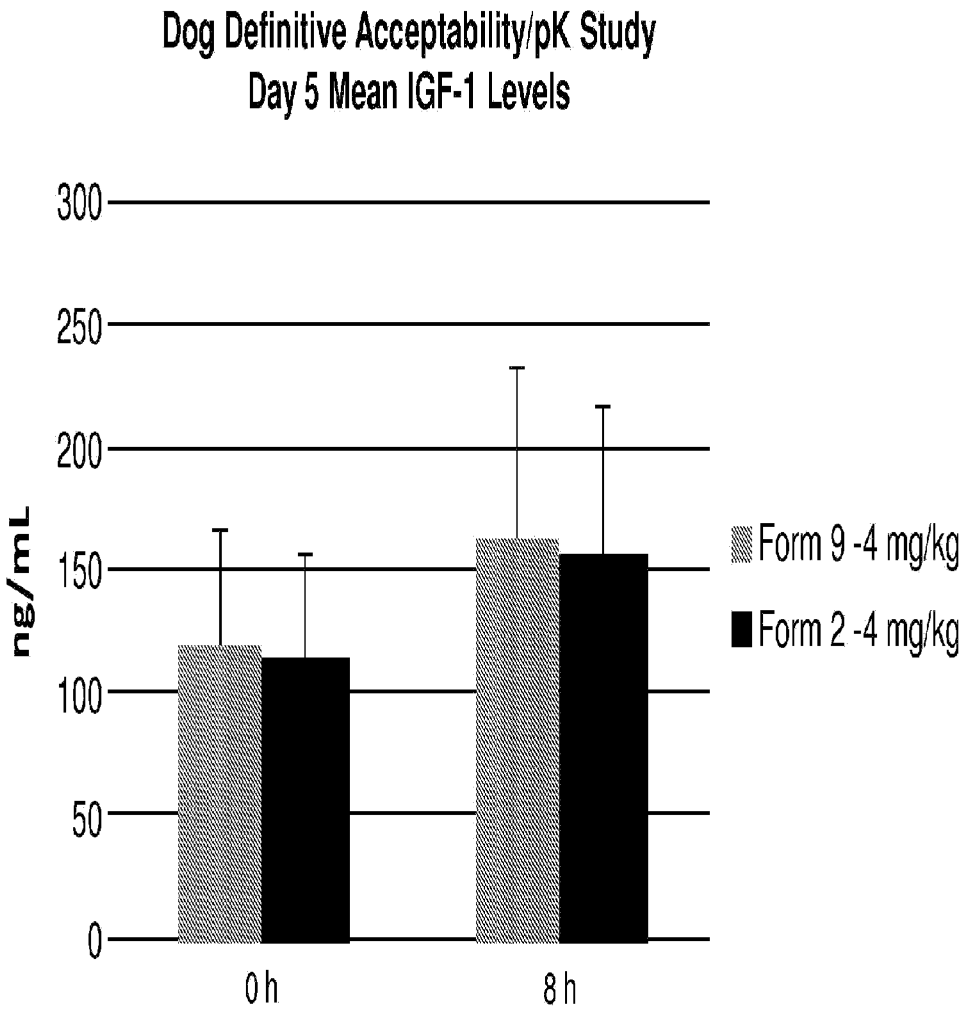

Dog Definitive Acceptability/pK Study
Day 5 Mean IGF-1 Levels
ng/mL
300
250
200
150
100
50
0
0 h
8 h
Form 9 -4 mg/kg
Form 2 -4 mg/kg

FIGURE 78

Parameter	Criteria	Number of Animals with Observation				
		Day 1	Day 2	Day 3	Day 4	Day 5
Immediate response to taste	Well accepted	4 / 5	0 / 5	3 / 5	4 / 5	0 / 5
	Accepted	1 / 5	4 / 5	2 / 5	0 / 5	3 / 5
	Poor	0 / 5	1 / 5	0 / 5	1 / 5	2 / 5
Head shaking	None	5 / 5	4 / 5	5 / 5	5 / 5	4 / 5
	Some	0 / 5	1 / 5	0 / 5	0 / 5	1 / 5
	Profuse	0 / 5	0 / 5	0 / 5	0 / 5	0 / 5
Resistance to administration	None	3 / 5	3 / 5	4 / 5	5 / 5	2 / 5
	Some	2 / 5	0 / 5	0 / 5	0 / 5	3 / 5
	Strong	0 / 5	2 / 5	1 / 5	0 / 5	0 / 5
Clinical observations	No Observations	4 / 5	0 / 5	1 / 5	1 / 5	2 / 5
	Licking	0 / 5	3 / 5	2 / 5	2 / 5	1 / 5
	Smacking of the mouth / lips	0 / 5	0 / 5	0 / 5	1 / 5	0 / 5
	Moderate salivation	0 / 5	0 / 5	1 / 5	0 / 5	2 / 5
	Excessive salivation	0 / 5	1 / 5	1 / 5	0 / 5	0 / 5
	Grimace	1 / 5	1 / 5	0 / 5	1 / 5	0 / 5

FIGURE 79

Parameter	Criteria	Number of Animals with Observation				
		Day 1	Day 2	Day 3	Day 4	Day 5
Immediate response to taste	Well accepted	5 / 5	1 / 5	1 / 5	3 / 5	0 / 5
	Accepted	0 / 5	1 / 5	3 / 5	2 / 5	5 / 5
	Poor	0 / 5	3 / 5	1 / 5	0 / 5	0 / 5
Head shaking	None	3 / 5	4 / 5	4 / 5	4 / 5	4 / 5
	Some	2 / 5	0 / 5	1 / 5	1 / 5	1 / 5
	Profuse	0 / 5	1 / 5	0 / 5	0 / 5	0 / 5
Resistance to administration	None	4 / 5	1 / 5	1 / 5	3 / 5	2 / 5
	Some	1 / 5	0 / 5	1 / 5	1 / 5	3 / 5
	Strong	0 / 5	4 / 5	3 / 5	1 / 5	0 / 5
Clinical observations	No Observations	3 / 5	0 / 5	1 / 5	1 / 5	0 / 5
	Licking	1 / 5	0 / 5	0 / 5	0 / 5	3 / 5
	Smacking of the mouth / lips	0 / 5	1 / 5	0 / 5	1 / 5	0 / 5
	Moderate salivation	1 / 5	1 / 5	3 / 5	1 / 5	2 / 5
	Excessive salivation	0 / 5	3 / 5	1 / 5	1 / 5	0 / 5
	Grimace	0 / 5	0 / 5	0 / 5	1 / 5	0 / 5

FIGURE 80

Parameter	Criteria	Number of Animals with Observation				
		Day 1	Day 2	Day 3	Day 4	Day 5
Immediate response to taste	Well accepted	4 / 5	2 / 5	3 / 5	1 / 5	0 / 5
	Accepted	1 / 5	0 / 5	1 / 5	4 / 5	2 / 5
	Poor	0 / 5	3 / 5	1 / 5	0 / 5	3 / 5
Head shaking	None	4 / 5	2 / 5	4 / 5	4 / 5	2 / 5
	Some	1 / 5	3 / 5	1 / 5	1 / 5	3 / 5
	Profuse	0 / 5	0 / 5	0 / 5	0 / 5	0 / 5
Resistance to administration	None	3 / 5	0 / 5	3 / 5	3 / 5	3 / 5
	Some	2 / 5	1 / 5	0 / 5	0 / 5	2 / 5
	Strong	0 / 5	4 / 5	2 / 5	2 / 5	0 / 5
Clinical observations	No Observations	2 / 5	1 / 5	2 / 5	1 / 5	0 / 5
	Licking	0 / 5	0 / 5	1 / 5	0 / 5	2 / 5
	Smacking of the mouth / lips	1 / 5	1 / 5	0 / 5	1 / 5	0 / 5
	Moderate salivation	1 / 5	1 / 5	2 / 5	1 / 5	3 / 5
	Excessive salivation	0 / 5	2 / 5	0 / 5	1 / 5	0 / 5
	Grimace	1 / 5	0 / 5	0 / 5	1 / 5	0 / 5

FIGURE 81

Parameter	Criteria	Number of Animals with Observation				
		Day 1	Day 2	Day 3	Day 4	Day 5
Immediate response to taste	Well accepted	1 / 5	0 / 5	1 / 5	1 / 5	0 / 5
	Accepted	3 / 5	2 / 5	3 / 5	1 / 5	3 / 5
	Poor	1 / 5	3 / 5	1 / 5	3 / 5	2 / 5
Head shaking	None	2 / 5	2 / 5	2 / 5	3 / 5	3 / 5
	Some	3 / 5	1 / 5	2 / 5	1 / 5	1 / 5
	Profuse	0 / 5	2 / 5	1 / 5	1 / 5	1 / 5
Resistance to administration	None	3 / 5	1 / 5	1 / 5	4 / 5	2 / 5
	Some	2 / 5	2 / 5	4 / 5	0 / 5	3 / 5
	Strong	0 / 5	2 / 5	0 / 5	1 / 5	0 / 5
Clinical observations	No Observations	0 / 5	0 / 5	0 / 5	0 / 5	0 / 5
	Licking	2 / 5	0 / 5	1 / 5	1 / 5	2 / 5
	Smacking of the mouth / lips	1 / 5	1 / 5	0 / 5	0 / 5	1 / 5
	Moderate salivation	1 / 5	0 / 5	1 / 5	1 / 5	1 / 5
	Excessive salivation	0 / 5	3 / 5	3 / 5	0 / 5	1 / 5
	Grimace	1 / 5	1 / 5	0 / 5	3 / 5	0 / 5

FIGURE 82

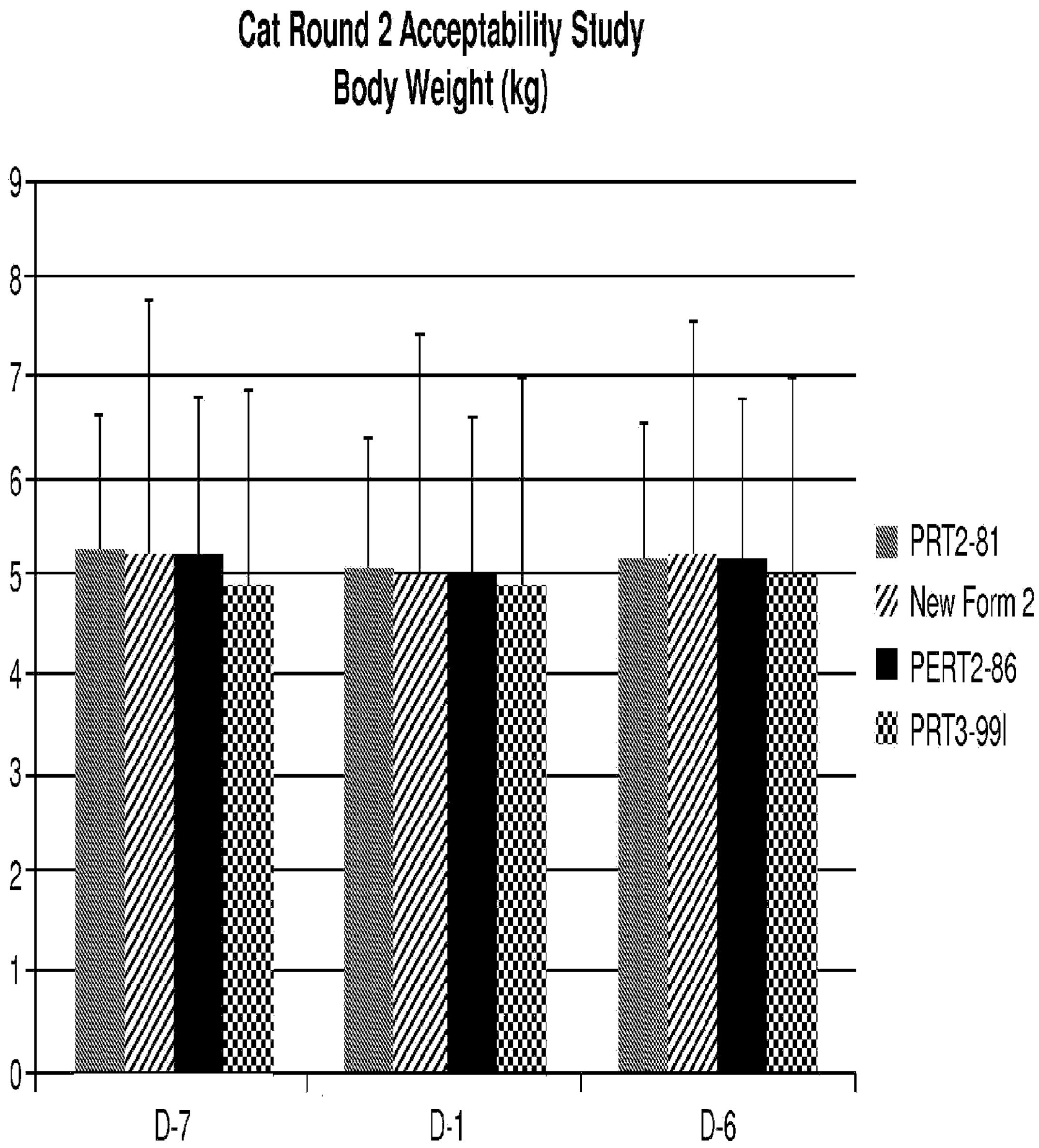

Cat Round 2 Acceptability Study
Body Weight (kg)
9
8
7
6
5
4
3
2
1
0
D-7
D-1
D-6
PRT2-81
New Form 2
PERT2-86
PRT3-99I

FIGURE 83

Group ID (Gender)	Acclim. Mean (g)	Post-Dose Mean (g)	Mean Difference (g)	Acclim. Mean (g/kg)	Post-Dose Mean (g/kg)	Mean Difference (g/kg)
1 (Males)	40	73	**33**	6.5	11.9	**5.3**
1 (Females)	30	59	**29**	8.3	16.2	**7.9**
2 (Males)	42	78	**36**	5.4	10.3	**4.9**
2 (Females)	34	75	**41**	10.9	23.3	**12.4**
3 (Males)	46	78	**32**	7.5	13.2	**5.6**
3 (Females)	45	57	**12**	13.0	16.5	**3.6**
4 (Males)	44	69	**25**	6.1	9.7	**3.6**
4 (Females)	45	60	**15**	13.2	17.7	**4.5**

FIGURE 84

Group	Day -3	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
1	35.0 ± 11.5	36.2 ± 23.7	37.4 ± 18.0	70.4 ± 36.1	62.0 ± 26.5	64.4 ± 30.7	73.0 ± 32.4	75.4 ± 27.8	58.2 ± 21.2
2	24.2 ± 8.2	48.5 ± 7.0	44.0 ± 12.3	67.6 ± 13.2	72.4 ± 7.3	76.0 ± 6.0	83.2 ± 7.9	87.2 ± 8.3	69.2 ± 12.9
3	43.8 ± 7.4	44.6 ± 13.1	47.6 ± 14.3	75.8 ± 33.3	69.4 ± 21.7	75.0 ± 28.1	70.0 ± 21.9	78.8 ± 22.1	49.4 ± 34.6
4	37.0 ± 9.8	49.4 ± 12.8	46.0 ± 5.8	65.0 ± 12.4	63.2 ± 8.7	67.0 ± 9.8	65.2 ± 11.5	72.0 ± 9.6	47.6 ± 27.1

FIGURE 85

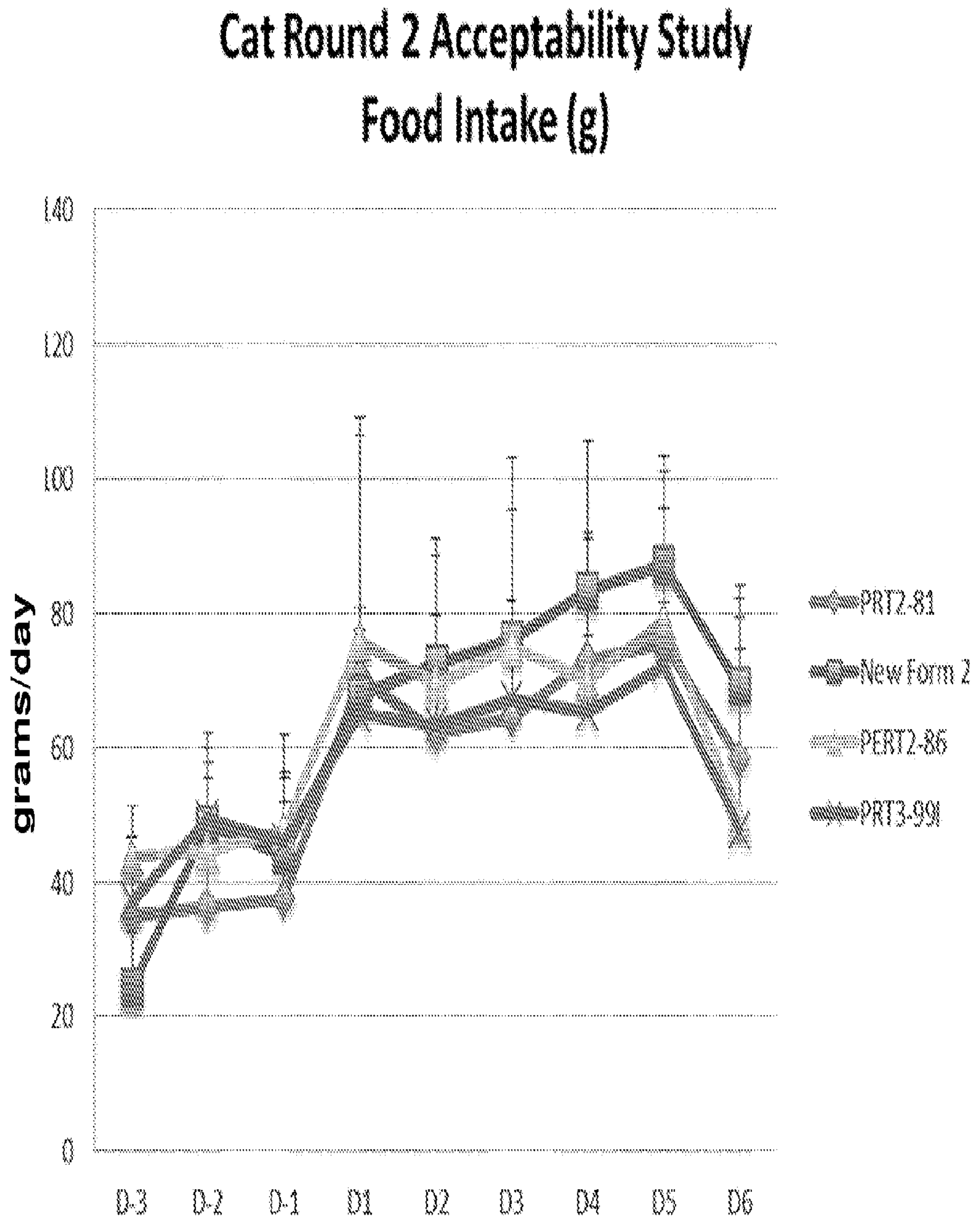

Cat Round 2 Acceptability Study
Food Intake (g)
grams/day
140
120
100
80
60
40
20
0
D-3
D-2
D-1
D1
D2
D3
D4
D5
D6
PRT2-81
New Form 2
PERT2-86
PRT3-99I

FIGURE 86

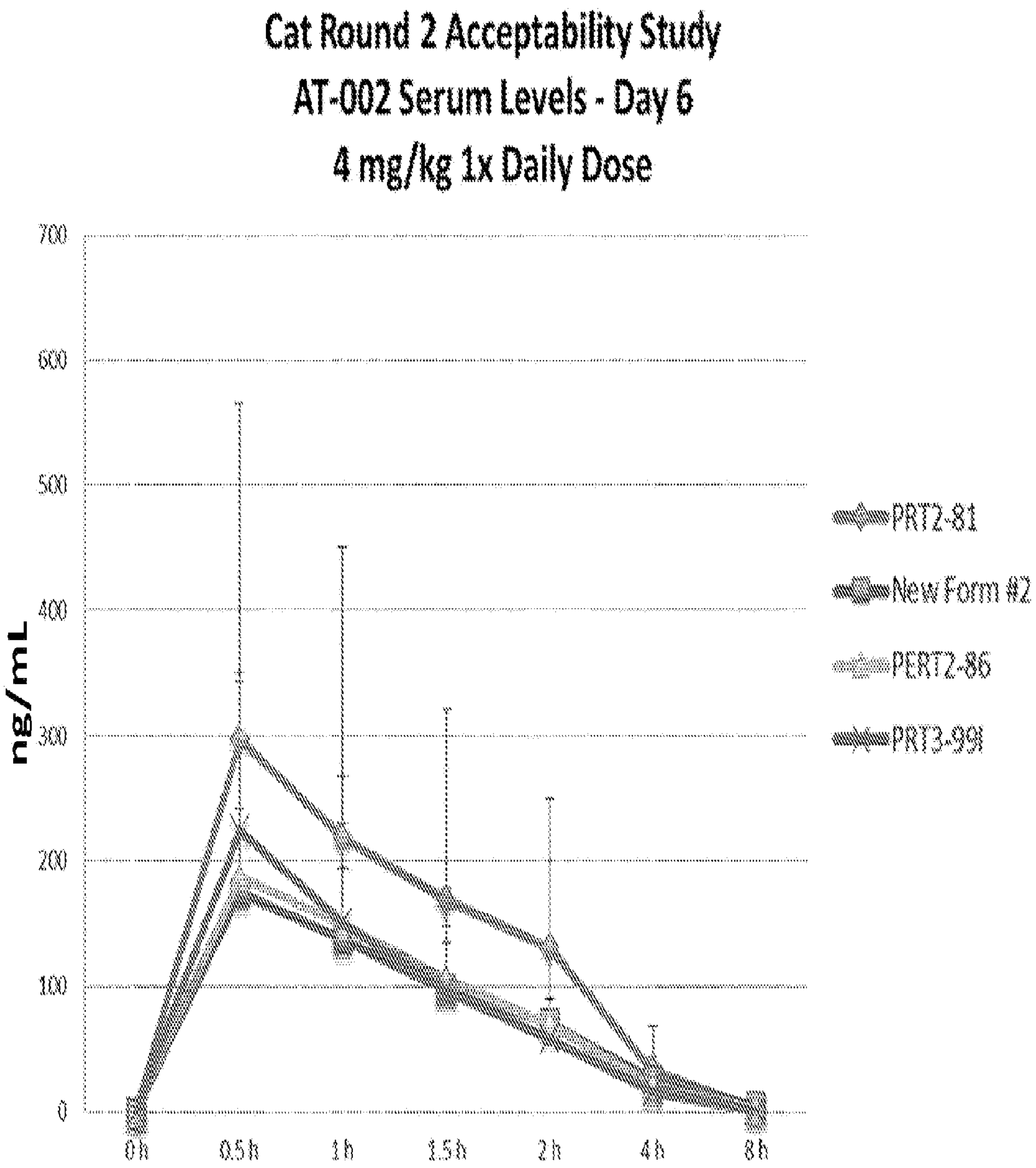

Cat Round 2 Acceptability Study
AT-002 Serum Levels - Day 6
4 mg/kg 1x Daily Dose
ng/mL
700
600
500
400
300
200
100
0
0 h
0.5 h
1 h
1.5 h
2 h
4 h
8 h
PRT2-81
New Form #2
PERT2-86
PRT3-99I

FIGURE 87

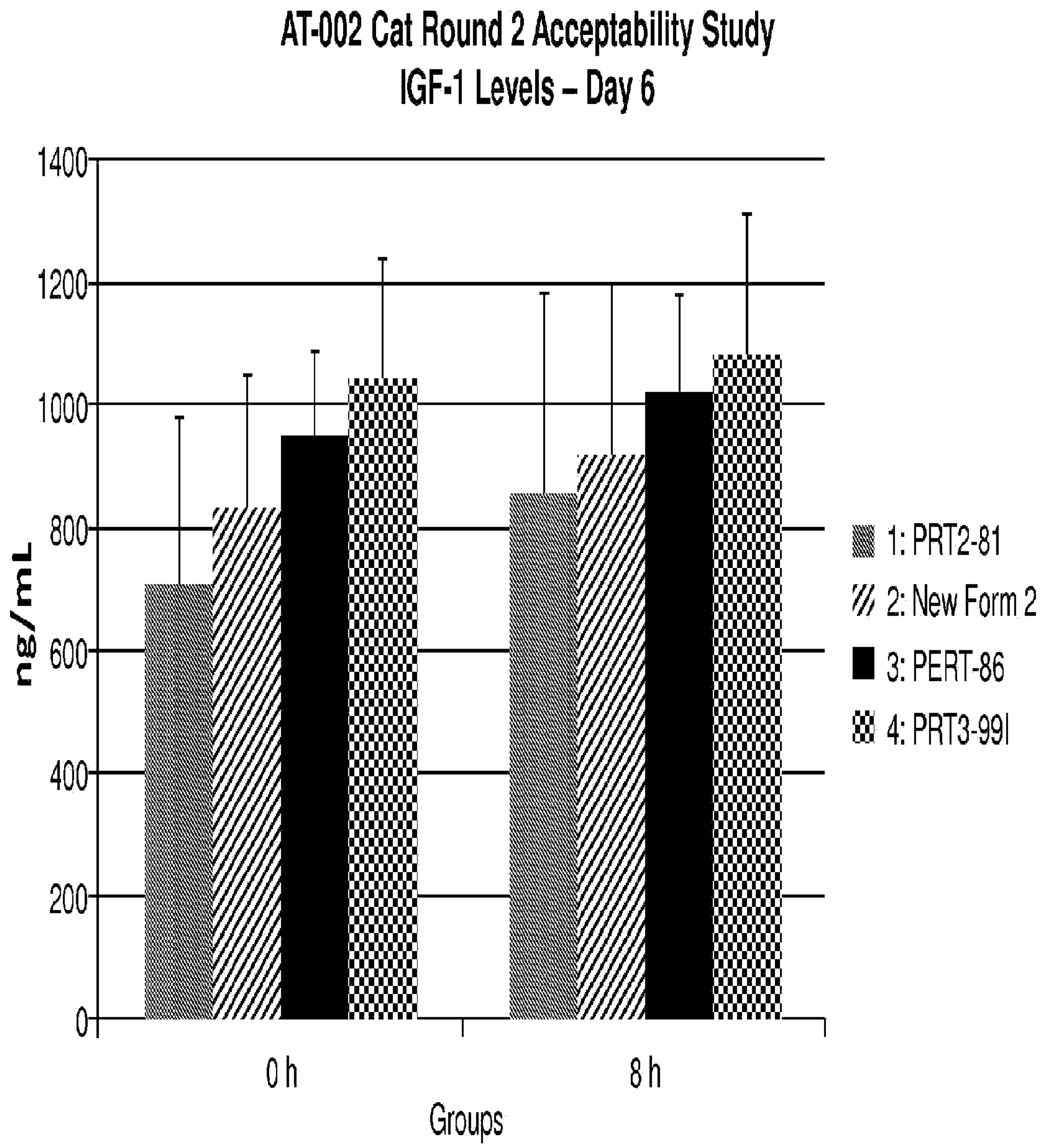

AT-002 Cat Round 2 Acceptability Study
IGF-1 Levels – Day 6
1400
1200
1000
800
600
400
200
0
ng/mL
0 h
8 h
Groups
1: PRT2-81
2: New Form 2
3: PERT-86
4: PRT3-99I

FIGURE 88

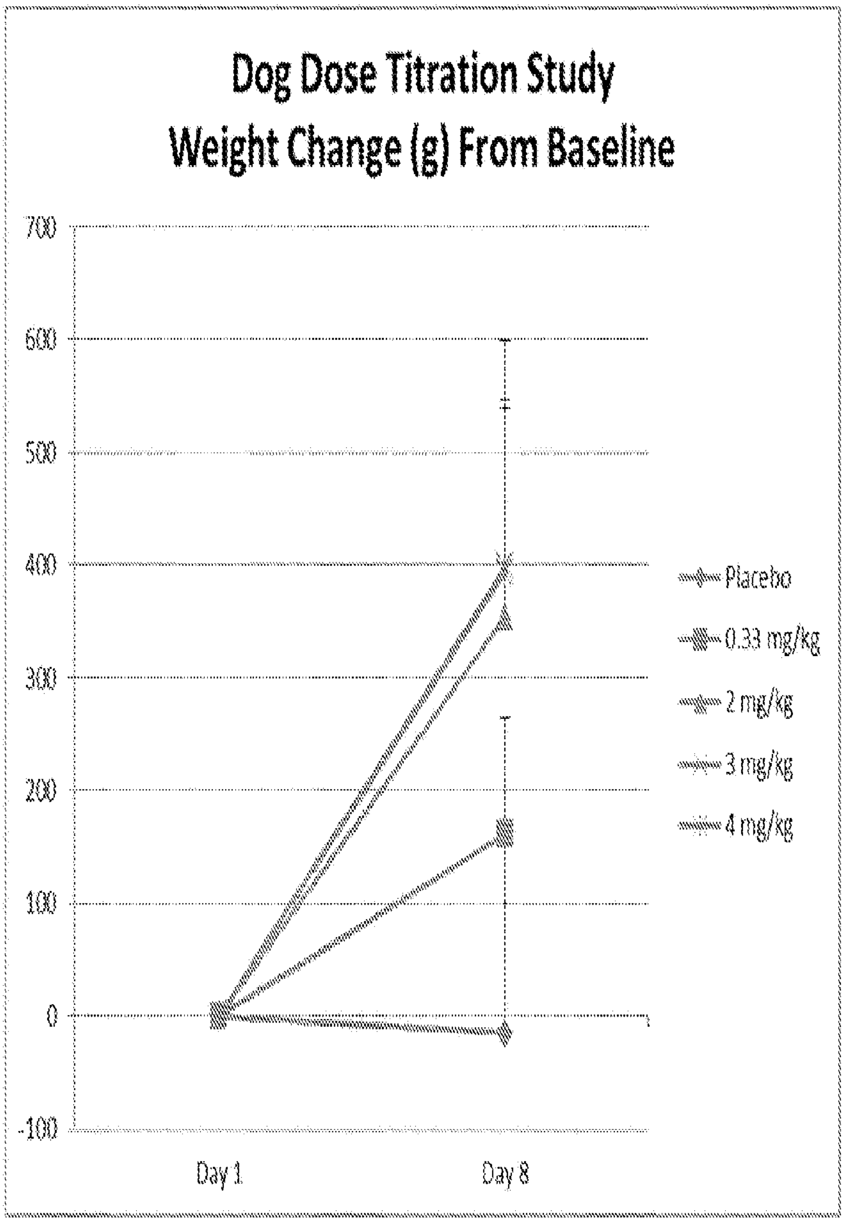

Dog Dose Titration Study
Weight Change (g) From Baseline
700
600
500
400
300
200
100
0
-100
Day 1
Day 8
Placebo
0.33 mg/kg
2 mg/kg
3 mg/kg
4 mg/kg

FIGURE 89

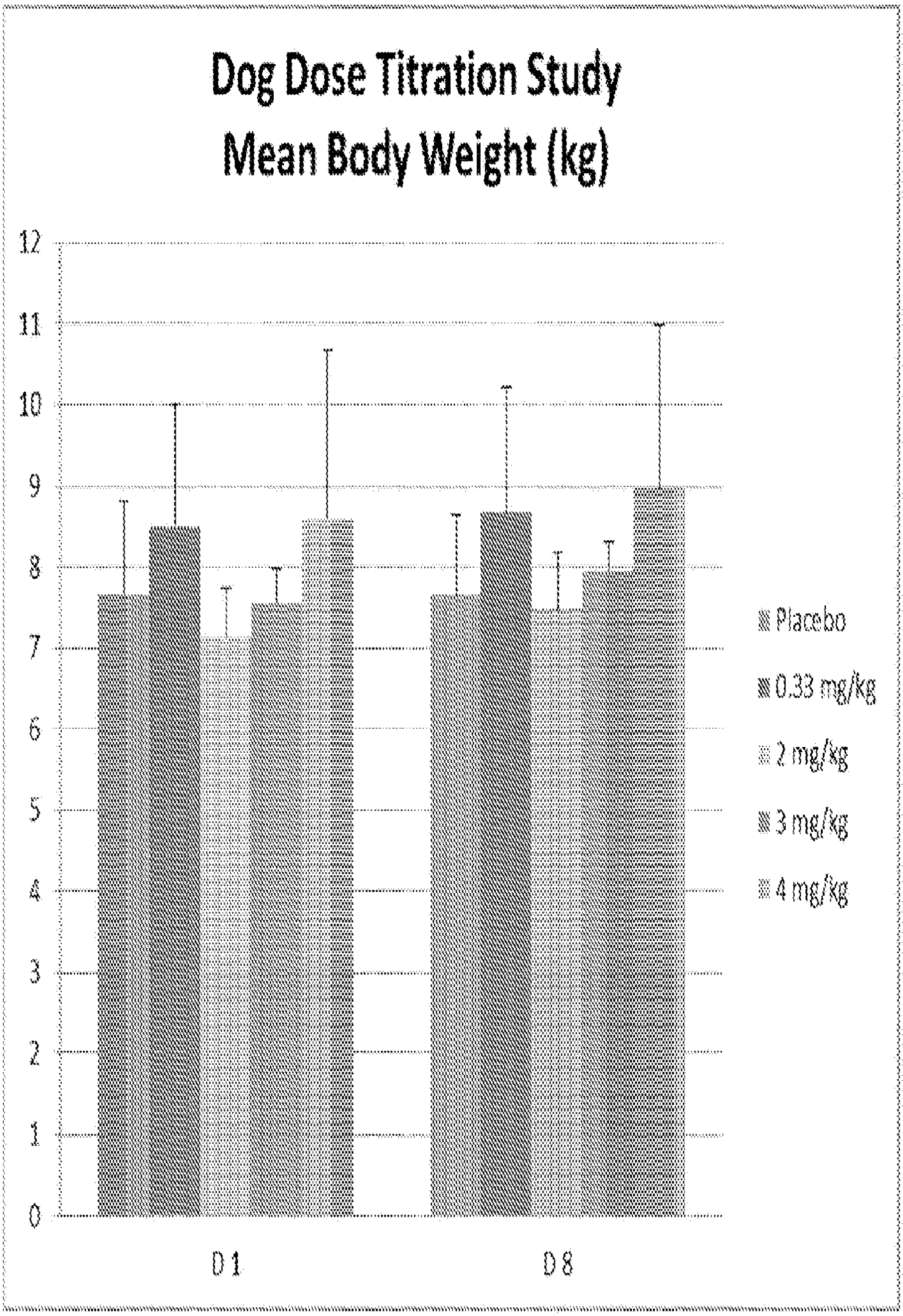

Dog Dose Titration Study
Mean Body Weight (kg)
12
11
10
9
8
7
6
5
4
3
2
1
0
D1
D8
Placebo
0.33 mg/kg
2 mg/kg
3 mg/kg
4 mg/kg

FIGURE 90

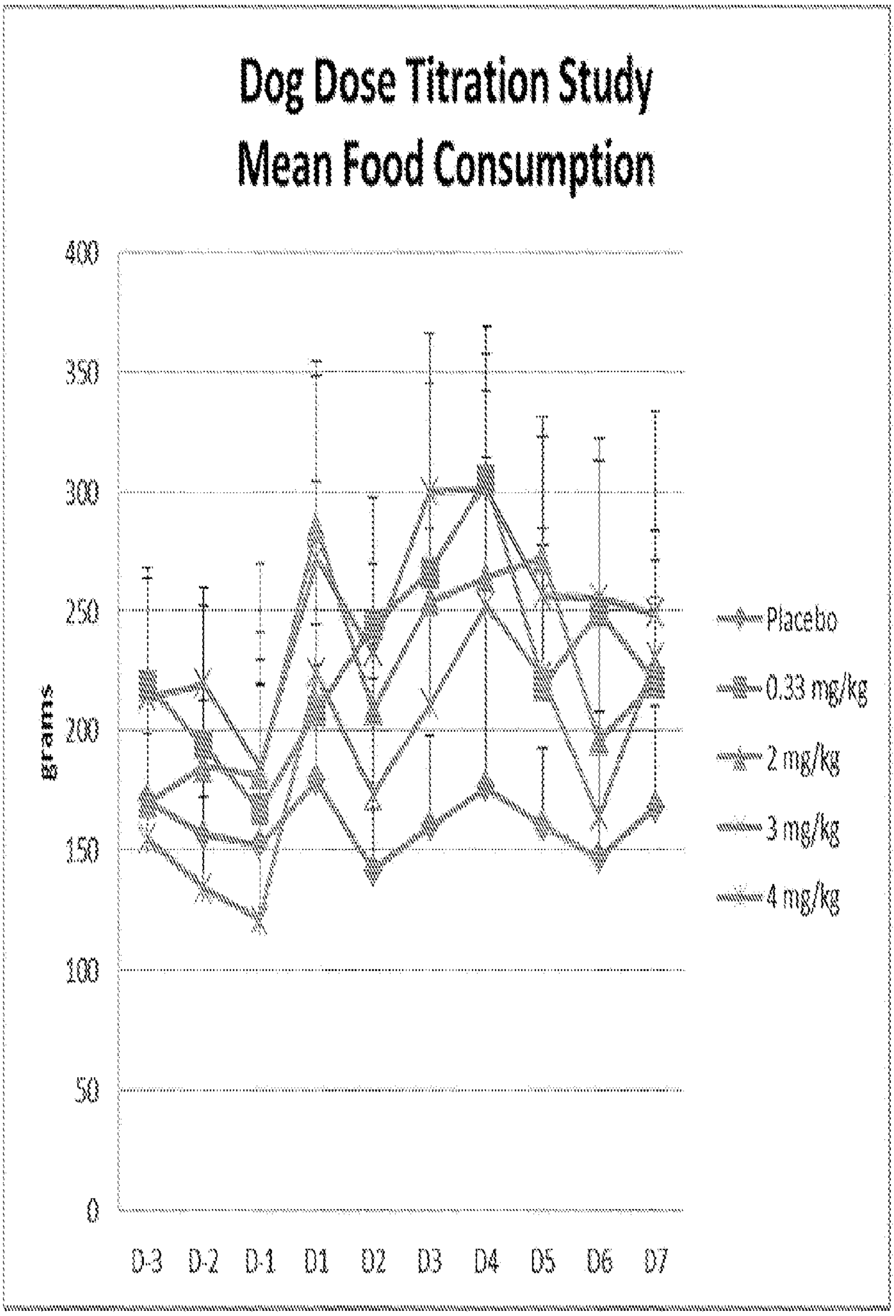

Dog Dose Titration Study
Mean Food Consumption
400
350
300
250
200
150
100
50
0
grams
D-3
D-2
D-1
D1
D2
D3
D4
D5
D6
D7
Placebo
0.33 mg/kg
2 mg/kg
3 mg/kg
4 mg/kg

FIGURE 91

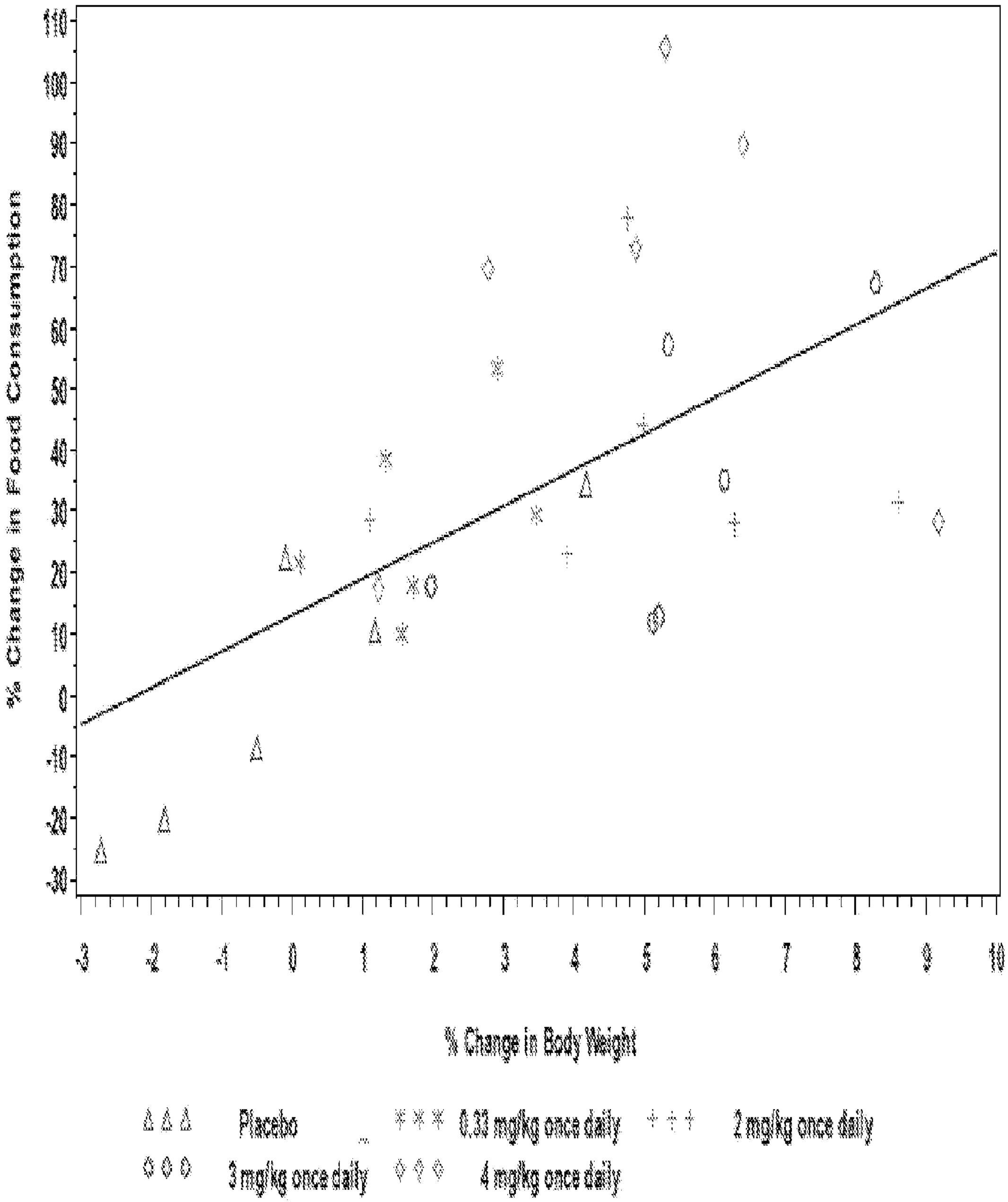

% Change in Food Consumption
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-3
-2
-1
0
1
2
3
4
5
6
7
8
9
10
% Change in Body Weight
Placebo
0.33 mg/kg once daily
2 mg/kg once daily
3 mg/kg once daily
4 mg/kg once daily

FIGURE 92

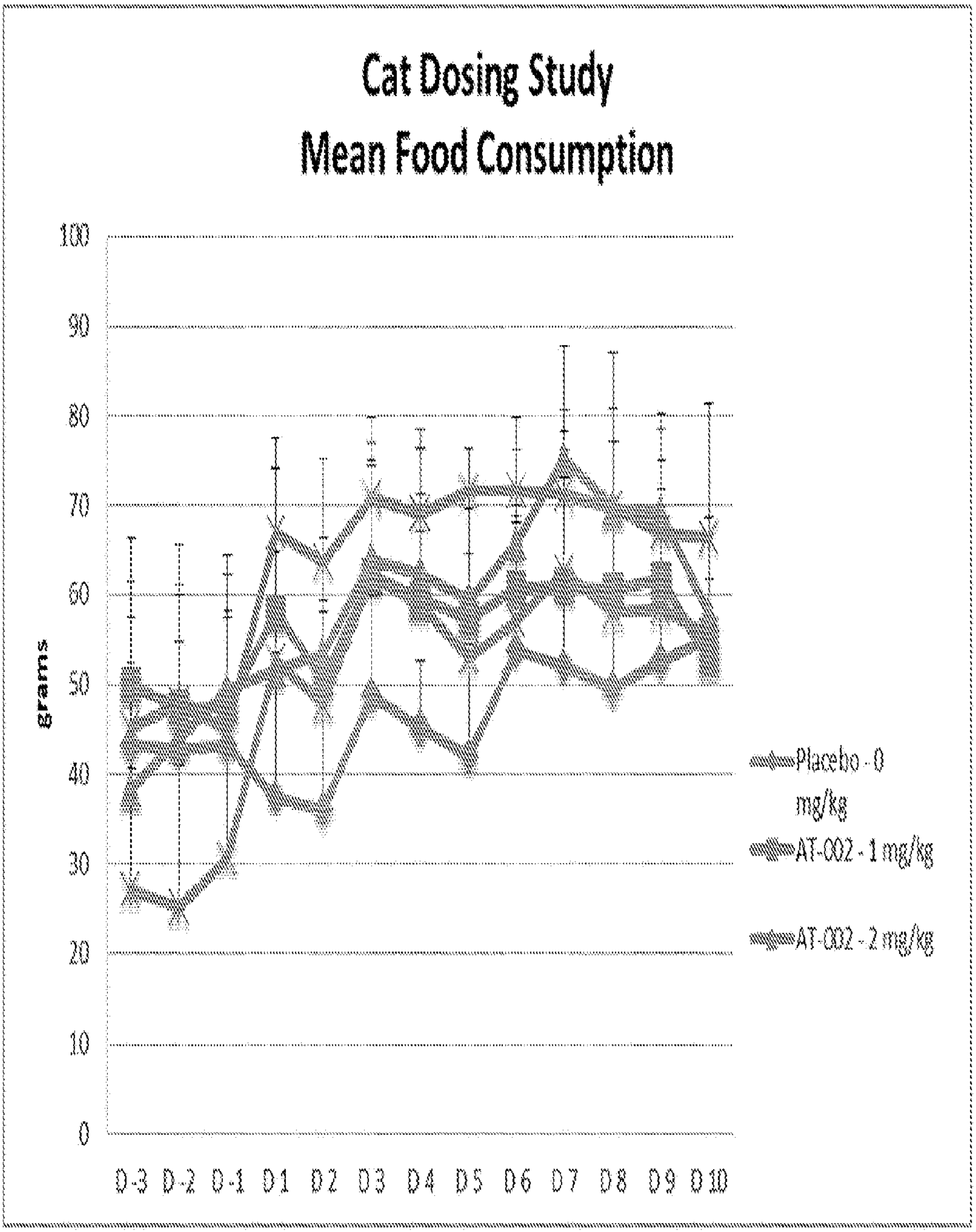

Cat Dosing Study
Mean Food Consumption
100
90
80
70
60
50
40
30
20
10
0
grams
D-3 D-2 D-1 D1 D2 D3 D4 D5 D6 D7 D8 D9 D10
Placebo - 0 mg/kg
AT-002 - 1 mg/kg
AT-002 - 2 mg/kg

FIGURE 93

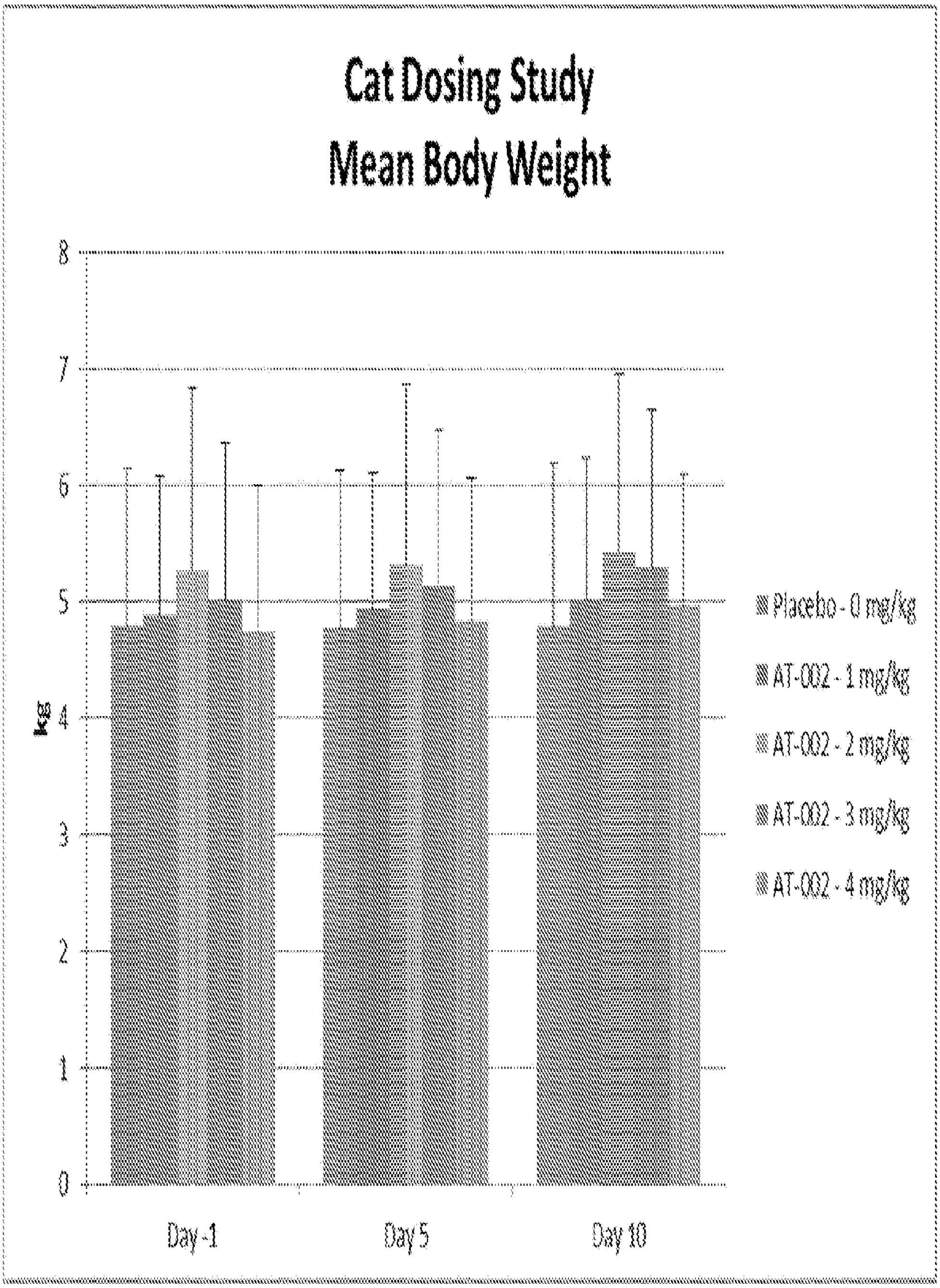

Cat Dosing Study
Mean Body Weight
8
7
6
5
4
3
2
1
0
kg
Day -1
Day 5
Day 10
Placebo - 0 mg/kg
AT-002 - 1 mg/kg
AT-002 - 2 mg/kg
AT-002 - 3 mg/kg
AT-002 - 4 mg/kg

FIGURE 94

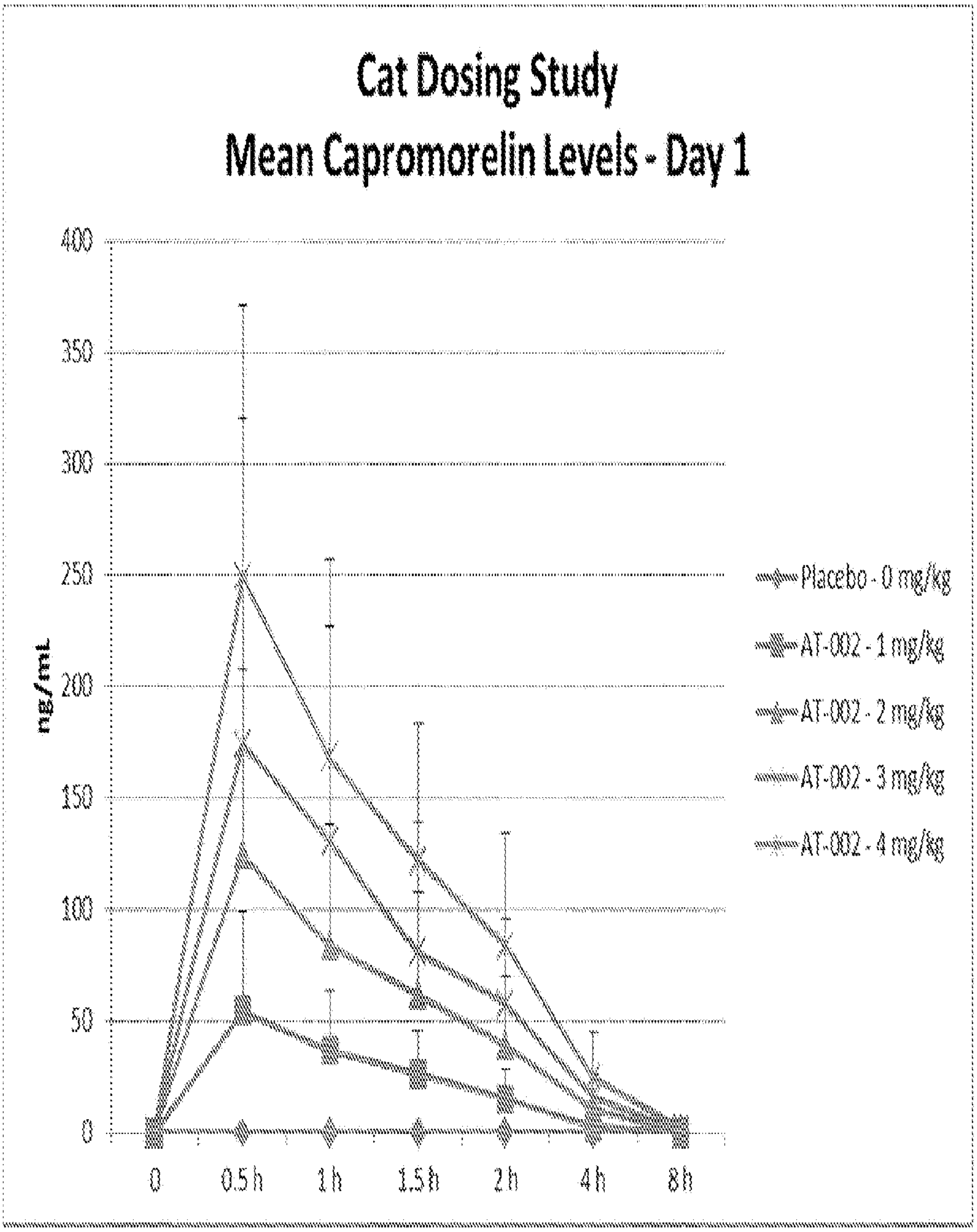

Cat Dosing Study
Mean Capromorelin Levels - Day 1
ng/mL
400
350
300
250
200
150
100
50
0
0
0.5 h
1 h
1.5 h
2 h
4 h
8 h
Placebo - 0 mg/kg
AT-002 - 1 mg/kg
AT-002 - 2 mg/kg
AT-002 - 3 mg/kg
AT-002 - 4 mg/kg

FIGURE 95

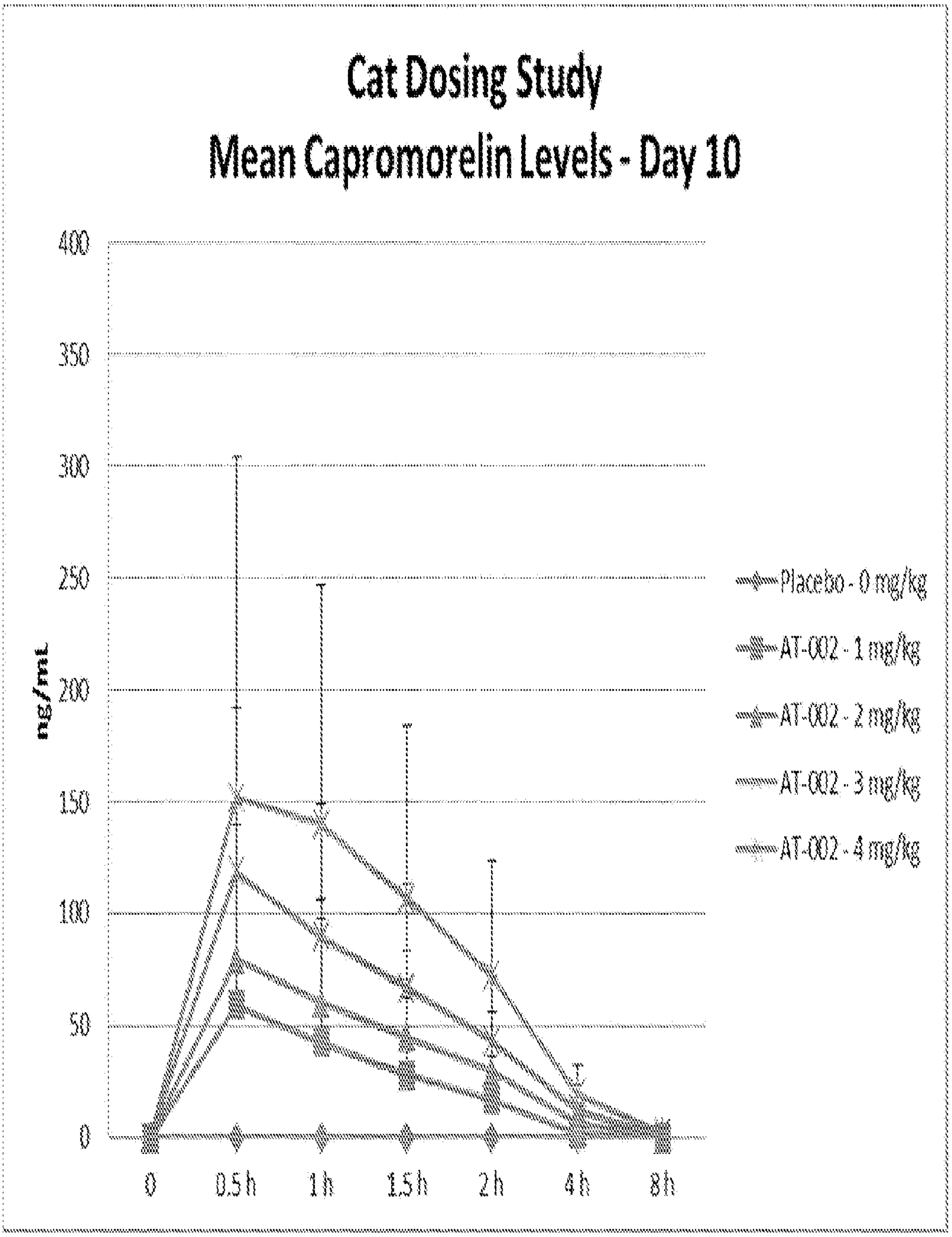

Cat Dosing Study
Mean Capromorelin Levels - Day 10
ng/mL
400
350
300
250
200
150
100
50
0
0
0.5 h
1 h
1.5 h
2 h
4 h
8 h
Placebo - 0 mg/kg
AT-002 - 1 mg/kg
AT-002 - 2 mg/kg
AT-002 - 3 mg/kg
AT-002 - 4 mg/kg

FIGURE 96

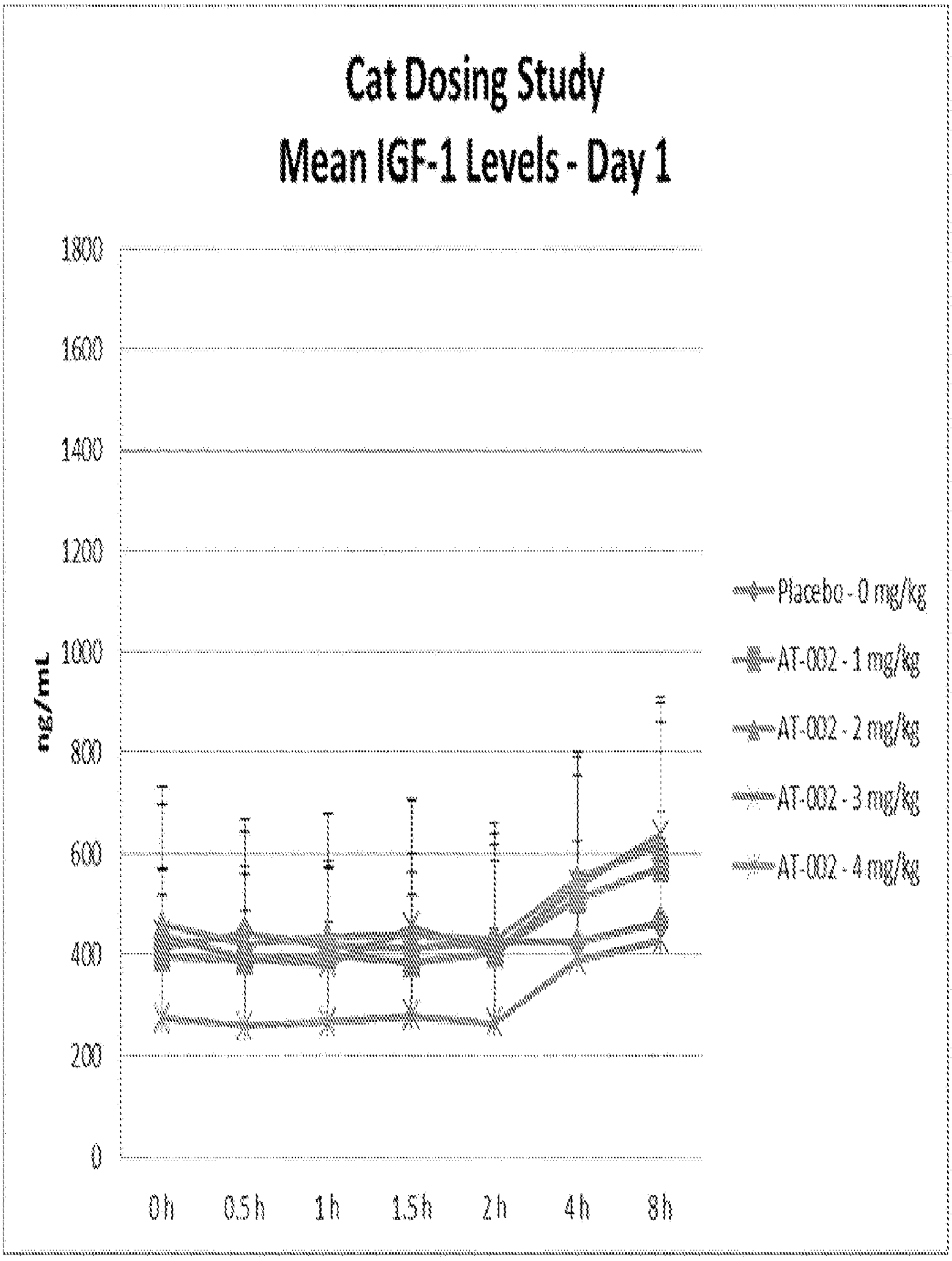

Cat Dosing Study
Mean IGF-1 Levels - Day 1
ng/mL
1800
1600
1400
1200
1000
800
600
400
200
0
0h
0.5h
1h
1.5h
2h
4h
8h
Placebo - 0 mg/kg
AT-002 - 1 mg/kg
AT-002 - 2 mg/kg
AT-002 - 3 mg/kg
AT-002 - 4 mg/kg

FIGURE 97

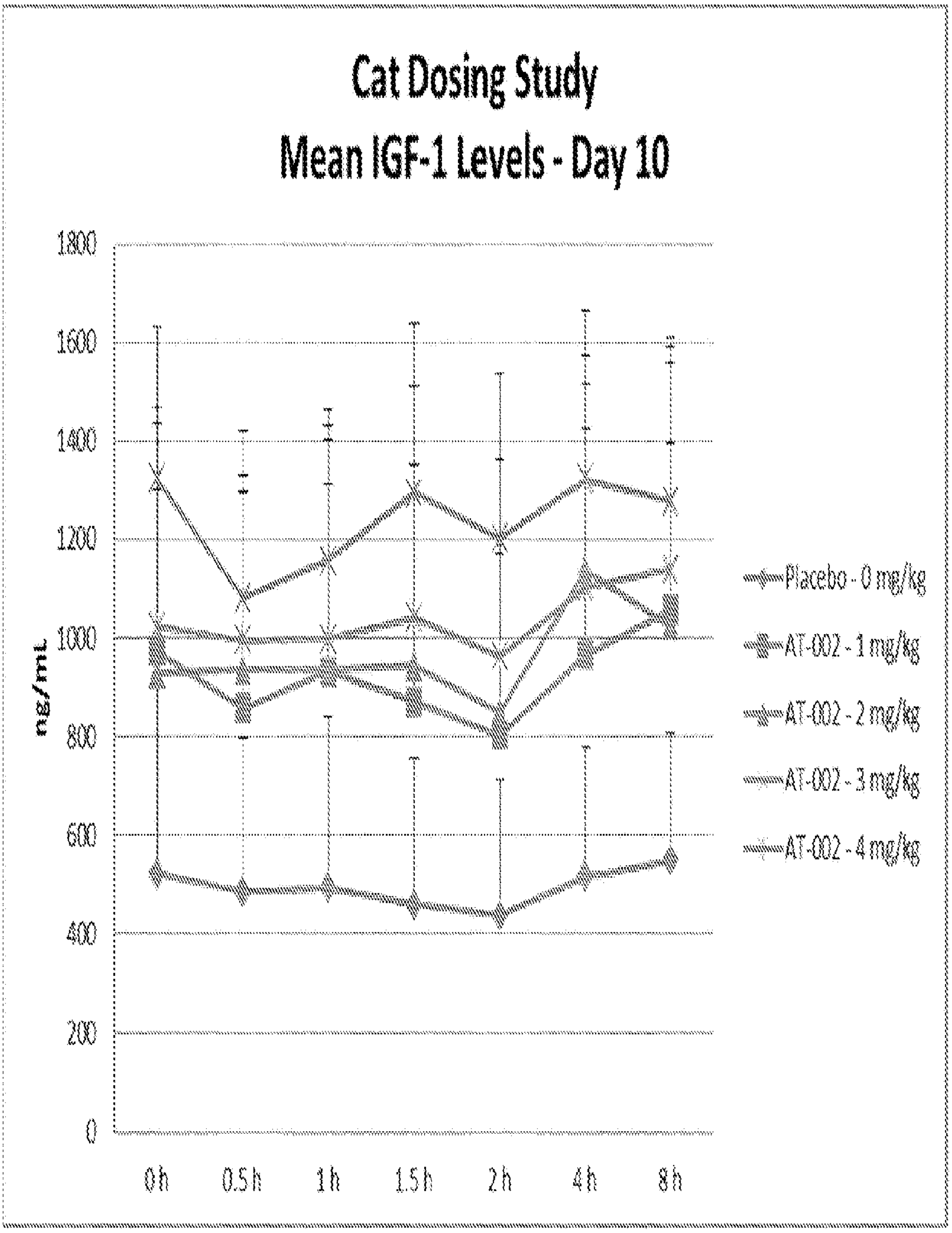

Cat Dosing Study
Mean IGF-1 Levels - Day 10
ng/mL
1800
1600
1400
1200
1000
800
600
400
200
0
0 h
0.5 h
1 h
1.5 h
2 h
4 h
8 h
Placebo - 0 mg/kg
AT-002 - 1 mg/kg
AT-002 - 2 mg/kg
AT-002 - 3 mg/kg
AT-002 - 4 mg/kg

FIGURE 98

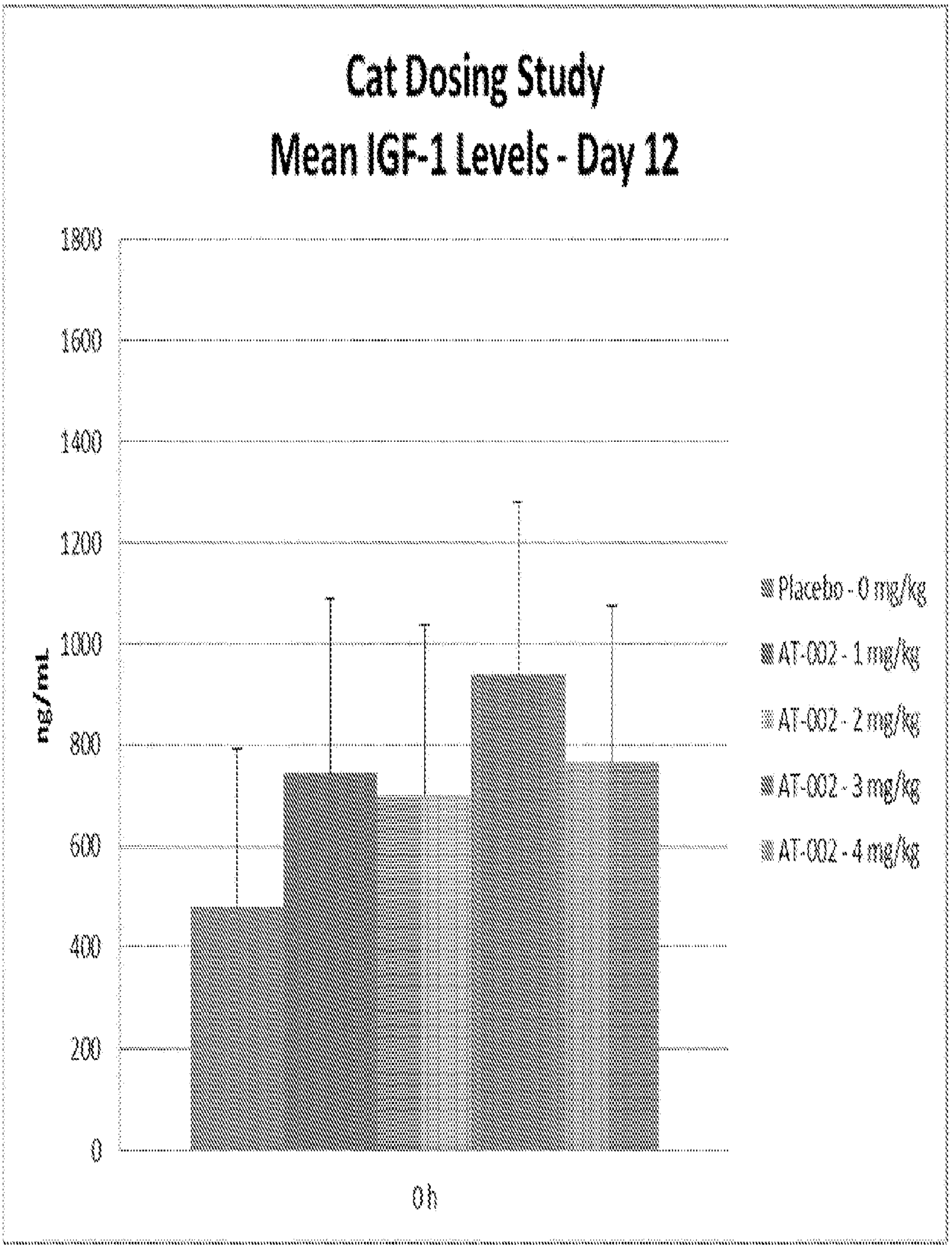

Cat Dosing Study
Mean IGF-1 Levels - Day 12
1800
1600
1400
1200
1000
800
600
400
200
0
ng/mL
0 h
Placebo - 0 mg/kg
AT-002 - 1 mg/kg
AT-002 - 2 mg/kg
AT-002 - 3 mg/kg
AT-002 - 4 mg/kg

FIGURE 99

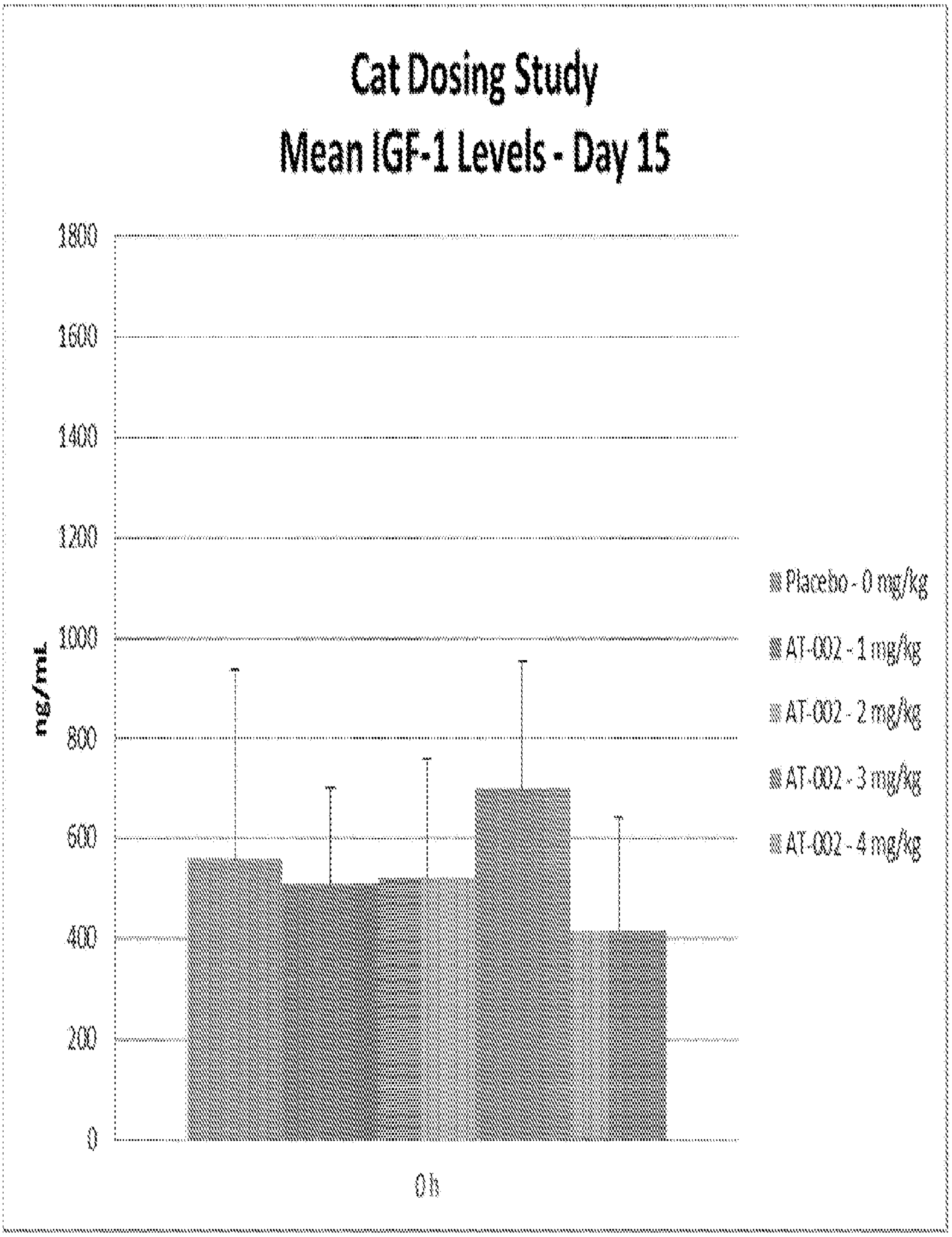
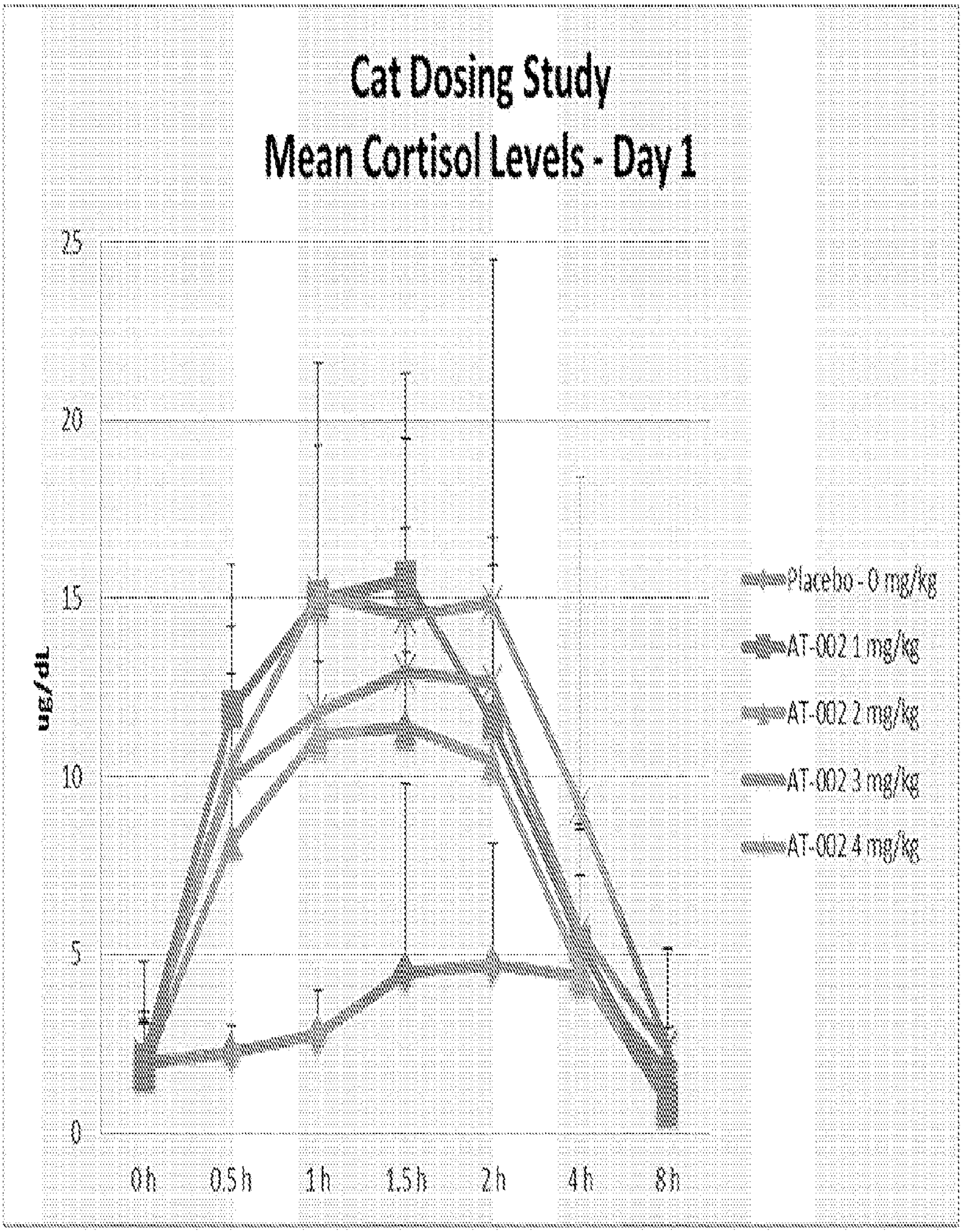

Cat Dosing Study
Mean IGF-1 Levels - Day 15
1800
1600
1400
1200
1000
800
600
400
200
0
ng/mL
0 h
Placebo - 0 mg/kg
AT-002 - 1 mg/kg
AT-002 - 2 mg/kg
AT-002 - 3 mg/kg
AT-002 - 4 mg/kg

FIGURE 100



Cat Dosing Study
Mean Cortisol Levels - Day 1
ug/dL
25
20
15
10
5
0
0 h
0.5 h
1 h
1.5 h
2 h
4 h
8 h
Placebo - 0 mg/kg
AT-002 1 mg/kg
AT-002 2 mg/kg
AT-002 3 mg/kg
AT-002 4 mg/kg

FIGURE 101

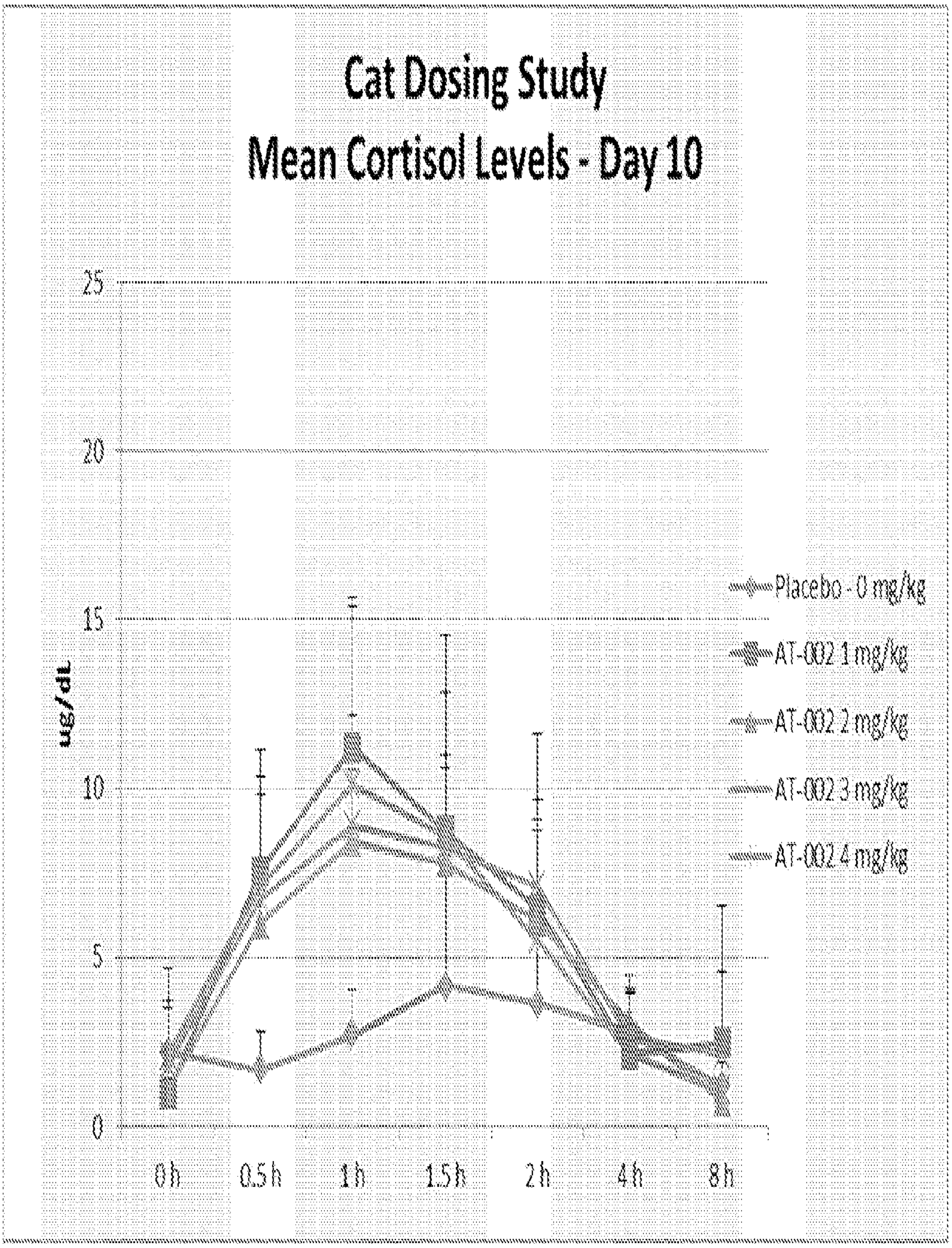

Cat Dosing Study
Mean Cortisol Levels - Day 10
ug/dL
25
20
15
10
5
0
0 h
0.5 h
1 h
1.5 h
2 h
4 h
8 h
Placebo - 0 mg/kg
AT-002 1 mg/kg
AT-002 2 mg/kg
AT-002 3 mg/kg
AT-002 4 mg/kg

FIGURE 102

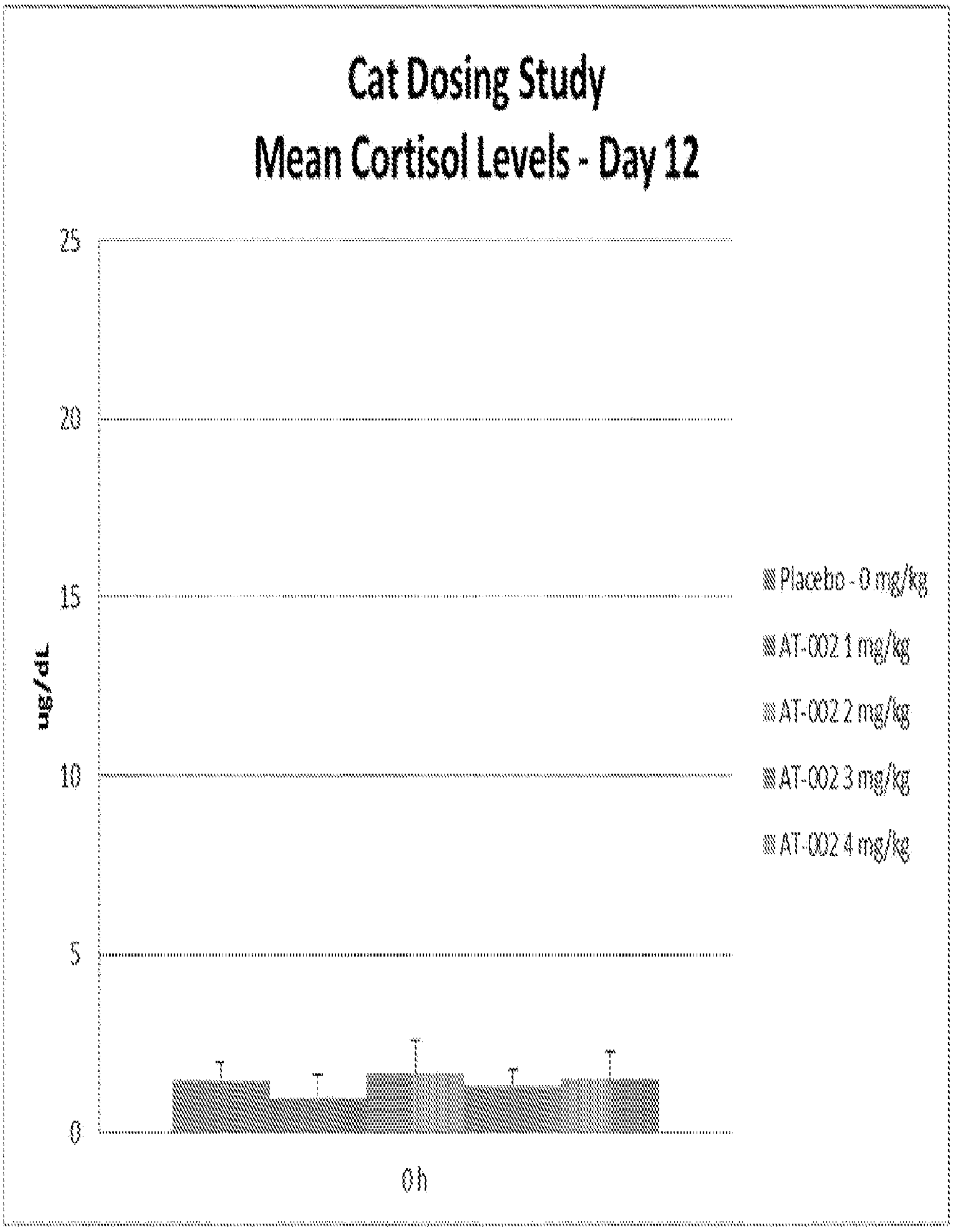

Cat Dosing Study
Mean Cortisol Levels - Day 12
25
20
15
10
5
0
ug/dL
0 h
Placebo - 0 mg/kg
AT-002 1 mg/kg
AT-002 2 mg/kg
AT-002 3 mg/kg
AT-002 4 mg/kg

FIGURE 103

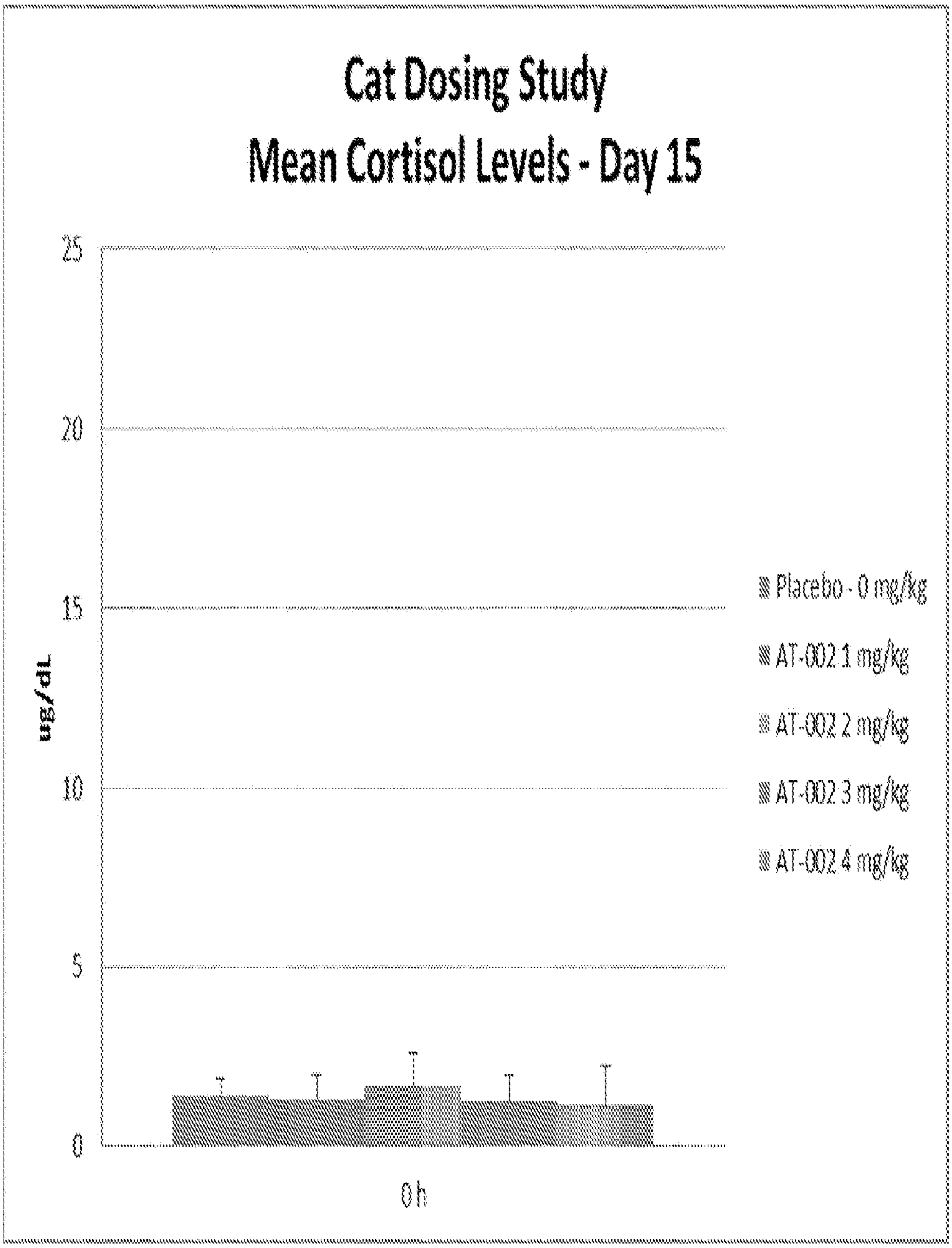

Cat Dosing Study
Mean Cortisol Levels - Day 15
25
20
15
10
5
0
ug/dL
0 h
Placebo - 0 mg/kg
AT-002 1 mg/kg
AT-002 2 mg/kg
AT-002 3 mg/kg
AT-002 4 mg/kg

FIGURE 104

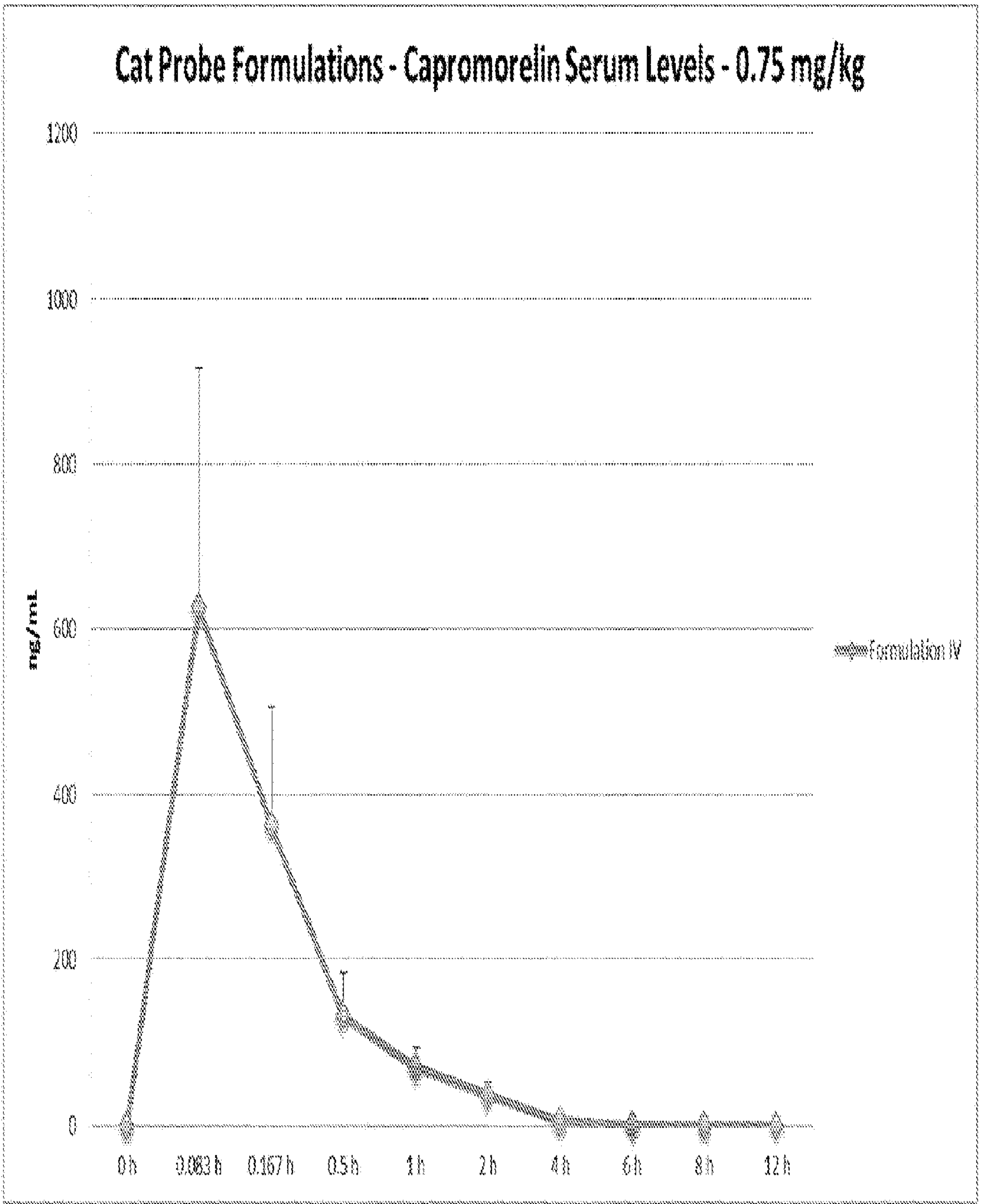
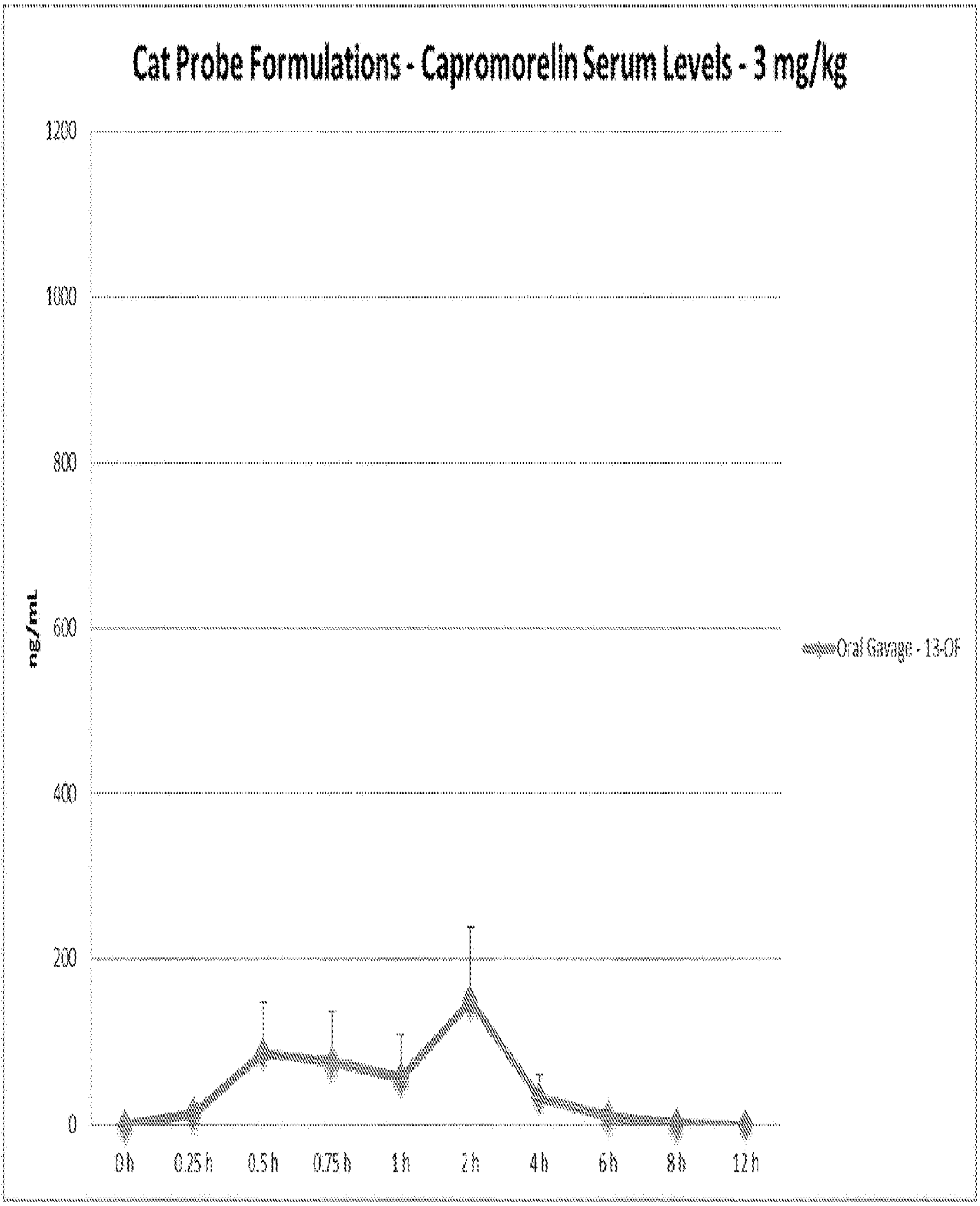

Cat Probe Formulations - Capromorelin Serum Levels - 0.75 mg/kg
1200
1000
800
600
400
200
0
ng/mL
0 h
0.083 h
0.167 h
0.5 h
1 h
2 h
4 h
6 h
8 h
12 h
Formulation IV

FIGURE 105



Cat Probe Formulations - Capromorelin Serum Levels - 3 mg/kg
1200
1000
800
600
400
200
0
ng/mL
0 h
0.25 h
0.5 h
0.75 h
1 h
2 h
4 h
6 h
8 h
12 h
Oral Gavage - 13-OF

FIGURE 106

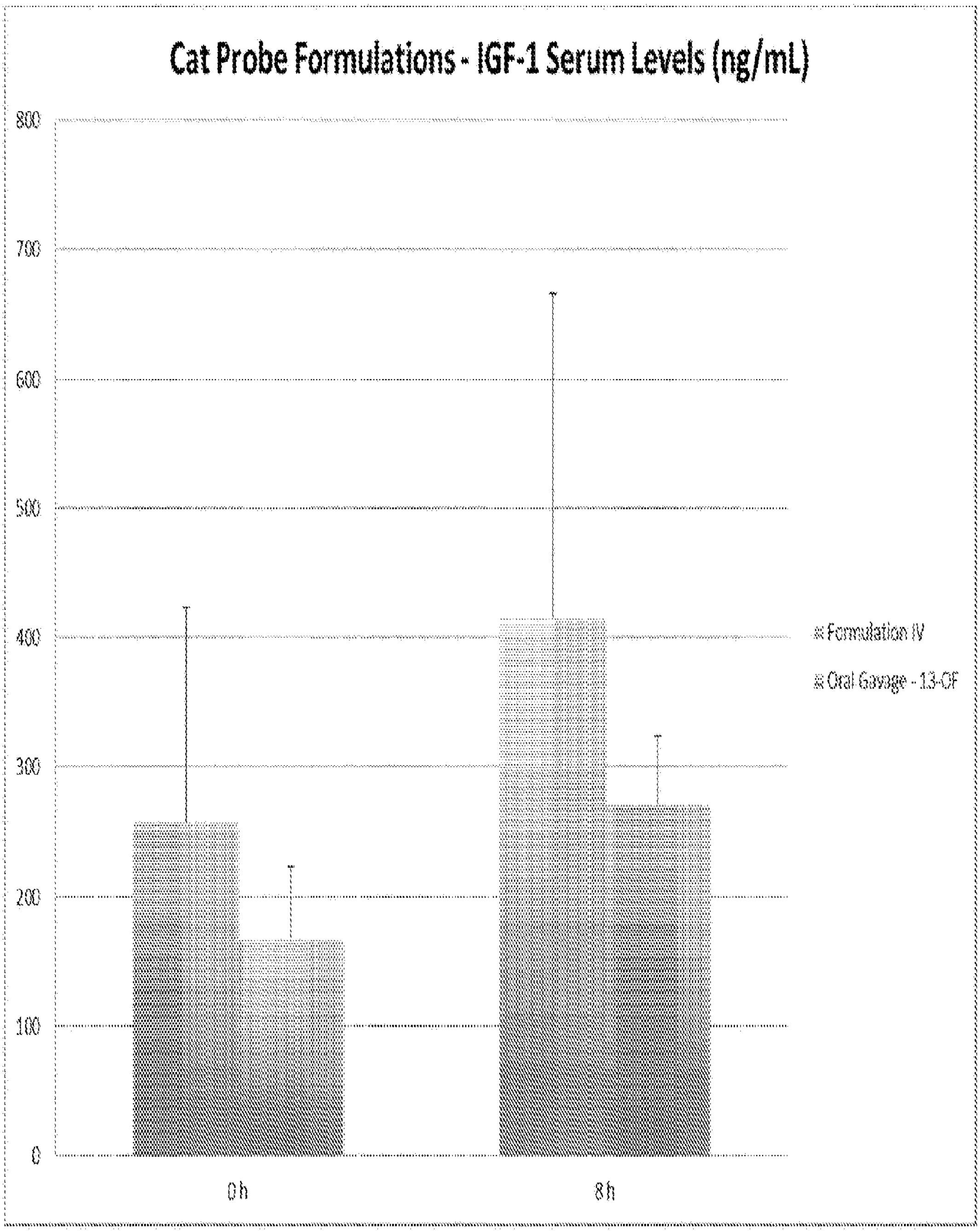

Cat Probe Formulations - IGF-1 Serum Levels (ng/mL)
800
700
600
500
400
300
200
100
0
0 h
8 h
Formulation IV
Oral Gavage - 13-CF

FIGURE 107

Parameter	Units	Mean	SD	SE	Min	Median	Max	Geometric mean	Harmonic mean	Pseudo SD
AUC Extrapolated	%	8.2	6.6	2.7	1.7	7.1	18.6	5.8	3.9	4.2
AUC 0-INF	hr*ng/mL	349.4	128.1	52.3	195.4	332.1	543.2	329.9	311.2	121.5
C0	ng/mL	1096.0	610.0	249.0	595.8	801.8	2090.7	976.3	886.4	372.1
Cl	mL/min/kg	31.1	11.6	4.7	17.8	30.0	49.5	29.3	27.7	10.5
T 1/2 λz	hr	0.90	0.16	0.07	0.68	0.85	1.12	0.89	0.87	0.16
λz	1/hr	0.793	0.145	0.059	0.619	0.814	1.019	0.782	0.771	0.143
MRT 0-INF	hr	0.84	0.23	0.09	0.60	0.75	1.21	0.82	0.79	0.19
Vss	L/kg	1.57	0.67	0.27	0.77	1.66	2.34	1.43	1.30	0.70
Vz	L/kg	2.39	0.91	0.37	1.30	2.22	3.52	2.25	2.11	0.87

FIGURE 108

Parameter	Units	Mean	SD	SE	Min	Median	Max	Geometric mean	Harmonic mean	Pseudo SD
AUC Extrapolated	%	2.9	0.8	0.4	2.0	2.5	3.9	2.8	2.7	0.7
AUC 0-INF	hr*ng/mL	470.1	222.8	99.6	267.0	371.8	801.6	431.7	399.6	165.3
Cl/F	mL/min/kg	95.9	39.4	17.6	47.8	103.1	143.5	88.8	81.5	42.3
Cmax	ng/mL	148.9	90.2	36.8	24.8	141.5	293.0	118.7	82.1	158.4
T 1/2 λz	hr	1.04	0.20	0.09	0.87	1.04	1.36	1.03	1.01	0.17
λz	1/hr	0.683	0.118	0.053	0.510	0.667	0.801	0.675	0.665	0.132
MRT 0-INF	hr	2.37	0.23	0.11	2.09	2.34	2.74	2.36	2.36	0.23
Tmax	hr	2.00	0.00	0.00	2.00	2.00	2.00	2.00	2.00	0.00
Vz/F	L/kg	8.28	2.94	1.32	5.63	7.87	12.91	7.90	7.57	2.36
Estimated F	%	34						33	32	
Estimated MAT	hr	1.53						1.55	1.56	

FIGURE 109

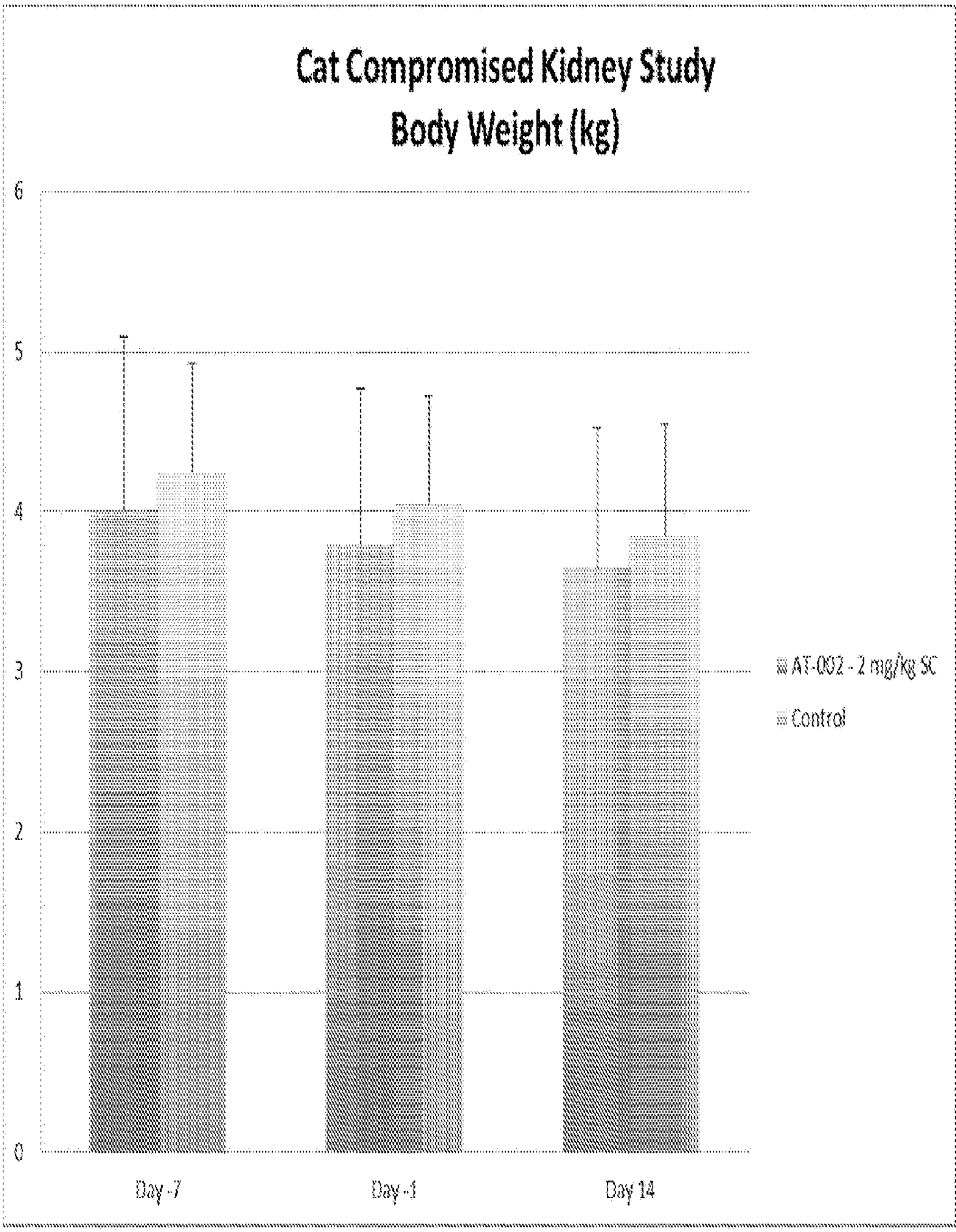

Cat Compromised Kidney Study
Body Weight (kg)
6
5
4
3
2
1
0
Day -7
Day -1
Day 14
AT-002 - 2 mg/kg SC
Control

FIGURE 110

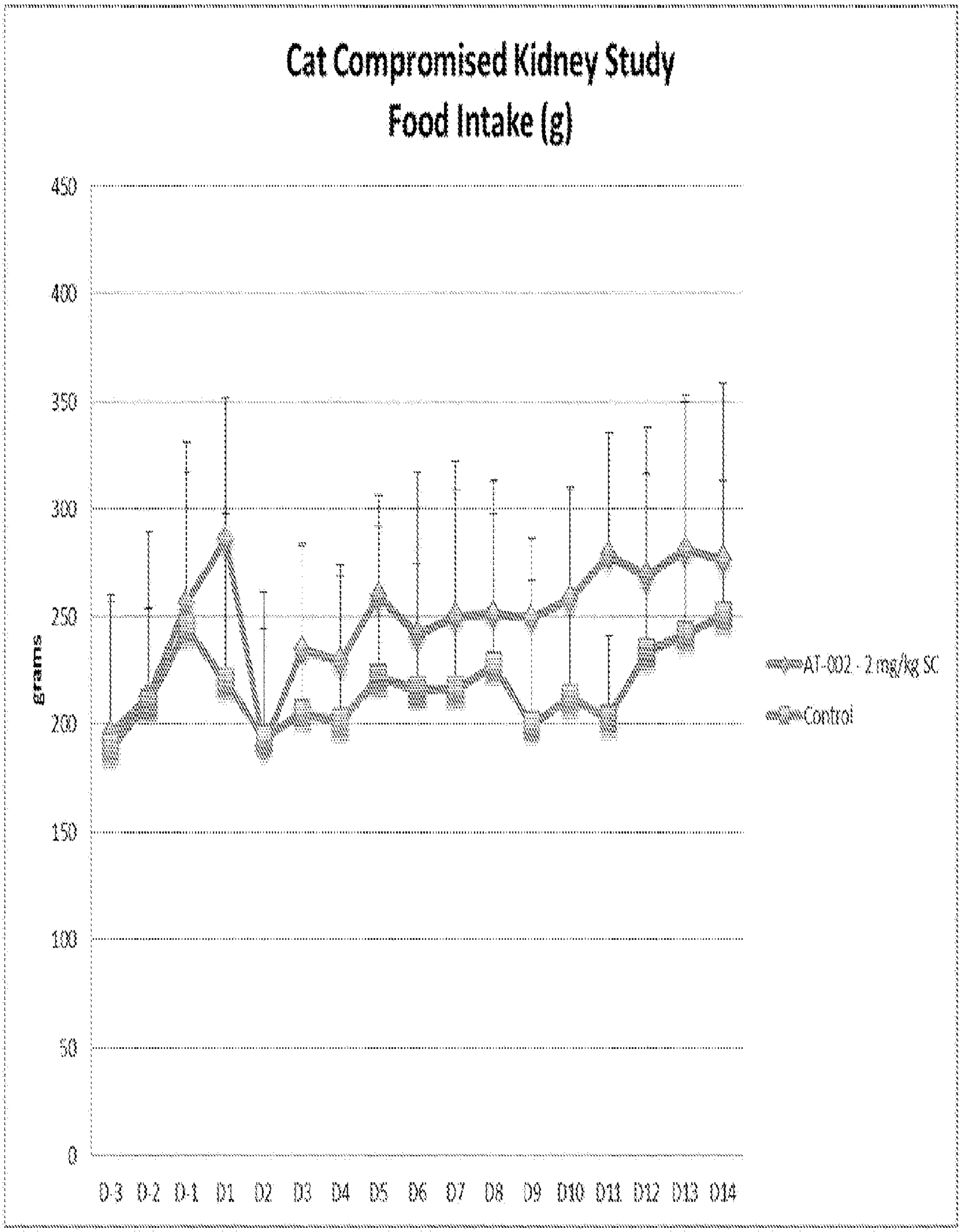

Cat Compromised Kidney Study
Food Intake (g)
grams
450
400
350
300
250
200
150
100
50
0
D-3 D-2 D-1 D1 D2 D3 D4 D5 D6 D7 D8 D9 D10 D11 D12 D13 D14
AT-002 - 2 mg/kg SC
Control

FIGURE 111

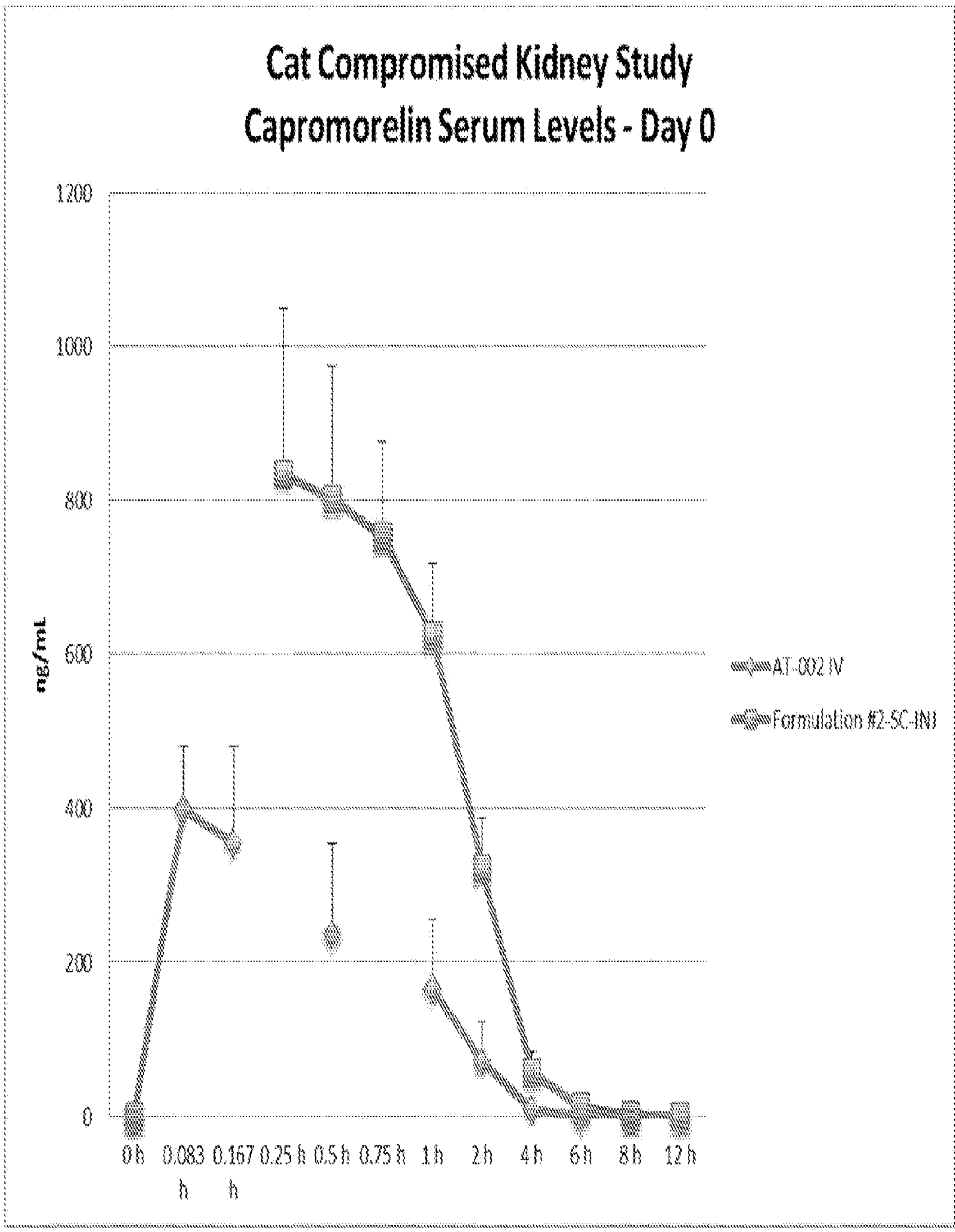

Cat Compromised Kidney Study
Capromorelin Serum Levels - Day 0
1200
1000
800
600
400
200
0
ng/mL
0 h
0.083 h
0.167 h
0.25 h
0.5 h
0.75 h
1 h
2 h
4 h
6 h
8 h
12 h
AT-002 IV
Formulation #2-SC-INJ

FIGURE 112

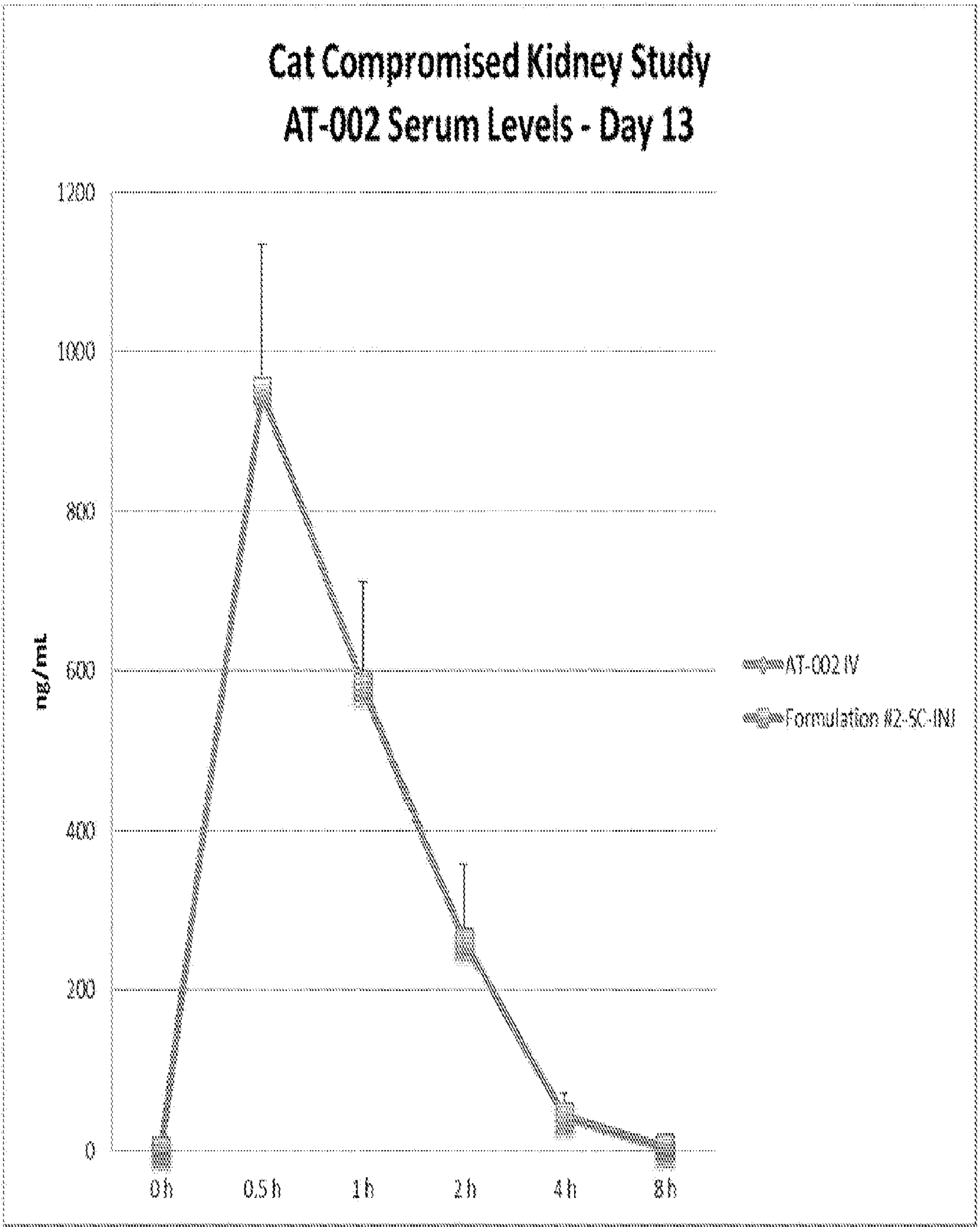

Cat Compromised Kidney Study
AT-002 Serum Levels - Day 13
1200
1000
800
600
400
200
0
ng/mL
0 h
0.5 h
1 h
2 h
4 h
8 h
AT-002 IV
Formulation #2-SC-INJ

FIGURE 113

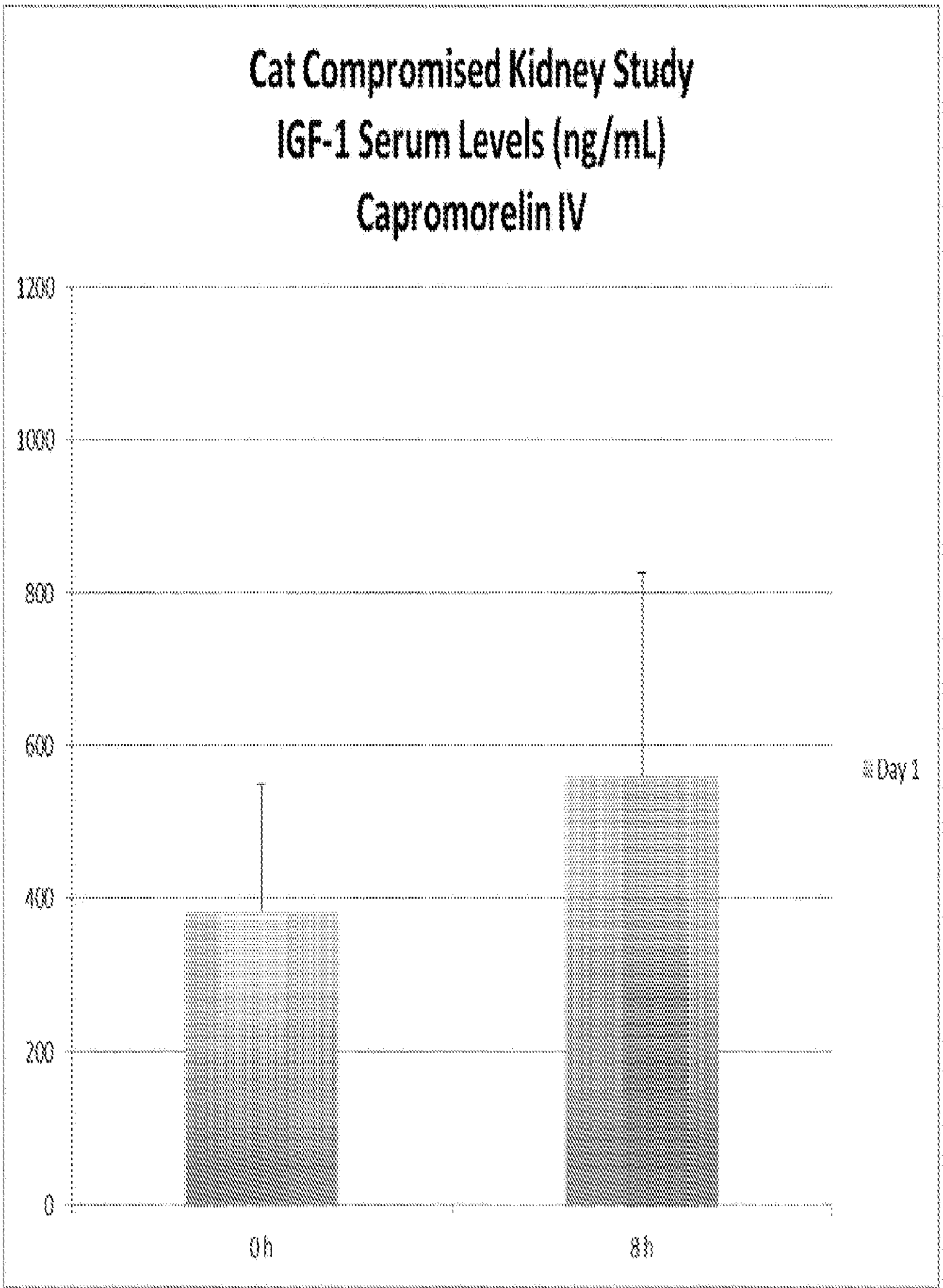

Cat Compromised Kidney Study
IGF-1 Serum Levels (ng/mL)
Capromorelin IV
1200
1000
800
600
400
200
0
0 h
8 h
Day 1

FIGURE 114

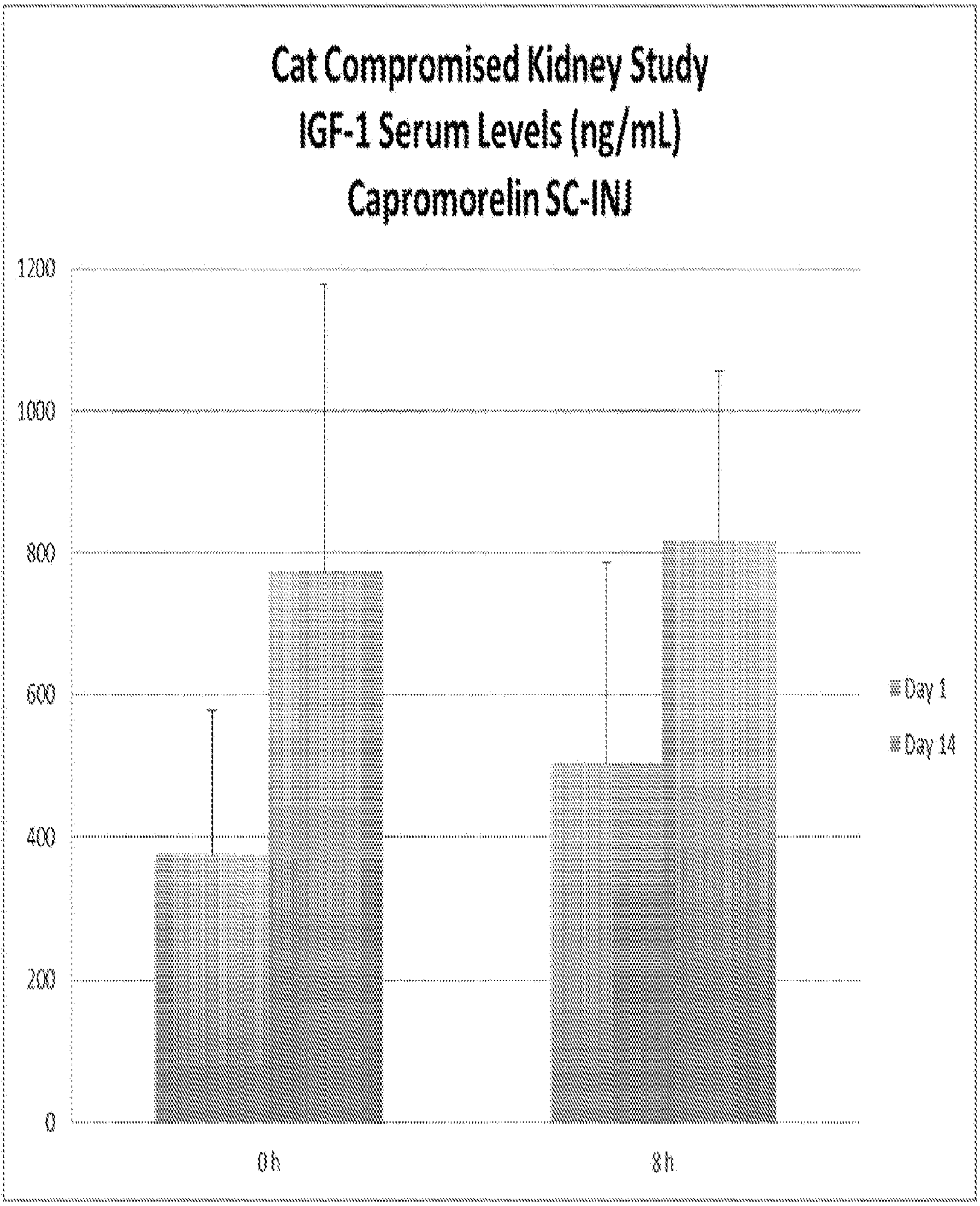

Cat Compromised Kidney Study
IGF-1 Serum Levels (ng/mL)
Capromorelin SC-INJ
1200
1000
800
600
400
200
0
0 h
8 h
Day 1
Day 14

FIGURE 115

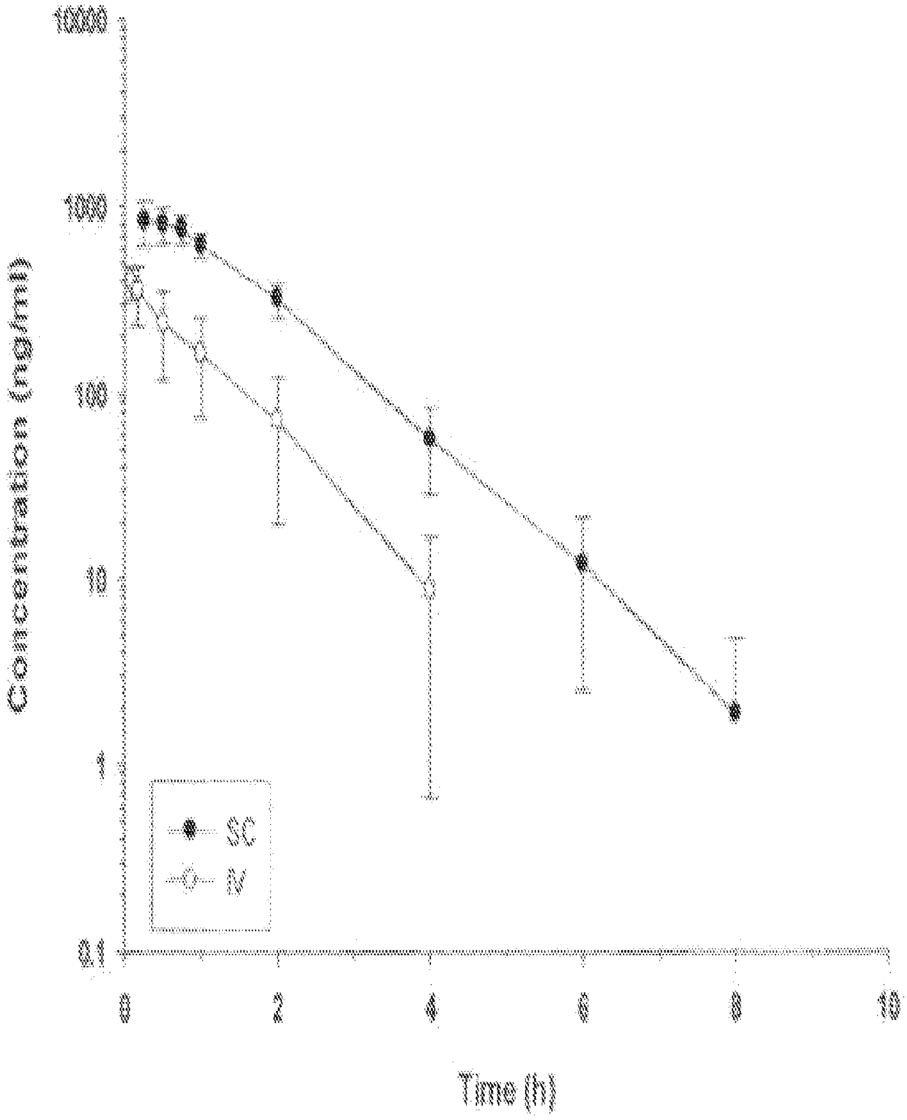

10000
1000
100
10
1
0.1
Concentration (ng/ml)
SC
IV
0
2
4
6
8
10
Time (h)

FIGURE 116

Parameter	Units	Mean	SD	SE	Min	Median	Max	Geometric mean	Harmonic mean	Pseudo SD
AUC_%Extrap_obs	%	4.6	6.7	2.7	1.4	1.8	18.2	2.7	2.1	1.0
AUCall	hr*ng/mL	458.7	233.0	95.1	213.7	383.5	874.4	415.6	379.1	186.6
AUCINF_obs	hr*ng/mL	475.7	232.3	94.8	261.4	389.5	900.6	436.8	406.1	158.3
C0	ng/mL	486	131	53	380	445	740	474	464	93
Cl_obs	mL/min/kg	23.8	9.2	3.7	10.7	25.0	37.0	22.1	20.3	11.2
HL_Lambda_z	hr	0.74	0.09	0.04	0.67	0.71	0.90	0.74	0.73	0.08
MRTINF_obs	hr	1.01	0.13	0.06	0.87	0.95	1.23	1.00	1.00	0.12
Vss_obs	L/kg	1.43	0.60	0.24	0.79	1.37	2.40	1.33	1.25	0.50
Vz_obs	L/kg	1.55	0.76	0.31	0.72	1.46	2.88	1.41	1.28	0.66

FIGURE 117

Parameter	Units	Mean	SD	SE	Min	Median	Max	Geometric mean	Harmonic mean	Pseudo SD
AUC_%Extrap_obs	%	0.7	0.4	0.2	0.4	0.6	1.5	0.6	0.6	0.3
AUCall	hr*ng/mL	1598.9	292.6	119.5	1165.6	1588.9	2017.4	1575.9	1552.3	310.3
AUCINF_obs	hr*ng/mL	1610.3	292.2	119.3	1171.5	1606.5	2024.6	1587.4	1563.8	313.0
Cl_F_obs	mL/min/kg	16.4	3.2	1.3	12.7	16.0	21.9	16.2	15.9	2.9
Cmax	ng/ml	905	147	60	626	979	1000	893	880	153
HL_Lambda_z	hr	0.83	0.14	0.06	0.64	0.81	1.03	0.82	0.81	0.14
MRTINF_obs	hr	1.41	0.18	0.07	1.14	1.39	1.63	1.40	1.39	0.19
Tmax	hr	0.46	0.19	0.08	0.25	0.50	0.75	0.42	0.39	0.19
Vz_F_obs	L/kg	1.15	0.17	0.07	0.92	1.15	1.38	1.14	1.13	0.18
F		1.27						1.37	1.45	
MAT	hr	0.40						0.40	0.39	

FIGURE 118